Supplementary Table 1. Glucocorticoids

Setting	Reference	Study characteristics	Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison)						Disease modification CONFIRMED
			Outcomes Year 1			Outcomes Years 2–5			>5y data
			Significant reduction in disease activity measured using a validated tool (i.e. SELENA-SLEDAI, BILAG, SRI-4)	Significant reduction in severe flare measured using a validated tool (i.e. SFI or BILAG)	Reduction in use of steroids* and/or immunosuppressants	Sustained improvement in multiple organ domains/no worsening in multiple organ domains	Prevention of severe flares	Continued reduction in use of steroids* and/or immunosuppressants	No change in SDI or delayed progression
Clinical trial	[1]	Design: A monocentric, 12-month, superiority, open-label, RCT (1:1) No. of patients: 124 Comparator: continuing prednisone 5 mg/day (maintenance) vs discontinuing prednisone (withdrawal)	NR	**Non-significant lower proportion of severe flare in maintenance vs withdrawal:** 1 patient vs 5; RR 0.2 (95% CI 0.1 to 1.5), p=0.096 **Proportion of patients experiencing a flare (SFI) was significantly lower in the maintenance group as compared with the withdrawal group:** 4 patients vs 17; RR 0.2 (95% CI 0.1 to 0.7), p=0.003 **BILAG was also significant:** maintenance 4 (7%) patients vs 17 (27%) patients in withdrawal; RR 0.2 (95% CI 0.1 to 0.7), p=0.003 **Time to first flare significant earlier for withdrawal vs maintenance:** HR 0.2 (95% CI 0.1 to	NR	NA	NA	NA	NA

				0.6), p=0.002					
Clinical trial	[2]	Design: matched controlled trial No. of patients:204 Comparator: maintenance 5 mg/day vs gradual taper over 2 years (withdrawal)	NR	**No significant differences in maintenance vs withdrawal in moderate or severe flares** (SLEDAI-2K increase of 4 or more) **Total flares (any increase in SLEDAI-2K) were fewer in the withdrawal group:** 17.6% vs 29.4%, p=0.023	NR	More patients in the maintenance group accrued new damage (expressed by any increase in SDI) at 24 months (17.6% vs 6.9%, p=0.022)	Moderate to severe flares, withdrawal vs maintenance at 24 months: 14.7% vs 27.5%, p=0.024	NR	NA

Clinical practice	[3]	Design: observational No. of patients: 287 ADU group: mean 5 mg/day prednisone at Year 1 vs IM department group: mean 16 mg/day prednisone at Year 1			HCQ was given to 89% of patients in the ADU group versus 39% in the IM group by year 1 (p<0.0001)	SLEDAI score decreased in both groups, resulting in comparable SLEDAI-2K scores at 5 years of: 2.8 for the ADU group vs 3.0 for the IM group (p=0.6).		HCQ was given to 100% of patients in the ADU group vs 52% in the IM group by Year 5 (p<0.0001)	Patients in the ADU group were less likely to accrue any damage (p=0.007)
	[4]	Design: cohort study No. of patients: 60 Group M: ≤30 mg/day vs group H: >30 mg/day prednisone	NR	NR	NR	NR	NR	NR	Patients in group H were more likely to accrue new damage (adjusted HR 3.85 (95% CI 1.03 to 14.2) 18 patients accrued new damage: 6 (20%) patients in group M vs 12 (40%) in group H (p=0.09) No patient in group M suffered GC-related damage, vs 5/30 (16.6%) patients in group H (p=0.02) No patient receiving ≤7.5mg/day prednisone accrued GC-related damage, vs 5/13 (14%) of those receiving >7.5 mg/day (p=0.04)

	[5]	Design: observational No. of patients: 173 Cruces Lupus cohort (CC) vs Bordeaux Lupus Cohort (BC)	**ClinROnT (clinical SLEDAI = 0, PGA < 0.5; treatment with HCQ, immunosuppressive drugs and/or prednisone ≤5 mg/day allowed) at Year 1, CC vs BC**: 84% vs 43%, p<0.001	NR	**Average oral prednisone dose during FU, CC vs BC:** 2.3 mg/day vs 7.2 mg/day, p<0.001 The proportion of patients ever receiving immunosuppressive drugs was similar in both groups	NR	NR	**Average oral prednisone dose during FU, CC vs BC:** 2.3 mg/day vs 7.2 mg/day, p<0.001 The proportion of patients ever receiving immunosuppressive drugs was similar in both groups	**ClinROnT (clinical SLEDAI=0, PGA<0.5; treatment with HCQ, immunosuppressive drugs and/or prednisone ≤5 mg/day allowed) during 5 years of FU, CC vs BC:** 70% vs 28%, p<0.001
	[6]	Design: observational cohort (note: FU does not equate to length of GC use) No. of patients: 230	NA	NA	NA	NA	NA	NA	**Risk of damage at Year 5, medium-high doses of prednisone (>7.5 mg/day) at end of fourth year of FU vs no prednisone:** adjusted OR 5.39 (95% CI 1.59 to 18.27) **GC-related damage at Year 5, medium-high doses of prednisone (>7.5 mg/day) at end of fourth year of FU vs no prednisone:** adjusted OR 9.9 (95% CI 1.1 to 84) **Risk of damage at Year 5, low dose (≤7.5 mg/day) prednisone vs no prednisone for risk of damage**: adjusted OR 1.65 (95% CI 0.53 to 5.10) **Risk of GC-related damage, low dose (≤7.5 mg/day) prednisone vs no prednisone for risk of damage**: adjusted OR 1.7 (95% CI 0.17 to 17)

	[7]	Design: Cross-sectional No. of patients: 357							**≥1 chronic organ damage:** 77.87% (n=278/357) Patients who received higher-dose GC therapy had higher mean SDI scores
	[8]	Design: Cohort study No. of patients: 223			Prednisone doses during the first month were associated with doses in Months 2–12 (p<0.001) 79% of patients who received low dose prednisone (≤7.5 mg/day) in Month 1 received low doses in Months 2–12. Patients receiving low dose prednisone during Month 1 were not more likely to be treated with doses >7.5 mg/day in Months 2–12 vs patients on no prednisone (OR 1.4, 95% CI 0.87 to 4.7)	NA	NA	NA	NA

ADU, autoimmune disease unit; BC, Bordeaux Lupus Cohort; BILAG, British Isles Lupus Assessment Group; CC, Cruces Lupus Cohort; CI, confidence interval; ClinROnT, clinical remission on treatment; FU, follow-up; GC, glucocorticoid; HCQ, hydroxychloroquine; HR, hazard ratio; IM, internal medicine; mg, milligram; NA, not available; NR, not relevant; OR, odds ratio; PGA, physician global assessment of disease activity; RCT, randomised controlled trial; RR, relative risk; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI, SELENA-SLEDAI flare index; SLEDAI, SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4.

Supplementary Table 2. Antimalarials

Setting	Reference	Study characteristics	Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison)						Disease modification CONFIRMED
			Outcomes Year 1			Outcomes Years 2–5			>5y data
			Significant reduction in disease activity measured using a validated tool (i.e. SELENA-SLEDAI, BILAG, SRI-4)	Significant reduction in severe flare measured using a validated tool (i.e. SFI or BILAG)	Reduction in use of steroids* and/or immunosuppressants	Sustained improvement in multiple organ domains/no worsening in multiple organ domains	Prevention of severe flares	Continued reduction in use of steroids* and/or immunosuppressants	No change in SDI or delayed progression
Hydroxychloroquine (HCQ)									
Clinical trial	[9]	Design: Prospective, randomised, trial of HCQ dose change and 7-month FU No. of patients: 171 Comparator: High (≥1000 ng/ml) HCQ vs low HCQ					**Severe flares, low HCQ group vs high-HCQ group:** n=3 vs n=0, p=0.27		

	[10]	Design: Retrospective, extension No. of patients: 47 Comparator: PBO	NA	NA	NA	NR	**Major flares at 42 months, HCQ vs PBO:** n=7/25 (28%) vs n=11/22 (50%) **RR for major flare HCQ vs PBO:** 0.43 (95% CI 0.17 to 1.12) **p=0.08** RR for nephritis flare: 0.26 (95% CI 0.03 to 2.54) not significant RR for vasculitis flare: 0.51 (95% CI 0.09 to 3.08) not significant RR for other flare: 0.65 (95% CI 0.17 to 2.41) not significant	NR	NR
Clinical practice	[11]	Design: Nested case-control study No. of patients: 302 (1:1 case:control) Patients with SDI >0 at 3 years were considered cases and patients with SDI=0 were controls	NA	NA	NA	Primary endpoint damage (SDI): In multivariate analysis, the use of HCQ remained significantly associated with less damage accrual (OR 0.34, [95% CI 0.132 to 0.867], p=0.0240)	NA	NA	NA

	[12]	Design: Retrospective cohort (LUMINA) No. of patients: 580 in total; 39 in multivariable analyses for effect of HCQ on integument damage (SLICC)	NA	NA	NA	**Final model**: After adjusting for integument manifestations (discoid rash, nailfold infarcts, photosensitivity and Raynaud's phenomenon), HCQ use was associated with a longer time-to-integument damage (HR 0.23 [95% CI 0.12 to 0.47]). **Alternative model 1**: Effect of HCQ was also present (HR 0.47 [95% CI 0.26 to 0.83]). **Alternative model 2:** Effect of HCQ remained but was nonsignificant (HR 0.71 [95% CI 0.37 to 1.37]). **Cumulative probability of developing integument damage at 5 years:** 5% for HCQ-takers vs 24% for non-takers (p<0.0001) .	NA	NA	
	[13]	Design: Retrospective cohort (LUMINA) No. of patients: 35 patients in the HCQ group	Disease activity by SLAM-R. Significant decrease in median SLAM-R scores with HCQ therapy (p=0.0157). **Change in SLAM-R score following HCQ therapy:**	NA	NA	NA	NA	NA	NA

			22 patients (62.86%) decreased scores, 10 patients (28.57%) increased scores 3 patients (8.57%) no change in scores						
	[14]	Design: Prospective cohort No. of patients:232 Patients were divided in two groups: ever and never treated with AM. Median time on AM was 52–months (range 3–228)				Only assessed time to thrombosis and overall survival. The Cox multiple-failure time survival analysis showed that AM were protective against thrombosis (HR 0.28 [95% CI 0.08 to 0.90])			Only assessed time to thrombosis and overall survival: Cumulative 15-year survival rate in the AM group was 0.95, vs 0.68 in the non-AM group (p<0.001)
	[15]	Design: Prospective cohort, HCQ reduction or discontinuation vs HCQ maintenance No of patients: 1460					Flare, defined as either subsequent need for therapy augmentation, increase of ≥4 points in the SLEDAI-2K, or hospitalisation for SLE. Adjusted HRs for first SLE flare were 1.20 (95% CI 1.04 to 1.38) for the HCQ reduction group and 1.56 (95% CI 1.31 to 1.86) for the discontinuation group, vs HCQ maintenance Average FU period in the HCQ reduction cohort was 2.0 years per patient (72% flaring in the		

							HCQ discontinuation cohort) Average FU in the other cohorts was about 1.7 years (50% flaring in the maintenance cohorts)		
	[16]	Design: Prospective long-term cohort study No. of patients: 151	NA	NA	NA	Mean (±SD) SDI at the first and last visits was 0.17±0.64 (range 0–6) and 1.64±2.1 (0–11), respectively (p<0.0001) **Mean (±SD) SLEDAI for the whole cohort:** 5.3±3.1 (range 0–17) **Maximal SLEDAI at any timepoint during the study period:** 14.5±8.2 (range 0–52) A statistically significant negative correlation between HCQ therapy and SDI was found (r=−0.22, p=0.015) In lupus patients, HCQ treatment significantly prolonged damage-free survival (p<0.0001) **Most commonly involved systems:**		NR	NA

						Neuropsychiatric (32.4%) and ophthalmic (18.5%)			
	[17]	Design: Longitudinal cohort study (LUMINA) No. of patients: 518	Patients not treated with HCQ were significantly more likely to have increased SLAM and SDI scores at time 0			**HCQ use was associated with a reduced risk of new damage accrual** HR 0.73 (95% CI 0.52 to 1.00), p=0.05 **After adjustment for the PS, HR among patients without damage at time 0:** 0.55 (95% CI 0.34 to 0.87), p=0.0111 **Compared with HR among patients with damage at time 0:** 1.106 (95% CI 0.70 to 1.74), p=0.6630 Analysis of the individual domains on the SDI was performed: no statistically significant decrease in damage accrual was demonstrated in the HCQ users (due to low number of events)			

	[18]	Design: Prospective cohort TLC No. of patients: 261 (175 HCQ, 88 chloroquine) Cases: Patients who achieved clinical remission for ≥1 year then ceased their AM Controls: patients who achieved clinical remission for ≥1 year and continued AM	NA	NA	NA	NR	**Total disease flares, withdrew AM vs continued AM:** 61.4% vs 45.1%, p=0.002 **Flares resulting in ≥4 SLEDAI-2K score, withdrew AM vs continued AM:** 34.1% vs 17.9%, p=0.001	NR	NA
Chloroquine diphosphate (CDP)									
Clinical trial	[19]	Design: Double-blind, PBO-controlled No. of patients: 23 Comparator: PBO	CDP group had a significant reduction in SLEDAI from 1 to 12 months From 4 months to 12 months, the CDP group had a lower SLEDAI score than the PBO group	Disease exacerbation: CDP 18% vs PBO 83%, p<0.01 Risk of flare-up 4.6 times greater in PBO group than CDP group Flare defined as an increase in SLEDAI score of ≥3 relative to the preceding evaluation and/or needing to change the therapeutic regimen	Reduction to ≤7.5 mg/day or ≤5 mg/day not reported Prednisone reduction in CDP: 82% vs PBO: 25%, p<0.01	NA	NA	NA	NA

AM, antimalarial medications; BILAG, British Isles Lupus Assessment Group; CDP, chloroquine diphosphate; CI, confidence interval; FU, follow-up; GC, glucocorticoid; HCQ, hydroxychloroquine; HR, hazard ratio; LUMINA, Lupus in Minorities: Nature versus Nurture cohort; OR, odds ratio; PBO, placebo; PS, propensity score; RR, relative risk; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI, SELENA-SLEDAI flare index; SLAM, systemic lupus activity measure; SLAM-R, systemic lupus activity measure-revised; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index 2000; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics; SRI-4, SLE Responder Index-4; TLC, Toronto Lupus Clinic.

Supplementary Table 3. Immunosuppressants

Setting	Reference	Study characteristics	Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison)						Disease modification CONFIRMED
			Outcomes Year 1			Outcomes Years 2–5			>5y data
			Significant reduction in disease activity measured using a validated tool (i.e. SELENA-SLEDAI, BILAG, SRI-4)	**Significant reduction in severe flare measured using a validated tool (i.e. SFI or BILAG)**	**Reduction in use of steroids* and/or immunosuppressants**	**Sustained improvement in multiple organ domains/no worsening in multiple organ domains**	**Prevention of severe flares**	**Continued reduction in use of steroids* and/or immunosuppressants**	**No change in SDI or delayed progression**
Azathioprine (AZA)									
Clinical trial	[20]	Design: Open-label, randomised clinical trial No. of patients: 240 Comparator: EC-MPS	NA	NA	NA	Resolution of disease activity (from BILAG A/B to BILAG D) was similar in both groups, in most individual body systems. Cardiorespiratory domain revealed more EC-MPS-treated patients reaching clinical remission at 3 months (p=0.015) Significant reduction in SLEDAI-2K score at Month 24 with EC-MPS vs AZA: p=0.006	**BILAG A/B flares, EC-MPS vs AZA:** 50.0% (n=60/120) vs 71.7% (n=86/120), p<0.001 **New BILAG A/B flares, EC-MPS vs AZA:** 8.3% (n=10/120) vs 21.7% (n=26/120), p=0.004	**Reduction of prednisone dose (<7.5) mg/day by Month 24 among patients taking ≥7.5 mg/day at inclusion, EC-MPS vs AZA:** 94.9% (n=93/98) vs 83.5% (n=86/103), p=0.027)	NA

	[21]	Design: 12 month open-label multicentre RCT. No. of patients: 89 Comparator: Ciclosporin	**Change in BILAG score between groups:** not significant	**Percentage of patients with BILAG A flares, AZA vs CsA**: 12% vs 17%, p=0.3 **Percentage of patients with BILAG B flares, AZA vs CsA:** 74% vs 75%, p>0.9	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **Mean change in prednisolone dose between baseline and 12 months, AZA vs CsA:** 10.7 mg (95% CI 8.8 to 12.7) vs 9.0 mg (95% CI 7.2 to 10.8) **Difference between groups, adjusted for baseline dose**: −1.7 mg (95% CI −4.4 to 0.9), p=0.2	NA	NA	NA	NA
Cyclophosphamide (CYC)									
Clinical trial	[22]	Design: Multicentre, prospective, randomised, open-Label, parallel-group clinical trial No. of patients: 306 Comparator: MMF	Remission (grade D of BILAG index) was achieved in ~60% of patients with an initial score indicating active disease MMF and CYC had similar efficacy across organ systems The CYC group had a change from baseline in mean (SD) SELENA-SLEDAI score of −7.3 (7.6) at Week 24.	2 patients in the CYC group experienced flares (SELENA-SLEDAI score ≥12 from baseline)					
Clinical practice	[23]	Design: Retrospective, observational No. of patients: 46 with severe neuropsychiatric SLE CYC in	NA	NA	NA	**Median (IQR) SLEDAI-2K at event:** 13.0 (11) **Median (IQR) SLEDAI-2K at last FU**: 0 (2) **Median (IQR) SDI at event:** 0 (1) **Median (IQR) SDI at**	NR	NR	NA

		combination with GCs				**last FU:** 1.0 (2)			
Methotrexate (MTX)									
Clinical trial	[24]	Design: Randomised, double-blind No. of patients: 86 Comparator: PBO	**SLAM-R total score mean during trial difference:** −0.86 points (96% CI −1.71 to −0.02), p=0.039 **SLEDAI mean during-trial difference:** −1.04 points (96% CI −2.59 to 0.52), p=0.174	NR	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **Average decrease in prednisolone, MTX vs PBO:** 1.33 mg/day (96% CI 0.06 to 2.72) reduction **Mean relative difference in average during trial daily dose, MTX vs PBO:** 22% reduction	NA	NA	NA	NA
Clinical practice	No relevant references found								
Mizoribine (MZR)									
Clinical trial	No relevant references found								

Clinical practice	[25]	Design: Retrospective cohort study No. of patients: 83 Comparator: MMF	NA	NA	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **Change in prednisolone dose was almost identical between groups** **Mean predicted prednisolone dose decreased from:** 14.4 to 9.4 mg at 1 year post-initiation of MZR and from 14.2 to 8.1 mg at 1 year post-initiation of MMF	**LLDAS over 2 years, MZR vs MMF:** 48.1% (n=25) vs 58.1% (n=18) **Remission (clinical SLEDAI=0, PGA <0.5, irrespective of serology, prednisolone dose ≤5 mg/day, and stable immunosuppressives) over 2 years, MZR vs MMF:** 25.0% (n=13) vs 48.3% (n=15)	**Flares, MZR vs MMF:** 32.7% (n=17) vs 9.7% (n=3) Cumulative incidences of flare were almost identical between the two groups (after adjusting for stabilised IPTW)	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** Prednisolone dose was steadily reduced in both groups Change in prednisolone dose was nearly identical between the two groups **Mean predicted prednisolone dose was decreased from:** 14.4 to 8.4 mg, at 2 years post-initiation of MZR and from 14.2 to 6.5 mg at 2 years post-initiation of MMF	NA

Mycophenolate mofetil (MMF)									
Clinical trial	[20]	Design: Open-label, randomised clinical trial No. of patients: 240 Comparator: AZA	NA	NA	NA	Resolution of disease activity (from BILAG A/B to BILAG D) was similar in both groups for most individual body sytems, except for the cardiorespiratory domain, with more EC-MPS-treated patients reaching clinical remission at 3 months (p=0.015) Significant reduction in SLEDAI-2K score at Month 24 with EC-MPS vs AZA: p=0.006	**BILAG A/B flares, EC-MPS vs AZA:** 50% (n=60/120) vs 71.7% (n=86/120), p<0.001 **New BILAG A flares, EC-MPS vs AZA:** 8.3% (n=10/120) vs 21.7% (n=26/120), p=0.004	**Reduction of prednisone dose (<7.5 mg/day) by month 24 among patients taking ≥7.5 mg/day at inclusion, EC-MPS vs AZA:** 94.9% (n=93/98) vs 83.5% (n=86/103) p=0.027	NA
Clinical trial	[22]	Design: Multicenter, prospective, randomised, open-label, parallel-group clinical trial No. of patients: 306 Comparator: CYC	Remission (grade D on BILAG index) was achieved in ~60% of patients, with an initial score indicating active disease MMF and CYC had similar efficacy across organ systems The MMF group had a change from baseline in SELENA-SLEDAI score of −7.0 ± 7.6 at Week 24	No patients in the MMF group experienced flares vs 2 patients in the CYC group (SELENA-SLEDAI score ≥12 from baseline)					

Clinical practice	[26]	Design: Observational cohort (TLC) No. of patients: 72 (received MMF for non-renal manifestations)	**SLEDAI-2K at baseline vs 12 months:** 5.7 ± 4.4 vs 4.5 ± 4.8, p<0.005 **Number of patients with SLEDAI-2K decrease by 4 at 12 months**: n=13 (18.1%), p<0.05	Disease flares (based on SLEDAI-2K increase ≥4) not significant between baseline and 12 months	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **CS dose reduction:** 61.1% (n=44/72), p<0.001 **Mean dose at baseline:** 18.4 ± 12.6 mg/day **Mean dose after 12 months:** 12.1 ± 9.0 mg/day	NA	NA	NA	NA
Clinical practice	[27]	Design: Retrospective cohort study No. of patients: 109	**SLEDAI-2K at start of MMF:** 5.9 ± 2.4 **Mean SLEDAI-2K values at 12 months:** 2.3 ± 2.2, p<0.0001	NR	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **Mean weekly GC dosage at start of MMF:** 87.5 ± 80.6 mg weekly, prednisone-equivalent **Mean weekly GC dosage at 12 months:** 22.1 ± 14.5 mg weekly, p<0.001	NA	NA	NA	NA
Clinical practice	[28]	Design: Retrospective No. of patients: 135 patients with SLE and 43 patients with systemic vasculitis	NR	NR	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **Mean prednisolone dose, baseline to after 12 months of MMF:** 21.7 mg/day to 8.3 mg/day, p<0.05	NA	NA	NA	NA

Clinical practice	[29]	Design: Retrospective, mean time period of FU after starting MMF was 14.8 months (range, 1.5–24) No. of patients: 67	NA	NA	NA	**Mean SLEDAI, before MMF vs after MMF initiation:** 4.8 ± 2.3 vs 4.2 ± 3.3, p=0.02 **Mean PGA, before MMF vs after MMF initiation:** 6.0 ± 1.2 vs 5.2 ± 1.4, p<0.001	**Mean flare rate before MMF vs after MMF intitiation:** 8.9 to 5.3 per 10 person-years, p=0.005 **Rate of severe flares, before MMF vs after MMF initiation:** 1.0 to 0.4 per 10 person-years, p=0.15, ns	After MMF initiation, mean prednisone dose was reduced on average 7.3 mg/day **Mean prednisone dosage before the start of MMF:** 15.4 (SD 12.8) mg/day **Mean prednisone dosage after the initiation of MMF:** 8.2 (SD 11.1) mg/day, p<0.001	
Clinical practice	[30]	Design: Observational, retrospective chart review No. of patients: 75	**>50% improvement in BILAG score from pre-MMF initiation to 1 year**: 49.3% (n=37/75)	NR	NR	**>50% improvement in BILAG score from pre-MMF initiation over 5 years:** 20% (n=15/75) Most improvement and clinical remissions: general and renal systems Most recurrences: musculoskeletal, mucocutaneous and haematological systems	Overall, most flares occurred in second and third year of MMF treatment	NR	NA
Leflunomide (LEF)									
Clinical trial	No relevant references found								
Clinical practice	[31]	Design: Retrospective observational No of patients:35	Significant reduction in PGA, SLEDAI and ESR with LEF vs PBO at about 5 months of treatment	NR		NR	NR	NR	NR

AZA, azathioprine; BILAG, British Isles Lupus Assessment Group; CI, confidence interval; CS, corticosteroid; CsA, cyclosporine A; CYC, cyclophosphamide; EC-MPS, enteric-coated mycophenolate sodium; ESR, erythrocyte sedimentation rate; FU, follow-up; GC, glucocorticoid; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LEF, leflunomide; LLDAS, Lupus Low Disease Activity State; MMF, mycophenolate mofetil; MTX, methotrexate; MZR, mizoribine; PBO, placebo; PGA, physician global assessment of disease activity; RCT, randomised controlled trial; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI, SELENA-SLEDAI flare index; SLAM-R, systemic lupus activity measure-revised; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4; TLC, Toronto Lupus Clinic.

Supplementary Table 4. Calcineurin inhibitors

Setting	Reference	Study characteristics	Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison)						Disease modification CONFIRMED
			Outcomes Year 1			Outcomes Years 2–5			>5y data
			Significant reduction in disease activity measured using a validated tool (i.e. SELENA-SLEDAI, BILAG, SRI-4)	**Significant reduction in severe flare measured using a validated tool (i.e. SFI or BILAG)**	**Reduction in use of steroids* and/or immunosuppressants**	**Sustained improvement in multiple organ domains/no worsening in multiple organ domains**	**Prevention of severe flares**	**Continued reduction in use of steroids* and/or immunosuppressants**	**No change in SDI or delayed progression**
Cyclosporine (CsA)									
Clinical trial	[21]	Design: Open label randomised No. of patients: 89 Comparator: AZA	**Change in BILAG score between groups:** not significant	**Percentage of patients with BILAG A flares, AZA vs CsA**: 12% vs 17%, p=0.3 **Percentage of patients with BILAG B flares, AZA vs CsA:** 74% vs 75%, p>0.9	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **Mean change in prednisolone dose between baseline and 12 months, AZA vs CsA:** 10.7 mg (95% CI 8.8 to 12.7) vs 9.0 mg (95% CI 7.2 to 10.8) **Difference between groups, adjusted for baseline dose**: −1.7 mg (95% CI −4.4 to 0.9), p=0.2	NA	NA	NA	NA
Clinical practice	[32]	Design: Clinical practice, patients refractory to GCs, average FU period 21.5 months No. of patients: 59	Mean SLEDAI score decreased significantly in dose-up GC (14.7 to 4.1) and stable GC (8.6 to 4.4) groups (both p<0.01)	Mean flare rate decreased by ~60% from 0.26 to 0.10 times/patient-year (but not severe flares)	Mean 12.2 mg to 8.6 mg reduction (p<0.01)				
Clinical practice	[33]	Design: Retrospective, 8-year FU	NR	NR	NR	Mean SLEDAI score reduced significantly during FU period (mean 8 years):	Disease flares requiring temporary therapy adjustment during FU: 20	Mean steroid dose reduction from 251 to 44 mg/day from baseline to end of FU	NR

		No. of patients: 40 SLE patients were recorded				22 at baseline vs 5 at end of FU (p<0.0001)	patients (14 severe and 6 moderate) for a total of 27 events	(p<0.0005)	
Tacrolimus (TAC)									
Clinical trial	[34]	Design: Single centre, prospective, open-label No. of patients: 21 Comparator: none	Mean SLEDAI scores improved significantly at 4, 12 and 24 weeks from baseline (p<0.01)						
Clinical practice	[35]	Design: Retrospective No. of patients: 34	**Responders (SLEDAI improved to the level experienced prior to the flare within 1 year) not significantly different between groups:** n=12/14 (86%) with TAC vs n=15/20 (75%) with GCs, p=0.67 **Mean SLEDAI at 12 months was not significantly different between the groups, TAC vs GCs:** 4.5 vs 2.9, p=0.16	NR	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** **The mean dose of GCs at 12 months, GCs vs TAC:** 9.7 mg/day vs 7.1 mg/day, p<0.05	NA	NA	NA	NA

AZA, azathioprine; BILAG, British Isles Lupus Assessment Group; CI, confidence interval; CsA, cyclosporine A; FU, follow-up; GC, glucocorticoid; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI, SELENA-SLEDAI Flare Index; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SRI-4, SLE Responder Index (4); TAC, tacrolimus.

Supplementary Table 5. Biologics

Setting	Reference	Study characteristics	Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison)						Disease modification CONFIRMED
			Outcomes Year 1			Outcomes Years 2–5			>5y data
			Significant reduction in disease activity measured using a validated tool (i.e. SELENA-SLEDAI, BILAG, SRI-4)	Significant reduction in severe flare measured using a validated tool (i.e. SFI or BILAG)	Reduction in use of steroids* and/or immunosuppressants	Sustained improvement in multiple organ domains/no worsening in multiple organ domains	Prevention of severe flares	Continued reduction in use of steroids* and/or immunosuppressants	No change in SDI or delayed progression
Belimumab (BEL)									
Clinical trial	[36]	Design: Randomised, Phase 3 No. of patients: 867 Comparator: PBO plus ST	**Reduction ≥4 points in SELENA-SLEDAI, BEL 10 mg/kg vs PBO:** n=169/290 (58%) vs n=132/287 (46%) OR 1.71 (95% CI 1.21 to 2.41), p=0.0024 **No worsening with BILAG, BEL 10 mg/kg vs PBO:** n=236/290 (81%) vs n=210/287 (73%) OR 1.62 (95% CI 1.09 to 2.42), p=0.0181	**SFI severe flare, BEL 10 mg/kg vs PBO:** n=40/290 (14%) vs n=66/287 (23%) OR 0.57 (95% CI 0.39 to 0.85), p=0.0055	**Prednisone dose reduced by ≥25% to ≤7.5 mg/day during Weeks 40–52, BEL 10 mg vs PBO:** n=38/204 (19%) vs n=23/192 (12%) OR 1.75 (95% CI 0.99 to 3.08), p=0.0526 **Prednisone dose reduced by ≥50% at Week 52, BEL 10 mg/kg vs PBO:** n=64/231 (28%) vs n=39/220 (18%) OR 1.78 (95% CI 1.13 to 2.79), p=0.0122	NA	NA	NA	NA

Clinical trial	[37]	Design: Phase 3, randomised No. of patients: 819 Comparator: PBO plus ST	**SRI response rate (≥4-point reduction in SELENA-SLEDAI score, no new BILAG A organ domain score and no more than 1 new BILAG B score and no worsening (increase <0.3) in PGA score vs baseline) at Week 52, BEL 10 mg/kg vs PBO:** 43.2% vs 33.5%, p=0.017 **≥4-point reduction in SELENA-SLEDAI score at Week 52, BEL 10 mg/kg vs PBO:** 46.5% vs 35.3%, p=0.006	NR	**Prednisone reduced by ≥25% to ≤7.5 mg/day during Weeks 40–52, BEL 10 mg/kg vs PBO:** 17.5% vs 12.7%, ns	**SRI response rate (≥4-point reduction in SELENA-SLEDAI score, no new BILAG A organ domain score and no more than 1 new BILAG B score) at Week 76, BEL 10 mg/kg vs PBO:** 38.5% vs 32.4%, p=0.13 **≥4-point reduction in SELENA-SLEDAI score at Week 76, BEL 10 mg/kg vs PBO:** 41.4% vs 33.8%	**SFI severe flares over 76 weeks, BEL 10 mg/kg vs PBO:** 20.5% vs 26.5% HR 0.77 (95% CI 0.54 to 1.09), p=0.13 **SFI severe flares Weeks 24–76, BEL 10 mg/kg vs PBO:** 15.7% vs 21.8% HR 0.70 (95% CI 0.46 to 1.07)	**Prednisone reduced by ≥25% to ≤7.5 mg/day during Weeks 64–76, BEL 10 mg/kg vs PBO:** 24.2% vs 17.5% **More patients treated with BEL receiving >7.5 mg/day prednisone at baseline lowered their dose to ≤7.5 mg/day over time through Week 76:** 25.8% vs 17.5%	NA
Clinical trial	[38]	Design: Phase 3 extension No. of patients: 738 Comparator: None	NA	NA	NA	**SDI score by organ involvement: change from baseline [mean (SD)] only found in the musculoskeletal organ system:** Increase of 0.1 (0.24) at study Year 8	-	**Reduction to ≤7.5 mg/day or ≤5 mg/day not reported** Percentage of patients with baseline steroid use >7.5mg/day experiencing a reduction in steroid dose generally increased over time (Year 1, 30.8%; Year 7, 67.8%)	**Mean SDI score at baseline:** 0.6 (SD 1.02) **Mean change from baseline at Year 8:** 0.2 (SD 0.56) **Patients with no change in SDI score at Year 8:** n=57/65 (87.7%)

Clinical trial	[39]	Design: Phase 3 continuation study No. of patients: 140 Comparator: PBO plus ST in parent study	**≥4-point reduction from baseline in SELENA-SLEDAI score from baseline at Year 1 midpoint**: 44.4% (n=104/234) **No new BILAG 1A or 2B organ domain scores at Year 1 midpoint:** 97.4% (n=258/265)	**≥1 SFI severe flare at Year 1 midpoint:** 5.6% (n=15/267)	NR	NR	NR	**Percentage of patients with a baseline dose of >7.5 mg/day who reduced their dose of prednisone to ≤7.5 mg/day at Year 3 midpoint:** 50.0% (n=32/64)	**Mean (SD) SDI score at baseline:** 1.2 (1.51) **Mean (SD) increase in SDI score at Year 7**: 0.4 (0.68)
Clinical trial	[40]	Design: Pooled OLE studies No. of patients: 998 Comparator: PBO plus ST in parent studies	NA	NA	NA	NA	NA	NA	**Mean (SD) change in SDI from baseline at Years 5–6:** 0.2 (0.48) **No change in SDI score:** n=343 (85.1%)
Clinical trial	[41]	Design: Pooled RCTs No. of patients: 966 Comparator: PBO plus ST in parent studies	NR	NR	**Overall mean cumulative change from baseline in CS dose at 1 year, BEL 10 mg/kg vs PBO:** 531 mg vs 916 mg, p<0.0001	NA	NA	NA	NA

Clinical trial	[42]	Design: Randomised, Phase 3 No. of patients: 677 Comparator: PBO plus ST	**At Week 52, the SRI-4 response rate (defined as a ≥4 point reduction from baseline in SELENA-SLEDAI score, no worsening [<0.3 point increase from baseline] in PGA and no new BILAG A organ domain score or two new BILAG B organ domain scores vs baseline) at Week 52, BEL 10 mg/kg vs PBO:** 53.8% vs 40.1% OR 1.99 (95% CI 1.40 to 2.82), p=0.0001 **Percentage of patients with a ≥4-point reduction in SELENA-SLEDAI at Week 52, BEL 10 mg/kg vs PBO:** 55.7% vs 42.2% OR 2.00 (95% CI 1.41 to 2.83), p=0.0001	**Severe flare, at Week 52, BEL 10 mg/kg vs PBO:** 12.0% vs 22.1% HR 0.50 (95% CI 0.34 to 0.73), p=0.0004	Patients with baseline prednisone dose >7.5 mg/day revealed a significant reduction in steroid use in favour of BEL 10 mg/kg (p=0.0228). Patients with prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Weeks 40–52, BEL 10 mg/kg vs PBO: 15.6% vs 10.9%, p=0.0721	NA	NA	NA	NA

Clinical trial	[43]	Design: Randomised No. of patients: 836 Comparator: PBO plus ST	**SRI-4 response rate (defined as ≥4-point reduction in the SELENA-SLEDAI score, no worsening [increase of 0.3 from baseline] in the PGA [on a 0–10-cm visual analogue scale], and no new BILAG A organ domain score or 2 new BILAG B organ domain scores) at Week 52 compared with baseline, BEL vs PBO:** 61.4% vs 48.4% OR 1.68 (95% CI 1.25 to 2.25), p=0.0006	**Risk of severe flare, BEL vs PBO:** HR 0.51 (95% CI 0.35 to 0.74), p=0.0004	**Reduction of CS dosage by ≥25%, to ≤7.5 mg/day, during Weeks 40–52, BEL vs PBO**: 18.2% vs 11.9% OR 1.65 (95% CI 0.95 to 2.84), p=0.0732	NA	NA	NA	NA
Clinical trial	[44]	Design: Randomised, Phase 3/4 (52 weeks), OLE (26 weeks) No. of patients: Randomised: 503; Open label: 334 Comparator: PBO plus ST	Not achieved The SRI–SLEDAI-2K response rate at Week 52 (primary endpoint) was numerically but not statistically greater with BEL (48.7%) vs PBO (41.6%) (OR 1.40 [95% CI 0.93 to 2.11], p=0.1068)	Patients in the BEL group had a reduced risk (23%) of experiencing a severe SFI flare at Week 52 than patients in the PBO group (HR 0.77 [95% CI 0.51 to 1.17], p=0.2264)	**Non significant:** 27/184 (14.7%) BEL vs 12/95 (12.6%) PBO patients reduced prednisone dose by ≥25% from baseline to ≤7.5 mg/day during Week 40 to Week 52 of the double-blind phase (OR 1.30 [95% CI 0.61 to 2.80], p=0.4996)	NA	Severe SFI flare experience during OLE phase: 4.0% (9 of 225) continuous BEL group vs 5.5% (6 of 109) of PBO-to-BEL group	Continuous BEL group: 31.9% of patients (44/138) achieved a reduction in prednisone dose to ≤7.5 mg/day compared with the start of the double-blind phase PBO-to-BEL group: 14.8% of patients (8/54) achieved this compared with the start of the OLE phase	NA
Clinical practice	[45]	Design: Post hoc longitudinal PS-matched BEL patients from BLISS LTE and ST from TLC No. of patients: 965 (BLISS 259, TLC 706); 5-year SDI outcome: 198 were PS matched (99	NA	**na**	NA	Among patients with ≥1 year of FU, BEL patients were 61% less likely to progress to a higher SDI score over any given year of FU versus ST patients (HR 0.391 [95% CI 0.253 to 0.605], p<0.001) 1 BEL patient had a	NA	NA	**Change in SDI score at Year 5:** Significantly lower for BEL patients vs with ST patients (−0.434 [95% CI −0.667 to −0.201], p<0.001

		BLISS, 99 TLC); ≥1-year organ damage progression analysis: 358 were PS matched (179 BLISS, 179 TLC) Comparator: ST				3.5% annual probability of organ damage progression vs an 8.7% annual probability of progression with ST alone			
Clinical practice	[46]	Design: Post hoc analysis of pooled data from 6 OBSERVE retrospective observational studies No. of patients: 830	**Mean (SD) change in SLEDAI-2K/SELENA-SLEDAI score between BEL initiation and Month 6** (n=344): −5.7 (4.5)	NR	**Reduction or discontinuation of oral GC dose after 6 months of BEL treatment:** n=518/663, 78.1% Of 526 patients receiving >7.5 mg/day dose of oral GC at BEL initiation, 52.6% of those with data for Month 6 (n=258/491) reduced their dose to ≤7.5 mg/day at Month 6	NA	NA	NA	NA
Clinical practice	[47]	Design: Retrospective, observational No. of patients: 501	Mean (SD) SELENA-SLEDAI scores reduced from 12.4 (3.62) at baseline to 5.9 (3.22) at Month 6 (maintained to Month 12) (n=122)	Of 251 patients with a ≥20% improvement in disease between Months 0 and 6, 249 (99.2%) reported no disease flare (worsening of disease) at Month 12	Overall mean dose of oral steroids was 19.9 mg/day at baseline and 6.3 mg/day at Month 12. For patients receiving >7.5 mg/day steroids at baseline, the mean (SD) dose at baseline was 22.0 (14.20) mg/day vs 9.1 (7.58) mg/day at Month 6	Mean (SD) SELENA-SLEDAI scores reduced from 12.4 (3.62) at baseline to 5.9 (3.22) at Month 6 (n=122). The lower score was maintained at Months 18 and 24 Did not look at individual organ domains	Of 251 patients with a ≥20% improvement in disease between Months 0 and 6, 249 (99.2%) reported no disease flare (worsening of disease) at Months 18 and 24	Overall mean dose of oral steroids was 19.9 mg/day at baseline and 6.1 mg/day at Month 24. Mean steroid dose reductions were achieved by all 3 high disease subgroups For patients receiving >7.5 mg/day steroids at baseline, the mean (SD) dose at baseline was 22.0 (14.20) mg/day vs 6.4 (9.44) mg/day at Month 24	NA

Clinical practice	[48]	Design: Retrospective, observational No. of patients: 102	During the first 6 months of therapy, mean SLEDAI/SELENA-SLEDAI score decreased from 10.6 to 5.6	NR	Dose reduction in oral CS was observed: Number of patients receving <7.5 mg/day increased from n=27 at baseline to n=54 after 6 months Mean CS dose was 11.7 mg/day 6 months before BEL therapy, 13.7 mg/day at BEL start, and 7.6 mg/day after 6 months	NR	NR	NR	NA
Clinical practice	[49]	Design: Retrospective, observational No. of patients: 52	**Patients with assessments at both baseline and Month 6:** Mean PGA score improved by 18.4 (n=11) Mean SLEDAI-2K score improved by 2.6 (n=16)	NR	Mean (SD) GC dose at baseline: 13.6 (10.0) mg/day Mean GC dose at Month 6: 7.8 (5.8) mg/day	NA	NA	NA	NA
Clinical practice	[50]	Design: Retrospective, observational No. of patients: 64	The mean (SD) SELENA-SLEDAI score (n=57) showed a marked reduction, from 10.1 (6.2) at index to 4.5 (3.7) at 6 months post-index.	NR	Mean (SD) dose of GCs at index: 14.5 (12.5) mg/day Mean (SD) dose of GCs after 6 months: 6.4 (5.1) mg/day **Number of patients with decrease in GC dose to <7.5 mg/day among patients who received ≥7.5 mg/day GCs at index:** n=32/48 (66.7%)	NA	NA	NA	NA
Clinical practice	[51]	Design: Retrospective, observational No. of patients: 53	Decrease in mean SELENA-SLEDAI score from 8.0 at index to 3.6 at 6 months post-index	NR	Mean dose of oral GCs at index; 11.6 mg/day (n=42) Mean dose reduction of 5.7 mg/day to a	NA	NA	NA	NA

					mean dose of 5.9 mg/day (6 months post-index) 65% of patients who required a high dose (≥7.5 mg/ day) of CSs at index (n=31) had dose reductions to low (n=18 to <7.5 mg/day) or no (n=2 discontinued use) CSs at 6 months post-index				
Clinical practice	[52]	Design: Retrospective, observational No. of patients: 81	Mean (SD) SELENA-SLEDAI score decreased significantly from 11.21 (6.07) at index to 4.76 (4.16) at 6 months and 3.77 (4.41) at 12 months post-index (all p<0.001)	NR	Significant reductions in mean (SD) CS dose during treatment period: index: 14.6 (11.90) mg/day 12 months post-index: 5.2 (5.99 mg/day (p<0.01)	Mean (SD) SELENA-SLEDAI score decreased significantly from 11.21 (6.07) at index to 3.86 (3.38) at 18 months and 2.17 (2.18) at 24 months post-index (all p<0.001)	NR	Significant reductions in mean (SD) CS dose during treatment period: index: 14.6 (11.90) mg/day 24 months post-index: 4.78 (3.63) mg/day (p=0.01)	NA
Clinical practice	[53]	Design: Exploratory post hoc analysis of patients from BLISS LTE trials matched to patients from TLC who received ST No. of patients:181 in each arm Comparator: ST	NR	NR	NR	NR	NR	NR	**5-year SDI score change:** BEL + ST = 0.265 ST = 0.718 p<0.001

Clinical practice	[54]	Design: Retrospective cohort study (BERLISS) No. of patients: 466	SRI-4 response achieved by 49.2% and 61.3% of patients receiving BEL at 6 and 12 months, respectively	Significant decrease in flare incidence at 12, 24, 36 and 48 months during BEL treatment vs corresponding period before BEL treatment (p<0.001) (but not severe flares) 7 patients experience severe flares	Prednisone daily dose reduced from a mean (SD) of 10.61 ± 8.61 at baseline to 5.28 ± 4.67 at 12 months (p<0.001)	36 new damage events in 29 patients (9.4%); 0.54 new damage events per 10 person-years Paients with SDI of 0 at baseline showed no significant damage increase at 1, 2 and 3 years after BEL treatment. Did not look at individual organ domains	Significant decrease in flare (non-severe) incidence at Months 12, 24, 36 and 48 during BEL treatment vs period before BEL treatment (p<0.001)	Prednisone daily dose reduced from 10.61 ± 8.61 at baseline to 3.55 ± 4.61 at 48 months (p<0.001)	NR
Rituximab (RTX)									
Clinical trial	[55]	Design: Randomised, double-blind, PBO-controlled No. of patients: 257 Comparator: PBO	No significant difference in major (15.9% PBO, 12.4% RTX) or partial (12.5% vs 17.2%) clinical response at Week 52 assessed using BILAG (p=0.9750)	Median time to first moderate/severe flare was ~4 months in both groups (p=0.8979)	NR	NR	NR	NR	NR
Clinical trial	[56]	Design: Exploratory analysis of a randomised, double-blind, PBO-controlled trial No. of patients: 257 Comparator: PBO	NR	No overall difference between RTX and PBO in preventing or delaying moderate to severe flares. For BILAG A severe flares (at least 1 new BILAG A score), RTX showed trend towards delayed time to first BILAG A flare vs PBO (HR 0.61 [0.37 to 1.01], p=0.052), and significantly reduced annualized A flare rate after achieving minimal disease activity (p=0.038)	NR	NR	NR	NR	NR

Clinical practice	[57]	Design: 14-year single-centre study No. of patients: 115	Significant decrease in mean (SD) BILAG score after 6 months of RTX treatment **1st RTX cycle Baseline:** 18.29±10.62 **6 Months**: 6.79±5.55, p<0.001 **Complete response after 6 months (BILAG A/B to C/D):** 43.0% (95% CI 33.7 to 52.3)	NR	NR	NR	NR	NR	NR
Clinical practice	[58]	Design: Long-term FU of first-line use of RTX shortly after diagnosis No. of patients: 16 Comparator: Patients who didn't receive B-cell depleting therapy but received ST	NR	NR	NR	No significant difference in SDI at end of FU (median 4.5 years)	**Flares (BILAG A or B in any of the organs/systems) during the FU (median 4.5 years):** global average flares were 2.63 (SD 3.01) in the RTX group vs 4.00 (SD 3.61) in the non-RTX group (p=0.14).	At 5 years of FU, RTX had accumulated about 1/3 (37.8%) of the prednisolone total dose vs the non-RTX group (p=0.01) Did not look at <7.5 mg/day	NR
Clinical practice	[59]	Design: Chart review study of heterogeneous patients who received RTX for drug-refractory SLE No. of patients: 15	13 (87%) patients achieved BILAG response by 12 months	9 patients flared within 12 months of RTX administration; significant increase in time to BILAG A/B flare with a second RTX course vs the first course (p=0.0014) (but not severe flares) 5 patients experienced a BILAG A flare by 12 months	Mean reduction in steroid use at 12 months (reduction after 1 course: 15.6 mg/day, p=0.007) However, mean was still above 7.5 mg/day at Month 12 (10.9 mg/day, p=0.003)	NR	NR	NR	NR

Clinical practice	[60]	Design: Observational study of patients refractory to ST given 2 or more RTX infusions No. of patients: 145	**ECLAM:** baseline = 4.11 (1.73) 12 months = 1.84 (1.67) p<0.001	NR	NR	NR	NR	NR	NR
Clinical practice	[61]	Design: Observational No. of patients: 178	Median (IQR) SLEDAI-2K score at baseline vs Month 6: 8 (5–12) vs 4 (0–7), p<0.001 Median (IQR) BILAG score at baseline vs Month 6: 15 (10–23) vs 3 (2 –12), p<0.0001		Median (IQR) GC dose at baseline vs Month 6: 11.25 mg (8.375 to 20) vs 7.5 mg (5 to 12), p<0.001				
Clinical practice	[62]	Design: Retrospective analysis of patients with refractory SLE treated with RTX No. of patients: 39	Significant reduction from baseline at 12 months in SLEDAI total/renal domains	NR	NR	Significant reduction from baseline at 24 and 36 months in SLEDAI total/renal domains	NR	NR	NR
Clinical practice	[63]	Design: Retrospective, descriptive, observational study of patients with refractory SLE treated with RTX No. of patients: 18	NR	NR	NR	NR	NR	Median steroid use at baseline vs at end of FU (mean 37.5 months): 25 mg/day vs 3.75 mg/day (p=0.0002) MMF was discontinued in all patients (p=0.0071 vs baseline)	NR
Clinical practice	[64]	Design: Retrospective, longitudinal study of patients not responsive to ST No. of patients: 116	Mean±SD SELENA-SLEDAI score at baseline was 14.6±10.0 vs 4.8±4.5 at 6 months after first course (p<0.001)	Mean±SD number of severe SFI criteria at baseline was 2.1±1.3 vs 0.37±0.76 at 6 months after first course (p<0.001)	Mean±SD prednisolone (mg/day) 32.4±57.3 vs 11.7±11.9 at 6 months after the first dose (p<0.001)				

Clinical practice	[65]	Design: Retrospective analysis of patients with refractory SLE No. of patients: 17	NR	NR	NR	NA	NA	NA	NA
Clinical practice	[66]	Design: Prospective cohort of Colombian patients with severe and refractory disease who received RTX after failure to respond to steroids and ≥ 1 other immuno-suppressant No of patients: 42	Numerical reduction in SLEDAI score at 12 months vs baseline (significance not tested)	NR	NR	Improvements observed in renal, neuropsychiatric, and haematological organ manifestations	NR	**Steroid dose:** Baseline average = 52.02 mg/day 24 months = 5.6 mg/day (significant)	NR
Clinical practice	[67]	Design: GRAID registry of patients with different autoimmune diseases given RTX off-label (SLE patients analysed) No. of patients: 85 with SLE	Mean SELENA-SLEDAI scores: decreased significantly from 12.2 to 3.3 during RTX treatment ($p<0.05$) (mean FU 9.6 ± 7.4 months)	NR	Proportion of patients requiring prednisone before vs after RTX: 86.1% vs 84.8% (not significant) **Necessity for IV methylprednisone use before vs after RTX:** 12.7% vs 1.3%, $p<0.05$	NA	NA	NA	NA
Clinical practice	[68]	Design: Patients receiving RTX for refractory or relapsing SLE between 2002 and 2008 in a single centre No. of patients: 31 (11 with active LN)	Significant reduction in BILAG at 12 months vs baseline ($p<0.001$)	NR	Median prednisolone dose at baseline vs 12 months: 10 mg/day vs 7.5 mg/day, $p<0.05$	Significant reduction in BILAG at 24 months vs baseline ($p<0.001$), but didn't look at organ domains	NR	Median prednisolone dose at baseline vs 24 months: 10 mg/day vs 5.5 mg/day, $p<0.001$ 50% of patients stopped immunosuppressants at 2 years	NR

Clinical practice	[69]	Design: 24-month clinical outcome of patients with SLE who received low doses of RTX, followed by HCQ, steroid, MMF No. of patients: 46	**MEX-SLEDAI:** 41.3% achieved remission at 12 months vs 0% at baseline (p<0.0001 vs baseline)	NR	NR	NR	NR	NR	NR
Clinical practice	[70]	Design: Hispanic patients with refractory SLE No. of patients: 52 (13 with LN)	Mean (SD) global MEX-SLEDAI score at baseline vs 6 months: (n=49) 4.9 (0.2) vs 1.1 (0.3), p=0.005	NR	RTX allowed the oral prednisone dose to be reduced from 25.7±9.1 mg/day at baseline to 11.4±7.2 mg/day (p=0.001)	NA	NA	NA	NA
Clinical practice	[71]	Design: Single-centre cohort No. of patients: 50	Decrease in median global BILAG scores from 12 to 5 (p<0.0001) after 6 months	NR	NR	NA	NA	NA	NA
Clinical practice	[72]	Design: Analysis of prospective registry data No. of patients:136	Mean (SD) SELENA-SLEDAI score decreased from 10.8 (8.8) to 3.4 (5.2) (p<0.0001) after mean (SD) 6 (3) months after RTX infusion	NR	Mean (SD) prednisone dosage decreased from 30.3 (23.6) to 12.3 (10.1) (p<0.0001) after mean (SD) 6 (3) months after RTX infusion	NA	NA	NA	NA
Clinical practice	[73]	Design: Retrospective analysis of RTX+CYC+methyl-prednisolone No. of patients: 18	**At least partial disease remission after first cycle of RTX+CYC+methyl-prednisolone at 12 months of FU:** 39% **At least partial disease remission after second cycle of RTX+CYC+methyl-prednisolone at 12 months of FU:** 65% **Reduction in median Global BILAG score after first cycle of**	The time to disease flare (new BILAG A score or two new consecutive B scores in any organ system) was significantly longer after the second cycle (p<0.001) 15/18 (82%) patients flared within 12 months after their first cycle of treatment Following retreatment: 8 (45%) patients flared within	NR	NA	NA	NA	NA

			treatment, at 12 months of FU: 12.5 to 5, p<0.05 **Reduction in median Global BILAG score after second cycle of treatment, at 12 months of FU:** 13.5 to 4, p<0.01	12 months 33% of patients had not flared following retreatment over mean FU 24.5 months					
Clinical practice	[74]	Design: Long-term FU study of RTX + CYC No. of patients: 32 Comparator: None	**Median global BILAG scores for RTX+CYC, baseline vs Month 6:** 13 (95% CI 11 to 15) vs 5 (95% CI 4 to 6) (n=29, p<0.0001)	12/30 patients remained well with no flare following one cycle of RTX+CYC **Mean time to flare after RTX+CYC (n=18):** 10 months (range 3–28). **Time to flare post-RTX+CYC initiation:** 5/18 patients flared <6 months 9/18 patients flared between 6 and 12 months 4 patients flared after 12 months	NR	NR	NR	NR	NA
Obinutuzumab									
Clinical trial	No relevant references found								
Ocrelizumab									
Clinical trial	No relevant references found								

Abatacept (ABT)									
Clinical trial	[75]	Design: Exploratory, 12-month, Phase 2b, randomised, PBO-controlled trial of patients with SLE + polyarthritis, discoid lesions, pleuritis and/or pericarditis No. of patients: 180 Comparator: PBO	NR	**Proportion of patients with new BILAG A/B flare at 12 months:** ABT (79.7%) vs PBO (82.5%) (not significant) **Proportion of patients with a new BILAG A flare:** ABT (40.7%) vs PBO (54.4%) Treatment differences largest in the polyarthritis group	NR	NR	NR	NR	NR
Clinical practice	[76]	Design: Retrospective No. of patients: 11	Median (IQR) SLEDAI decreased from 6 (2 to 20) to 4 (0 to 20) at 6 months (p=0.031)						
Anifrolumab (ANI)									
Clinical trial	[77]	Design: Randomised, double-blind Phase 3 trial with PBO/150/300 mg ANI arms No. of patients: 457 Comparator: PBO (with ST)	Primary endpoint of SRI-4 at Week 52 not met – similar percentage of patients had SRI-4 response with ANI 300 mg (36%) and PBO (40%) (p=0.41)	The BILAG-based annualised flare rate was numerically lower for ANI (0.6) vs PBO (0.72; RR 0.83 [95% CI 0.60 to 1.14])	A numerically greater percentage of patients with ≥10 mg/day prednisone at randomisation in the ANI 300 mg group (41%) than the PBO group (32%) achieved reduction to the target (≤7.5 mg/day)	NR	NR	NR	NR
Clinical trial	[78]	Design: Randomised, Phase 3 No. of patients: 362 Comparator: PBO	**BICLA response at Week 52**: 47.8% with ANI, 31.5% with PBO (p=0.001)	No significant reduction at Week 52 between PBO and ANI 300 mg for annualised flare rate	Significantly more patients (p=0.01) had reduction to ≤7.5 mg/day in GC dose with ANI (51.5%) vs PBO (30.2%), among patients with GC dose ≥10 mg/day at	NR	NR	NR	NR

					baseline				
Clinical trial	[79]	Design: Phase 2b, randomised, double-blind of ANI at 300 mg and 1000 mg vs PBO (with ST) No. of patients: 305 Comparator: PBO	Significantly more patients had an SRI-4 response at Week 52 with ANI 300 mg (62.6%) vs PBO (40.2%), p<0.001 Significant treatment differences also found for BICLA, SLEDAI, PGA	No significant differences in BILAG A or 2B flare rate at Week 52	Significant difference at Week 52 in proportion of patients achieving GC taper criteria to ≤7.5 mg/day with ANI 300 mg (56.4%) vs PBO (26.6%), p=0.001	NR	NR	NR	NR
Clinical trial	[80]	Design: Phase 2 in patients with high IFN-1 signature and CLASI of ≥10; 150 mg and 300 mg ANI studied No. of patients: 36 (FAS) Comparator: PBO	CLASI response at Week 54, ANI 300 mg vs ANI 150 mg vs PBO: 91% (n=10/11) vs 80% (n=8/10) vs 44% (n=4/9) Mean change in CLASI activity score from baseline to Week 52 was −10.2 (SD 4.8) in the ANI 150 mg group, −13.2 (3.9) in the ANI 300 mg group, and −6.3 (8.1) in the PBO group	NR	ANI group had lower mean GC dose/day at Week 52 (4.4 mg/day) vs PBO (7.5 mg/day), but not statistically tested	NR	NR	NR	NR
Clinical trial	[81]	Design: 3-year OLE of patients who completed MUSE Phase 2b trial No. of patients: 246 completed the RCT, 218 enrolled in the OLE, 139 completed 3 years of treatment	NR	NR	NR	Reductions in SLEDAI-2K observed over 160 weeks Mean global SDI score was generally stable over time Didn't look at individual domains	NR	NR	NR

		Comparator: None (OLE)							
Clinical trial	[82]	Design: Patients from Phase 2b MUSE trial No. of patients: 256	NR	NR	NR	NR	NR	NR	NR
Clinical trial	[83]	Design: Open Label Phase 2 for 3 years No. of patients: 17 Comparator: None			SRI-4 response with oral CS tapering: 2/12 patients (day 169) and in 2/11 patients (day 365)	14 /17 patients in stage 1 of the trial had a ≥4-point reduction in SLEDAI-2K 13 patients achieved mild disease (SLEDAI-2k ≤4) from a baseline score >4 Didn't look at organ domains or organ damage		-	
Clinical trial	[84]	Design: Post hoc analysis of Phase 2b MUSE trial focussed on rash and arthritis measures No. of patients: 201 Comparator: PBO	Significantly greater percentage of patients with ANI (44.3%) vs PBO (14.8%) had SLEDAI-2K rash resolution (p<0.001) at Week 52 Significantly greater % of patients with ANI (56.7%) vs PBO (42.4%) had SLEDAI-2K–defined near-resolution of arthritis (p=0.032)	NR	NR	NR	NR	NR	NR

Clinical trial	[85]	Design: Patients who completed TULIP + 3 years of LTE TULIP extension No. of patients: 547 (efficacy comparisons 536) Comparator: PBO	NR	NR	NR	ANI had greater improvements in SLEDAI-2K and sustained improvement over time vs PBO Mean global SDI score remained stable in both groups	Overall annualised flare rate was 0.1 in ANI and 0.2 in PBO The majority of flares were mild to moderate	In each of the 4 study years, the GC dose was lower with ANI vs PBO At the end of Year 4, 9.9% in ANI group had GC dose >7.5 mg/day vs 29.3% in PBO	
Clinical trial	[86]	Design: Phase 3 TULIP 1 and TULIP 2 pooled data No. of patients: 726 Comparator: PBO		ANI had lower annualised flare rates than PBO (rate ratio 0.75 [95% CI 0.60 to 0.95]) and prolonged time to first flare , (HR 0.70 [95% CI 0.55 to 0.89]) (flares were defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B scores vs the previous visit)	Patients were tapered to ≤7.5 mg/day	Patients who received ANI had greater mean improvement from baseline in SLEDAI-2K vs PBO to Week 216, didn't look at organ domains or organ damage			

ABT, abatacept; ANI, anifrolumab; BEL, belimumab; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CS, corticosteroid; CYC, cyclophosphamide; ECLAM, European Consensus Lupus Activity Measurement; FAS, full analysis set; FU, follow-up; GC, glucocorticoid; GRAID, German Registry of Autoimmune Diseases; HCQ, hydroxychloroquine; HR, hazard ratio; INF-1, type 1 interferon; IQR, interquartile range; IV, intravenous; LN, lupus nephritis; LTE, long-term extension; MEX-SLEDAI, Mexican-Systemic Lupus Erythematosus Disease Activity Index; MMF, mycophenolate mofetil; OLE, open-label extension; OR, odds ratio; PBO, placebo; PGA, physician global assessment of disease activity; PS, propensity score; RCT, randomised controlled trial; RTX, rituximab; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI, SELENA-SLEDAI flare index; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4; ST, standard therapy; TLC, Toronto Lupus Cohort.

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