

Supplementary Material

TABLE S1 Summary of protocol deviations

Protocol deviation categorisation	Number of protocol deviations
Bloods/urine	94
General	1
IMP	1
Inclusion/exclusion criteria	6
Laboratory	21
Lung function	47
Patient choice/health	84
Prohibited medications	14
Spirometry	365
Vital Signs	9
6MWT	5
Questionnaires	12
Total	659

The majority of deviations pertaining to spirometry and lung function were a consequence of sites failing to perform tests within 1 hour of the time of spirometry/lung function performed at baseline.

TABLE S2 – Unadjusted mixed effects model for FVC change

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
baseFVC	0.999	0.022	46.1	0.000	0.957	1.042
Week 2	-0.040	0.048	-0.8	0.412	-0.134	0.055
Week 4	0.009	0.049	0.2	0.852	-0.087	0.106
Week 8	-0.065	0.049	-1.3	0.184	-0.162	0.031
Week 12	0.056	0.050	1.1	0.258	-0.041	0.153
Week 16	0.004	0.050	0.1	0.930	-0.093	0.101
Week 20	0.038	0.050	0.8	0.445	-0.059	0.135
Week 24	0.112	0.049	2.3	0.022	0.017	0.208
Week 48	0.154	0.050	3.1	0.002	0.056	0.251
Rituximab#Week 0	-0.017	0.057	-0.3	0.767	-0.128	0.095
Rituximab#Week 2	0.009	0.058	0.2	0.871	-0.103	0.122
Rituximab#Week 4	-0.083	0.059	-1.4	0.159	-0.198	0.032
Rituximab#Week 8	0.073	0.059	1.2	0.215	-0.042	0.188
Rituximab#Week 12	-0.076	0.059	-1.3	0.201	-0.191	0.040
Rituximab#Week 16	-0.021	0.059	-0.3	0.728	-0.137	0.096
Rituximab#Week 20	-0.039	0.060	-0.6	0.518	-0.157	0.079
Rituximab#Week 24	-0.038	0.059	-0.6	0.518	-0.155	0.078
Rituximab#Week 48	-0.057	0.063	-0.9	0.363	-0.180	0.066

_cons	0.063	0.077	0.8	0.413	-0.088	0.215
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TABLE S3 – Fixed effects model adjusted to baseline for FVC

	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
baseFVC	0.989	0.013	78.5	0.000	0.965	1.014
Week 2	-0.038	0.059	-0.6	0.523	-0.155	0.079
Week 4	-0.002	0.060	-0.0	0.970	-0.121	0.116
Week 8	-0.090	0.060	-1.5	0.138	-0.208	0.029
Week 12	0.041	0.061	0.7	0.505	-0.079	0.160
Week 16	-0.009	0.061	-0.1	0.882	-0.128	0.110
Week 20	0.024	0.061	0.4	0.688	-0.095	0.144
Week 24	0.099	0.060	1.6	0.100	-0.019	0.217
Week 48	0.138	0.061	2.3	0.024	0.018	0.259
Rituximab#Week 0	0.000	0.059	0.0	0.994	-0.115	0.116
Rituximab#Week 2	0.026	0.060	0.4	0.667	-0.092	0.143
Rituximab#Week 4	-0.062	0.061	-1.0	0.310	-0.183	0.058
Rituximab#Week 8	0.118	0.061	1.9	0.055	-0.003	0.238
Rituximab#Week 12	-0.041	0.062	-0.7	0.505	-0.162	0.080
Rituximab#Week 16	0.012	0.062	0.2	0.848	-0.110	0.134
Rituximab#Week 20	-0.005	0.063	-0.1	0.933	-0.129	0.119
Rituximab#Week 24	-0.002	0.062	-0.0	0.976	-0.124	0.120

Rituximab#Week 48	-0.024	0.067	-0.4	0.715	-0.155	0.106
_cons	0.023	0.050	0.5	0.642	-0.075	0.122

TABLE S4 – Unadjusted fixed effects model for FVC change

	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
Week 2	-0.024	0.177	-0.1	0.894	-0.371 0.324
Week 4	0.022	0.180	0.1	0.903	-0.331 0.375
Week 8	-0.042	0.180	-0.2	0.816	-0.395 0.312
Week 12	0.097	0.181	0.5	0.591	-0.258 0.453
Week 16	0.018	0.181	0.1	0.921	-0.338 0.374
Week 20	0.052	0.181	0.3	0.776	-0.304 0.407
Week 24	0.124	0.179	0.7	0.489	-0.227 0.475
Week 48	0.216	0.182	1.2	0.236	-0.142 0.574
Rituximab#Week 0	0.044	0.175	0.3	0.802	-0.300 0.388
Rituximab#Week 2	0.058	0.178	0.3	0.742	-0.291 0.408
Rituximab#Week 4	-0.026	0.183	-0.1	0.889	-0.384 0.333
Rituximab#Week 8	0.134	0.183	0.7	0.465	-0.225 0.493
Rituximab#Week 12	-0.026	0.184	-0.1	0.886	-0.387 0.335
Rituximab#Week 16	0.044	0.185	0.2	0.813	-0.319 0.407
Rituximab#Week 20	0.043	0.188	0.2	0.818	-0.326 0.412
Rituximab#Week 24	0.027	0.185	0.1	0.884	-0.336 0.390
Rituximab#Week 48	0.072	0.198	0.4	0.717	-0.318 0.461

_cons	2.206	0.124	17.8	0.000	1.963	2.449
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FIGURE S1 – Boxplot of observed FVC values (in litres) by visit

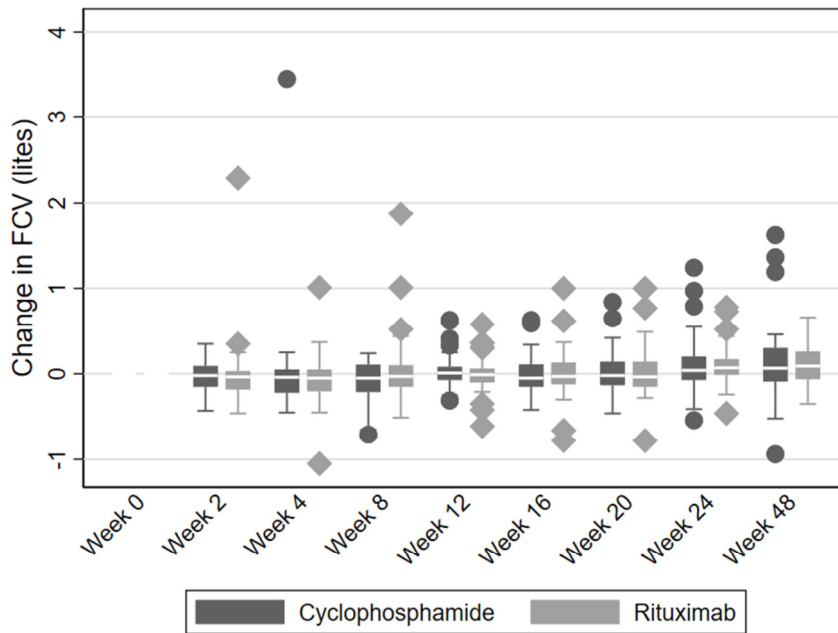


TABLE S5 – Adjusted mixed effects model with removal of one outlier value. Pt 89

(Cyclophosphamide) had a 3.46 folds increase at week 4 (results: W0: 1.4 ; W2: 1.56; W4 4.85; there were no more measurements).The second highest increase was 2.45 fold for patient 40, week 8 (Rituximab).Pt 89's Week 4 measurement was omitted in the sensitivity analysis below using the same model as for the primary outcome.

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
baseFVC	1.003	0.020	49.4	0.000	0.963 1.042

Week 2	-0.040	0.043	-0.9	0.359	-0.124	0.045
Week 4	-0.067	0.044	-1.5	0.133	-0.153	0.020
Week 8	-0.080	0.044	-1.8	0.069	-0.166	0.006
Week 12	0.041	0.044	0.9	0.353	-0.046	0.128
Week 16	-0.010	0.044	-0.2	0.814	-0.097	0.076
Week 20	0.023	0.044	0.5	0.603	-0.064	0.110
Week 24	0.098	0.044	2.2	0.026	0.012	0.183
Week 48	0.139	0.045	3.1	0.002	0.051	0.226
Rituximab#Week 0	-0.008	0.052	-0.1	0.884	-0.109	0.094
Rituximab#Week 2	0.019	0.052	0.4	0.718	-0.084	0.121
Rituximab#Week 4	0.001	0.054	0.0	0.984	-0.104	0.106
Rituximab#Week 8	0.097	0.053	1.8	0.069	-0.008	0.202
Rituximab#Week 12	-0.052	0.054	-1.0	0.337	-0.157	0.054
Rituximab#Week 16	0.003	0.054	0.1	0.949	-0.102	0.109
Rituximab#Week 20	-0.015	0.055	-0.3	0.787	-0.122	0.092
Rituximab#Week 24	-0.014	0.054	-0.3	0.789	-0.120	0.091
Rituximab#Week 48	-0.034	0.057	-0.6	0.553	-0.145	0.078
_cons	0.038	0.065	0.6	0.559	-0.089	0.165

TABLE S6 – Unadjusted mixed effects model for DLco

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
baseDLCO	1.024	0.035	29.7	0.000	0.957	1.092
Week 12	-0.037	0.096	-0.4	0.703	-0.225	0.152
Week 24	0.058	0.092	0.6	0.530	-0.123	0.239
Week 48	0.134	0.097	1.4	0.167	-0.056	0.324
Rituximab#Week 0	-0.003	0.121	-0.0	0.982	-0.240	0.235
Rituximab#Week 12	0.111	0.127	0.9	0.383	-0.139	0.361
Rituximab#Week 24	0.183	0.127	1.4	0.149	-0.065	0.431
Rituximab#Week 48	0.116	0.134	0.9	0.388	-0.147	0.379
_cons	-0.082	0.144	-0.6	0.570	-0.363	0.200

TABLE S7 – Unadjusted fixed effects model for DLco

ITMPFTLCO	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
Week 12	0.061	0.327	0.2	0.852	-0.583	0.705
Week 24	0.060	0.318	0.2	0.850	-0.565	0.685
Week 48	0.208	0.330	0.6	0.529	-0.441	0.856
Rituximab#Week 0	0.115	0.320	0.4	0.720	-0.514	0.744
Rituximab#Week 12	0.100	0.331	0.3	0.763	-0.551	0.751
Rituximab#Week 24	0.179	0.325	0.5	0.583	-0.461	0.819
Rituximab#Week 48	0.220	0.356	0.6	0.536	-0.479	0.920
_cons	3.348	0.225	14.9	0.000	2.905	3.790

TABLE S8 – Unadjusted mixed effects model for EQ5D

EQ5D_score	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
baseQLQ_EQ5D	0.76	0.05	15.5	0.000	0.66	0.85
Week 24	4.02	2.93	1.4	0.169	-1.71	9.76
Week 48	-0.65	2.99	-0.2	0.828	-6.50	5.21
Rituximab#Week 0	0.42	2.95	0.1	0.888	-5.36	6.20
Rituximab#Week 24	3.17	3.17	1.0	0.318	-3.05	9.39
Rituximab#Week 48	4.98	3.36	1.5	0.138	-1.61	11.57
_cons	13.61	3.47	3.9	0.000	6.82	20.41

TABLE S9 – Unadjusted fixed effects model for EQ5D

EQ5D_score	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
Week 24	7.42	4.35	1.7	0.089	-1.14	15.98
Week 48	2.84	4.42	0.6	0.521	-5.87	11.55
Rituximab#Week 0	2.83	4.25	0.7	0.507	-5.55	11.20
Rituximab#Week 24	3.68	4.53	0.8	0.418	-5.25	12.60
Rituximab#Week 48	3.96	4.79	0.8	0.409	-5.47	13.40
_cons	55.27	2.99	18.5	0.000	49.38	61.17

TABLE S10 – Unadjusted mixed effects model for global disease activity score (GDAS)

GDAS_score	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
baseQLQ_GDAS	0.60	0.06	9.8	0.000	0.48	0.72
Week 24	-2.89	0.34	-8.5	0.000	-3.55	-2.22
Week 48	-2.78	0.35	-7.9	0.000	-3.47	-2.09
Rituximab#Week 0	-0.18	0.35	-0.5	0.613	-0.86	0.51
Rituximab#Week 24	-0.12	0.36	-0.3	0.751	-0.83	0.60
Rituximab#Week 48	0.91	0.40	2.2	0.025	0.12	1.70
_cons	1.99	0.39	5.1	0.000	1.22	2.76

TABLE S11 – Unadjusted fixed effects model for global disease activity score (GDAS)

GDAS_score	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
Week 24	-2.72	0.44	-6.2	0.000	-3.59	-1.85
Week 48	-2.63	0.46	-5.7	0.000	-3.54	-1.72
Rituximab#Week 0	-0.45	0.44	-1.0	0.317	-1.32	0.43
Rituximab#Week 24	-0.44	0.44	-1.0	0.328	-1.31	0.44
Rituximab#Week 48	0.34	0.50	0.7	0.494	-0.64	1.32
_cons	5.03	0.31	16.2	0.000	4.41	5.64

Table S12 – Unadjusted mixed effects model for KB-ILD

KBILD_Total	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
baseQLQ_KBILD	0.74	0.05	14.0	0.000	0.64	0.85
r						
Week 24	9.56	2.80	3.4	0.001	4.07	15.04
Week 48	5.79	2.84	2.0	0.041	0.22	11.35
Rituximab#Week 0	1.31	3.08	0.4	0.671	-4.72	7.33
Rituximab#Week 24	0.50	3.24	0.2	0.877	-5.84	6.84
Rituximab#Week 48	1.39	3.42	0.4	0.685	-5.31	8.08
_cons	11.77	3.26	3.6	0.000	5.38	18.16

TABLE S13 – Unadjusted fixed effects model for KB-ILD.

KBILD_Total	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
Week 24	10.33	4.46	2.3	0.021	1.55	19.12
Week 48	7.01	4.51	1.6	0.122	-1.88	15.90
Rituximab#Week 0	5.10	4.39	1.2	0.246	-3.54	13.74
Rituximab#Week 24	3.05	4.61	0.7	0.508	-6.02	12.13
Rituximab#Week 48	1.50	4.88	0.3	0.759	-8.11	11.11
_cons	45.94	3.09	14.9	0.000	39.86	52.02

TABLE S14 – Unadjusted mixed-effects model for SGRQ

SGRQ_score	COEF.	STD. ERR.	Z	P> z	[95% CONF. INTERVAL]	
baseQLQ_SGRQ	0.84	0.06	13.5	0.000	0.72	0.97
order						
Week 24	-4.94	2.66	-1.9	0.064	-10.16	0.28
Week 48	-6.67	2.71	-2.5	0.014	-11.97	-1.36
Arm#order						
Rituximab#Week 0	-0.64	3.10	-0.2	0.836	-6.72	5.44
Rituximab#Week 24	0.67	3.28	0.2	0.838	-5.76	7.11
Rituximab#Week 48	2.68	3.40	0.8	0.430	-3.98	9.35
_cons	8.74	4.12	2.1	0.034	0.67	16.81

TABLE S15 - Unadjusted fixed effects model for SGRQ

SGRQ_score	COEF.	STD. ERR.	T	P> T	[95% CONF. INTERVAL]	
order						
Week 24	-7.03	4.59	-1.5	0.127	-16.06	2.01
Week 48	-7.62	4.64	-1.6	0.102	-16.76	1.52
Arm#order						
Rituximab#Week 0	-4.12	4.56	-0.9	0.367	-13.10	4.86
Rituximab#Week 24	-3.45	4.75	-0.7	0.468	-12.80	5.90
Rituximab#Week 48	-1.78	4.97	-0.4	0.720	-11.56	8.00
_cons	56.19	3.19	17.6	0.000	49.91	62.47

TABLE S16 – Unadjusted mixed effects model for mRss

mRSS_score	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
baseQLQ_mRSS	0.87	0.07	12.8	0.000	0.73	1.00
r						
Week 12	3.27	1.27	2.6	0.010	0.79	5.75
Week 24	1.21	1.22	1.0	0.320	-1.18	3.59
Week 48	-0.11	1.24	-0.1	0.930	-2.54	2.32
Rituximab#Week 0	0.29	1.48	0.2	0.846	-2.61	3.18
Rituximab#Week 12	-3.83	1.63	-2.4	0.018	-7.02	-0.64
Rituximab#Week 24	-3.69	1.64	-2.3	0.024	-6.90	-0.49
Rituximab#Week 48	-3.10	1.80	-1.7	0.085	-6.62	0.43
_cons	0.95	1.06	0.9	0.372	-1.13	3.03

TABLE S17 – Unadjusted fixed effects model for mRss

mRSS_score	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
Week 12	2.98	2.66	1.1	0.266	-2.29	8.24
Week 24	2.13	2.58	0.8	0.411	-2.97	7.23
Week 48	-1.08	2.58	-0.4	0.675	-6.19	4.02
Rituximab#Week 0	2.15	2.66	0.8	0.420	-3.11	7.42
Rituximab#Week 12	-2.00	2.84	-0.7	0.482	-7.62	3.62
Rituximab#Week 24	-2.09	2.85	-0.7	0.466	-7.72	3.55
Rituximab#Week 48	0.67	3.10	0.2	0.830	-5.46	6.79
_cons	7.08	1.71	4.1	0.000	3.69	10.47

Lab safety results

TABLE S18 – subjects, by visit, with white blood cell count below the lower limit of normal.

Subject	Visit	White cell count (x10⁹/l)	Treatment
44	Week 24	3.5	Cyclophosphamide
58	Screening	3.8	Cyclophosphamide
58	Week 2	2.9	Cyclophosphamide
58	Week 4	3.7	Cyclophosphamide
58	Week 8	3.5	Cyclophosphamide
58	Week 16	3.8	Cyclophosphamide
58	Week 24	3.5	Cyclophosphamide
58	Week 48	3.7	Cyclophosphamide
74	Screening	2.5	Rituximab
74	Week 0	2.1	Rituximab
74	Week 2	2.1	Rituximab
74	Week 4	2.8	Rituximab
74	Week 8	3.5	Rituximab
74	Week 12	2.7	Rituximab
74	Week 16	2.9	Rituximab
74	Week 20	2.8	Rituximab
74	Week 24	3.2	Rituximab
74	Week 48	3.2	Rituximab
92	Week 0	3.7	Rituximab
97	Week 2	3.6	Cyclophosphamide

Subject	Visit	White cell count (x10⁹/l)	Treatment
103	Screening	3.9	Rituximab
103	Week 12	3.1	Rituximab
103	Week 16	3.7	Rituximab

TABLE S19 – subjects, by visit, with neutrophil count below the lower limit of normal.

Subject	Visit	Neutrophil count (x10⁹/l)	Treatment
74	Week 0	1.2	Rituximab
74	Week 2	1.3	Rituximab

TABLE S20 – subjects, by visit, with creatinine level above the upper limit of normal.

Subject	Visit	Creatinine ($\mu\text{mol/L}$)	Treatment
24	Week 16	122	Cyclophosphamide
49	Week 4	124	Rituximab
49	Week 12	121	Rituximab
49	Week 24	127	Rituximab
82	Week 20	127	Cyclophosphamide
84	Screening	143	Cyclophosphamide
84	Week 0	143	Cyclophosphamide
84	Week 2	159	Cyclophosphamide
84	Week 4	165	Cyclophosphamide
84	Week 8	150	Cyclophosphamide
93	Week 20	121	Cyclophosphamide
100	Week 0	123	Cyclophosphamide

TABLE S21 – subjects, by visit, with a rise in creatinine from baseline.

Subject	Visit	Creatinine ($\mu\text{mol/L}$)	Baseline creatinine ($\mu\text{mol/L}$)	Treatment
16	Week 24	85	56	Rituximab
36	Week 12	53	35	Rituximab
36	Week 16	57	35	Rituximab
60	Week 20	56	37	Rituximab
96	Week 2	115	59	Rituximab
98	Week 16	86	53	Cyclophosphamide
98	Week 24	83	53	Cyclophosphamide

TABLE S22 – subjects, by visit, with alanine aminotransferase level above the upper limit of normal.

Subject	Visit	ALT (U/L)	Treatment
3	Screening	85	Cyclophosphamide
19	Week 0	99	Rituximab
21	Screening	99	Rituximab
28	Week 4	85	Cyclophosphamide
32	Week 16	97	Cyclophosphamide
36	Screening	99	Rituximab
44	Week 8	86	Cyclophosphamide
44	Unscheduled	99	Cyclophosphamide
49	Week 0	89	Rituximab
49	Week 4	88	Rituximab
49	Week 8	87	Rituximab
49	Week 24	82	Rituximab
55	Screening	92	Cyclophosphamide
80	Screening	90	Cyclophosphamide
81	Week 12	99	Cyclophosphamide
89	Screening	93	Cyclophosphamide

TABLE S23 – subjects, by visit, with alkaline phosphatase level above the upper limit of normal.

Subject	Visit	ALP (U/L)	Treatment
82	Unscheduled	283	Cyclophosphamide

