Statistical Analysis Plan (SAP)

RECITAL

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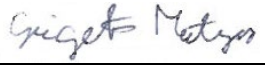
Mr Matyas Szigeti		Trial Statistician	04/12/2019

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1. Study objectives

1.1. Primary objective

- To demonstrate that intravenous Rituximab has superior efficacy compared to current best treatment (intravenous Cyclophosphamide) for CTD-ILD. This will be measured by assessment of change in FVC at 24 weeks.

1.2. Secondary objectives

- To compare the safety profile of Rituximab to intravenous Cyclophosphamide in individuals with CTD-ILD.
- To assess the health economic benefits of Rituximab compared to current standard of care for CTD-ILD – including measurements of healthcare utilisation, Quality of Life (QoL) and carer burden.
- To evaluate a range of exploratory biomarkers for disease severity, prognosis and treatment response in CTD-ILD.

2. Version History

The definitions of ITT population and Safety analysis population have been corrected in Version 1.0.

The definition of ITT population (in Chapter 5.4 has) changed to: “all subjects who have met all the entry criteria for the trial and been randomised **and received at least one dose of study drug** (version 1.0) from: “all subjects who have met all the entry criteria for the trial and been randomised” (version 0.2).

The definition of safety population (in Chapter 5.7) changed •to “all subject who has been randomised” (version 1.0) as defined in the protocol from “All subjects that have received at least **one dose of a treatment** will be included in the safety analysis.” (version 0.2).

3. Background / Introduction

3.1. Background

Interstitial Lung Disease (ILD) is characterised by inflammation and/or fibrosis that results in thickening and distortion of the alveolar wall with consequent impairment of gas exchange. Affected individuals typically present with progressive breathlessness which frequently causes respiratory failure and death. There are many described causes of ILD, however, one of the commonest is that resulting from lung involvement by systemic autoimmune disease. This group of conditions, the Connective Tissue Diseases (CTD), are an important cause of disability and death in the working age population. Over the last decade improvements in therapy for the CTDs has seen the prognosis for individuals with these conditions dramatically improve. Despite these improvements in care there has been little, if any, change in therapy for ILD occurring as a consequence of CTD. For this reason for those individuals with CTD, respiratory disease has grown in importance. For many CTD sufferers disease-associated ILD is now the major cause of disability and exercise limitation whilst in systemic sclerosis it is now the principal cause of mortality in this patient group.[1]

The pathogenesis of CTD-ILD is complex and poorly understood. It is however, generally accepted that underlying immune system dysfunction and immune-mediated pulmonary inflammation are critical to CTD-ILD development and progression. Abnormalities of cellular and humoral immune function have been described in ILD associated with SSc[2-4], idiopathic inflammatory myopathy and several other CTDs[5]. The mechanism by which these processes lead on to fibrosis remains poorly understood as do the factors that determine which individuals with CTD develop ILD. Nonetheless evidence from treatment trials suggest that modulation of inflammation with immunosuppressant therapies, particularly Cyclophosphamide, results in some regression of ILD and prevents the development of further fibrosis.

Different CTDs manifest varying forms of ILD. Individuals with scleroderma and Mixed Connective Tissue Disease (MCTD) most commonly develop the histological lesion of non-specific interstitial pneumonia. Those with idiopathic inflammatory myositis typically have combined organising pneumonia and NSIP (referred to in the literature as fibrosing organising pneumonia). By contrast to these conditions, individuals with rheumatoid disease frequently have fibrosis with the histological pattern of usual interstitial pneumonia and tend to be resistant to therapy with high dose immunosuppression.

The field of rheumatology has seen rapid developments over the last decade with the introduction of a range of monoclonal antibody therapies that have revolutionised the standard of care for this patient group. Despite this there have been few if any improvements in the management of CTD associated ILD. Currently, standard of care for severe, progressive CTD-ILD includes immunosuppression with intravenous Cyclophosphamide (600 mg/m2) administered monthly for 6 months, followed by maintenance oral

immunosuppression[6,7]. Occasionally, this intensive immunosuppressive therapy fails to control pulmonary inflammation and alternative therapies may be required. Rituximab, a chimeric (human/mouse) monoclonal antibody with a high affinity for the CD20 surface antigen expressed on pre-B and B-lymphocytes, results in rapid depletion of B cells from the peripheral circulation for 6 to 9 months[8,9]. Evidence for the effectiveness of B cell depletion exists in a number of immune-mediated conditions, including rheumatoid arthritis[10-12], ANCA-associated vasculitis[13,14] and immune Thrombocytopenic Purpura[15] (TTP). Several case series suggest Rituximab may also be effective in ILD occurring in the context of immunological over-activity, with favourable responses reported in anti-synthetase (ASS) associated ILD[16] and SSc-ILD[17-18]. The investigators' own experience has demonstrated Rituximab to be an effective, potentially life-saving therapeutic intervention in the treatment of very severe, progressive CTD-ILD unresponsive to conventional immunosuppression[19].

It is hoped that this study will advance the standard of care for individuals with CTD-ILD. Despite current best treatment, individuals with extensive ILD due to scleroderma have a median survival of less than 5 years and a similar poor prognosis is observed in individuals with inflammatory myositis and MCTD20. If Rituximab can be shown to improve six month and one year lung function in this group then it is to be hoped that this will translate in to improvements in longer term survival and associated reductions in morbidity. The simplified dosing regimen for Rituximab when compared to Cyclophosphamide also affords the potential for reducing the burden on patients (and their carers) of frequent hospital attendances. Similarly, although drug costs are higher for Rituximab, it is hoped that a Full Economic Costing (FEC) will demonstrate savings based on reduced utilisation of healthcare resources and fewer hospital visits.

3.2. Study Design

The study is a UK multi-centre, prospective, randomised, double blind, double dummy trial of intravenous Rituximab compared with intravenous Cyclophosphamide in patients with severe, progressive CTD-ILD.

3.3. Treatment Groups

Subjects will be randomised into two groups with one group receiving Rituximab and placebo and the other group receiving Cyclophosphamide and placebo, according to the summary set out in section 2.5.

3.4. Study Population

Patients for whom the treating physician has made the decision, on clinical grounds, to intervene with intravenous immunosuppression to minimize the risk of progressive lung damage as a result of associated defined CTD.

A total of 116 patients with confirmed Connective Tissue Disease (systemic sclerosis, idiopathic interstitial myopathy or mixed connective tissue disease) and associated Interstitial Lung Disease will be randomised with 58 in the Rituximab arm and 58 in the Cyclophosphamide arm. Patients will be followed up for 48 weeks.

3.5. Intervention Being Tested

Treatments will be administered according to the table below. The dosage for obese subjects will be modified as specified in the IMP manual.

Table 1: Summary of Treatment Groups	**Rituximab group**	**Cyclophosphamide group**
Day 0	IV active rituximab 1000mg	IV 600 mg/m_2 body surface area
Day 14	IV active rituximab 1000mg	Placebo
Week 4	Placebo	IV 600 mg/m_2 body surface area
Week 8	Placebo	IV 600 mg/m_2 body surface area
Week 12	Placebo	IV 600 mg/m_2 body surface area
Week 16	Placebo	IV 600 mg/m_2 body surface area
Week 20	Placebo	IV 600 mg/m_2 body surface area

3.6. Missing Data

Every effort will be made to minimise missing baseline and outcome data in this trial. Reasons for non-entry will be collected using the InForm comment facilities.

4. Variables of Analysis

4.1. Primary Efficacy Variable

- Change in Forced Vital Capacity (FVC, expressed in mL) at week 24

4.2. Secondary Efficacy Variables

- Change in diffusing capacity for carbon monoxide (DLco) at 24 weeks
- Change in health related quality of life scores (SGRQ, SF-36, K-BILD)
- Change in global disease activity score
- Change in 6 minute walk distance over 48 weeks
- Change in FVC and DLco at 48 weeks
- Absolute categorical change of %FVC at 24 and 48 weeks (decrease by > 5%, increase by >5% and change within <5%)
- Absolute categorical change of %FVC at 24 and 48 weeks (decrease by > 10%, increase by >10% and change within <10%)
- 48 week rate of change in FVC
- Disease related mortality (adjudicated by steering committee at close of study)
- Overall survival
- Progression free survival (i.e. avoiding any of the following: mortality, transplant, treatment failure [see below] or decline in FVC > 10% compared to baseline)
- Treatment failure (as determined by need for transplant or rescue therapy with either open label Cyclophosphamide or Rituximab at any point until 48 weeks).
- Total corticosteroid requirement over 48 weeks
- Change from baseline in SpO2 at 24 and 48 weeks
- Healthcare utilisation during study period (visits to primary care, unscheduled hospital visits, emergency admissions)
- Scleroderma specific endpoints (change in scleroderma HAQ, modified Rodnan Skin Score (mRSS))

4.3. Safety Variables

- Vital signs (Temperature, Weight, Pulse, Blood Pressure, oxygen saturations,oxygen status, respiratory rate)
- Physical examination (skin, lungs, cardiovascular, abdomen)
- Laboratory tests (Blood counts, urea, electrolytes, liver function tests, urinalysis)
- Adverse and serious adverse events
- Discontinuation of Rituximab or Cyclophosphamide due to intolerance or side effects.

4.4. Exploratory Variables

- Change in lymphocyte subsets in relation to efficacy outcomes

- Change in plasma cytokine levels following therapy and in relation to markers of disease activity (FVC, DLco, QoL, global disease scores)
- Outcome in relation to underlying CTD

5. Statistical Methodology

5.1. Recruitment and protocol compliance

Details about patient enrolment, treatment allocation, follow-up and inclusion in analysis will be provided using a patient flow diagram as recommended by the CONSORT statement [20]. Recruitment, compliance, mortality and protocol deviations will be summarised by underlying CTD diagnosis (see Table 1). A breakdown of the reasons for exclusion will also be provided in tabular form. Additionally, listings and summaries of the major and minor protocol deviations will be produced. A protocol deviation will be classified as major if it significantly effects patient safety or the scientific value of the trial (recorded as serious in the protocol deviations eCRF).

5.2. Baseline characteristics

Baseline characteristics of all randomised subjects will be summarised by treatment group using appropriate descriptive statistics (see Table 2)**.**
Additionally baseline characteristics data will be checked for outliers.

5.3. Withdrawals, crossovers and missing data

Before starting the data analysis, the level and pattern of the missing data in the baseline variables and outcomes, and any treatment group crossovers, will be established by forming appropriate tables. The likely causes of any missingness and crossovers will be investigated. This information will be used to determine whether the level and type of missing data and the crossover rate have the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects.

5.4. Primary Efficacy Analysis

- Analysis of the primary outcome will be by intention to treat. In other words, data is included in respect of all subjects who have met all the entry criteria for the trial and been randomised and received at least one dose of study drug. The data is analysed according to the initial randomisation groups with no changes made in respect of subsequent withdrawals or crossovers.
- The hypothesis to be tested is that Rituximab is superior to Cyclophosphamide. The study will be considered positive if statistical significance at the level of 0.05 (two tailed) is achieved.
- To test the hypothesis above and estimate the difference in FVC at week 24 and it's 95% Confidence Interval, a three-level hierarchical (mixed/multi-level) model will be used:

  Let FVC_{iw} represent the FVC (in ml) for patient i at week w and $t(i)$ represent the treatment given to individual i (Rituximab or Cyclophosphamide). So we model FVC_{iw} as the sum of four components:

$$DS_{iw} = intercept_i + change\ over\ time_{t(i)w} + CTD_i + residual\ error_{id}$$

- Intercept term: represents the estimate FVC on week 0 (the start of the treatment, fist visit after randomsation). This term will comprise an individual level random effect which will be drawn from a distribution parameterised using the associated centre level random effect. Hence the unexplained variation in the diary scores will be split into three components corresponding to the three levels of the model, i.e. the variation attributable to the centre (between centre variation) and the individual

(between individual variation), as well as the residual variation (within individual variation). CDT diagnosis stratum (categorical) used for randomisiation will be added as a covariate. Other baseline covariates might be added if further analysis reveals a substantial imbalance.

- Change over time term: this represents a coefficient which captures the changes in FVC over time (measured in weeks) and an interaction term between time and treatment. This interaction term will capture the difference in change of FVC between the two treatment groups per week. The magnitude at 24 weeks and its 95% Confidence Interval will be calculated to answer the research question.

  Linear change is assumed over time with different slopes (the interaction term represents the difference in the slope), however alternatives will be considered as the rate of change not constant over the 24 weeks period. Alternatives are to include quadratic and square root term. This will be assessed before the unblinding.

Residual error term: it is assumed that the residual errors have a Normal distribution.

5.5. Secondary Efficacy Analysis

- Analysis of secondary efficacy outcomes will also be by intention to treat.
- Change in continuous physiological variables between baseline and 48 weeks will be assessed by similar multilevel model as described for the primary outcome.
- Categorical change in physiological variables will be measured using chi-squared tests under the null hypothesis of no difference between the treatment groups.
- Mortality, treatment failure and progression free survival will be measured using Kaplan-Meier estimates. A log rank test will be used to compare treatment groups and a Cox proportional hazards model will be used to determine hazard ratios for survival analyses.

5.6. Sensitivity Analyses on Efficacy

- A dataset formed by allocating patients to treatment arm ‘as treated’ will be used for a sensitivity analysis of the primary outcome. The ‘as treated’ dataset may differ from the ‘intention-to-treat’ dataset in respect of any patients who switch between treatment groups due to treatment failure.
- A per protocol analysis of the primary outcome will also be carried out. The per protocol analysis will include only those subjects who complete the full course of treatment as set out in the protocol.
- If there are significant discrepancies between the timing of visits as set out in the protocol and the actual dates when measurements are taken, then the impact of using an imputation-based adjustment to the primary outcome in respect of these timing discrepancies may be investigated.

5.7. Safety Analysis

- All subjects that have received at least one dose of a treatment will be included in the safety analysis. Special consideration will be given to subjects that have changed from one treatment arm to the other, taking into account the timing of any adverse events in relation to the treatment change and the clinical investigator’s assessment of the relationship to the study treatment.
- In general safety analyses will be descriptive and no hypothesis testing is planned.
- Time to trial drug discontinuation will be analyzed using Kaplan-Meier estimates. Frequency, severity and causal relationship of adverse events will be tabulated by

system organ class (SOC) and preferred term (PT) after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Statistical analysis and reporting of adverse events will concentrate on treatment emergent adverse events. To this end, all adverse events with an onset after the first dose of study medication up to a period of 28 days (inclusive) after the last dose of study medication will be considered 'treatment emergent' and will be assigned to the treatment phase for evaluation. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Other adverse events will be assigned either to the screening or post treatment, or post study phase, as appropriate.

- For laboratory evaluations, treatment groups will be compared descriptively with regard to the distribution of the parameters as well as to frequency and percentage of patients with abnormal values (outside the reference range) or clinically relevant abnormal values.
- Changes from baseline (calculated directly for each subject) in vital signs parameters as well as weight (but not height) will be summarized by treatment group.
- The blood tests detailed below are of specific safety interest and regular checks will be performed to identify values outside the cut off value and will be reviewed by the CI and DMC.

Description	Cut off value
White cell count	<4 $x10^9$/L
Neutrophils	1.5 $x10^9$/L
Creatinine	> ULN or 1.5Xbaseline value
Alanine aminotransferase (ALT)	> 2XULN
Alkaline phosphatase (ALP)	> 2XULN
Bilirubin	> 2XULN

5.8. Exploratory Analysis

Exploratory biomarker analyses may use linear or logistic regression as appropriate. At a minimum appropriate plots or tables will be drawn. An analysis of outcome (as measured by change in FVC) according to underlying CTD diagnosis will be undertaken.

5.9. Interim Analysis

No formal interim analysis is planned. A regular review of safety data will be conducted to monitor the safety of patients in the trial. A Data Monitoring Committee (DMC) will follow number of deaths, early discontinuation due to Adverse Events (AEs) and Serious Adverse Events (SAEs) in an un-blinded fashion. The first meeting will be held to review all available data after the 12_{th} randomized patient has completed the week 24 visit and periodically thereafter. The complete details will be outlined in a DMC charter to be agreed by the DMC members at the start of the study.

5.10. Analyses not forming part of this analysis plan

The protocol refers to exploratory biomarker analyses based on stored blood samples. This part of the study will be carried out at a later date and such analyses are therefore not included here.

The cost-effectiveness evaluation will be carried out separately and also does not form part of this analysis plan.

5.11. Tables to present

This section contains examples of the tables we plan to produce as part of the statistical analysis.

Table 1: Number of screened subjects, number of randomised subjects, number (%) of subjects who completed the course of treatment and number of protocol deviations by underlying CTD diagnosis and treatment group

	Rituximab	Cyclophosphamide	Total
Screened Patients			
Systemic sclerosis			
Idiopathic interstitial myopathy			
Mixed Connective Tissue Disease			
Total			
Randomised Patients			
Systemic sclerosis			
Idiopathic interstitial myopathy			
Mixed Connective Tissue Disease			
Total			
Completed course of treatment			
Systemic sclerosis			
Idiopathic interstitial myopathy			
Mixed Connective Tissue Disease			
Total			
Died			
Systemic sclerosis			
Idiopathic interstitial myopathy			
Mixed Connective Tissue Disease			
Total			
Major protocol deviations			
Systemic sclerosis			
Idiopathic interstitial myopathy			
Mixed Connective Tissue Disease			
Total			
Minor protocol deviations			
Systemic sclerosis			
Idiopathic interstitial myopathy			
Mixed Connective Tissue Disease			
Total			

Table 2: Baseline characteristics by treatment group

	Rituximab (N =)	Cyclophosphamide (N =)	Total
Age (years)	Mean (SD)	Mean (SD)	Mean (SD)
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Ethnicity			
White	n(%)	n(%)	n(%)
Black	n(%)	n(%)	n(%)
Asian	n(%)	n(%)	n(%)
Mixed	n(%)	n(%)	n(%)
Other	n(%)	n(%)	n(%)
Not reported	n(%)	n(%)	n(%)
Connective tissue disease type			
Systemic sclerosis	n(%)	n(%)	n(%)
Idiopathic interstitial myopathy	n(%)	n(%)	n(%)
Mixed Connective Tissue Disease	n(%)	n(%)	n(%)
Time since onset of CTD (years)	Mean (SD)	Mean (SD)	Mean (SD)
Vital signs			
Height (cm)	Mean (SD)	Mean (SD)	Mean (SD)
Weight (kg)	Mean (SD)	Mean (SD)	Mean (SD)
O_2 saturations (%)	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
Receiving oxygen			
Yes	n(%)	n(%)	n(%)
No	n(%)	n(%)	n(%)
Haematology			
Haemoglobin (g/dL)	Mean (SD)	Mean (SD)	Mean (SD)
White blood cells (x10^9/L)	Mean (SD)	Mean (SD)	Mean (SD)
Platelets (x10^9/L)	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
Biochemistry			

Urea (mmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
Creatinine (µmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
Glucose (mmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
CRP (mg/L)	Mean (SD)	Mean (SD)	Mean (SD)
Calcium (mmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
Sodium (mmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
Potassium (mmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
Creatine Kinase (U/L)	Mean (SD)	Mean (SD)	Mean (SD)
ESR (mm/h)	Mean (SD)	Mean (SD)	Mean (SD)
Liver function			
Albumin (g/L)	Mean (SD)	Mean (SD)	Mean (SD)
Bilirubin (µmol/L)	Mean (SD)	Mean (SD)	Mean (SD)
Protein (g/L)	Mean (SD)	Mean (SD)	Mean (SD)
AST (U/L)	Mean (SD)	Mean (SD)	Mean (SD)
ALT (U/L)	Mean (SD)	Mean (SD)	Mean (SD)
Gamma-GT (U/L)	Mean (SD)	Mean (SD)	Mean (SD)
ALP (U/L)	Mean (SD)	Mean (SD)	Mean (SD)
Spirometry			
FEV_1 (ml)	Mean (SD)	Mean (SD)	Mean (SD)
FEV_1 % predicted (%)	Mean (SD)	Mean (SD)	Mean (SD)
FVC (ml)	Mean (SD)	Mean (SD)	Mean (SD)
FVC % predicted (%)	Mean (SD)	Mean (SD)	Mean (SD)
Pulmonary Function			
TLC (L)	Mean (SD)	Mean (SD)	Mean (SD)
RV (L)	Mean (SD)	Mean (SD)	Mean (SD)
Alveolar volume (L)	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
TLCOc (CO/min/kPa)	Mean (SD)	Mean (SD)	Mean (SD)
TLCOc % predicted (%)	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
KCOc (CO/min/kPa)	Mean (SD)	Mean (SD)	Mean (SD)
KCOc % predicted (%)	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
Immunoglobulins			
IgG (g/L)	Mean (SD)	Mean (SD)	Mean (SD)
IgA (g/L)	Mean (SD)	Mean (SD)	Mean (SD)
IgM (g/L)	Mean (SD)	Mean (SD)	Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)
6 Minute walk distance (m)	Mean (SD)	Mean (SD)	Mean (SD)
SF36 (score)	Mean (SD)	Mean (SD)	Mean (SD)

Scleroderma Health Assessment (score)	Mean (SD)	Mean (SD)	Mean (SD)
Kings Brief ILD (score)	Mean (SD)	Mean (SD)	Mean (SD)
St George's Respiratory Questionnaire (score)	Mean (SD)	Mean (SD)	Mean (SD)
EQLD (score)	Mean (SD)	Mean (SD)	Mean (SD)
Modified Rodnan Skin Score (score)	Mean (SD)	Mean (SD)	Mean (SD)
Global Disease Activity Scale (score)	Mean (SD)	Mean (SD)	Mean (SD)

Table 3: Number of adverse events by phase, classification, relationship to study medication and treatment group

Phase	Classification	Relation	Rituximab	Cyclophosphamide	Total
Screening	Not serious	Not related *	# events	# events	# events
	Serious	Not related *	# events	# events	# events
Treatment emergent	Not serious	Not related * Related **	# events	# events	# events
	Serious	Not related * Related **	# events	# events	# events
Post treatment	Not serious	Not related * Related **	# events	# events	# events
	Serious	Not related * Related **	# events	# events	# events
Post study	Not serious	Not related * Related **	# events	# events	# events
	Serious	Not related * Related **	# events	# events	# events

⋆ relationship to study medication is unrelated or unlikely

** relationship to study medication is possible, probable or definite

Table 4: Number of patients with adverse events by MedDRA term and treatment group

RITUXIMAB (N=)		Mild		Moderate		Severe		Total	
System organ class	**Event**	**Related**	**Not related**	**Related**	**Not related**	**Related**	**Not related**	**Related**	**Not related**
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CYCLOPHOSPHAMIDE (N=)		**Mild**		**Moderate**		**Severe**		**Total**	
System organ class	**Event**	**Related**	**Not related**	**Related**	**Not related**	**Related**	**Not related**	**Related**	**Not related**
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Table 5: Common treatment emergent adverse events by treatment group

Event	Rituximab	Cyclophosphamide	Total
	n(%)	n(%)	n(%)

Table 6: Completeness of FVC data by underlying CTD diagnosis, time and treatment group

	Rituximab - subjects	Rituximab – FVC data	Cyclophosphamide - subjects	Cyclophosphamide – FVC data
Systemic sclerosis Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Week 48	N miss(%)*	N† miss(%)	N miss(%)*	N¬ miss(%)
Idiopathic interstitial myopathy Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Week 48				
Mixed Connective Tissue Disease Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Week 48				
Total Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Week 48				

* number of subjects with at least one missing FVC measurement(%)

† number of expected FVC measurements

¬ number of missing FVC measurements(%)

Table 7: Distribution of completeness of FVC data at 24 weeks by underlying CTD diagnosis and treatment group

Number of missing FVC measurements	Rituximab – subjects (N =)	Cyclophosphamide – subjects (N =)
Systemic sclerosis 0 1 2 3 4 5-6 7+	n(%)	n(%)
Idiopathic interstitial myopathy 0 1 2 3 4 5-6 7+		
Mixed Connective Tissue Disease 0 1 2 3 4 5-6 7+		
Total 0 1 2 3 4 5-6 7+		

Table 8: Primary and secondary outcomes (excluding survival analyses) by treatment group

Outcome	Rituximab (N =)	Cyclophosphamide (N =)	Rituximab – Cyclophosphamide*
Change in FVC at 24 weeks			
Continuous (mL, primary outcome)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI) P=
Decrease by >5%	n(%)		
Stay within ±5%	n(%)	n(%)	n(%)
Increase by >5%	n(%)	n(%)	n(%) P=
Decrease by >10%	n(%)	n(%)	n(%)
Stay within ±10%	n(%)		
Increase by >10%	n(%)	n(%)	n(%)
Change in FVC at 48 weeks	n(%)	n(%)	n(%) P=
Continuous (mL)	Mean (95%CI)	Mean(SD) (95%CI)	Mean P= (95%CI)
Change in DLCO			
At 24 weeks (mL)	Mean(SD)	Mean(SD)	Mean(SD) P=
At 48 weeks (mL)	Mean(SD)	Mean(SD)	Mean(SD) P=
Change in 6 minute walk distance			
At 48 weeks (m)	Mean(SD)	Mean(SD)	Mean(SD) P=
Change in SpO_2			
At 24 weeks (%, absolute)	Mean(SD)	Mean(SD)	Mean(SD) P=
At 48 weeks (%, absolute)	Mean(SD)	Mean(SD)	Mean(SD) P=
Change in QoL scores at 24 weeks			
SGRQ	Mean(SD)	Mean(SD)	Mean(SD) P=
SF36	Mean(SD)	Mean(SD)	Mean(SD) P=
K-BILD	Mean(SD)	Mean(SD)	Mean(SD) P=
Change in QoL scores at 48 weeks			
SGRQ	Mean(SD)	Mean(SD)	Mean(SD) P=
SF36	Mean(SD)	Mean(SD)	Mean(SD) P=
K-BILD	Mean(SD)	Mean(SD)	Mean(SD) P=

Total corticosteroid requirement over 48 weeks			
Change in scleroderma specific scores at 24 weeks			
Scleroderma Health Assessment	Mean(SD)	Mean(SD)	Mean(SD) P=
Modified Rodnan Skin Score	Mean(SD)	Mean(SD)	Mean(SD) P=
Change in scleroderma specific scores at 48 weeks			
Scleroderma Health Assessment	Mean(SD)	Mean(SD)	Mean(SD) P=
Modified Rodnan Skin Score	Mean(SD)	Mean(SD)	Mean(SD) P=

*difference between rituximab group and cyclophosphamide group; obtained as the coefficient of the treatment group variable in ANCOVA (continuous variables) or by simple subtraction of percentages (categorical variables). P-values obtained from ANCOVA model (continuous variables) or Chi-squared tests (categorical variables).

Table 9: Exploratory analysis: Change in FVC* by underlying CTD diagnosis

	Rituximab	Cyclophosphamide	Total
Systemic Sclerosis	Mean (SD)	Mean (SD)	Mean (SD)
Idiopathic interstitial myopathy	Mean (SD)	Mean (SD)	Mean (SD)
Mixed Connective Tissue Disease	Mean (SD)	Mean (SD)	Mean (SD)
Total	Mean (SD)	Mean (SD)	Mean (SD)

*Change in FVC is here calculated as the 24 week measurement less the baseline measurement for each individual subject

5.12. Figures to present

Figure 1 Overall survival by treatment group

<<Kaplan-Meier plot with a curve for each group, CI for hazard ratio and p-value>>

Figure 2 Survival by treatment group (disease related mortality only)

<<Kaplan-Meier plot with a curve for each group, CI for hazard ratio and p-value>>

Figure 3 Progression free survival by treatment group

<<Kaplan-Meier plot with a curve for each group, CI for hazard ratio and p-value >>

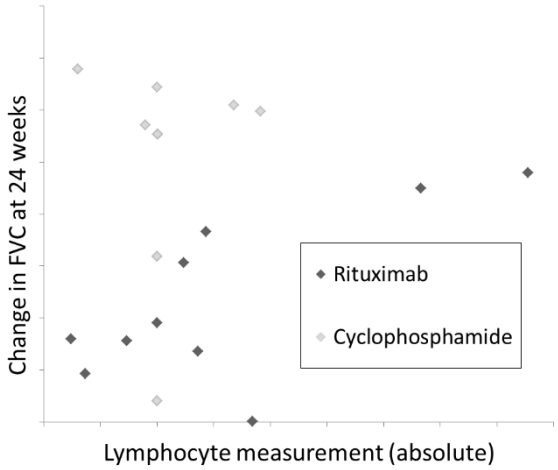
Figure 4 Treatment failure by treatment group

<<Kaplan-Meier plot with a curve for each group, CI for hazard ratio and p-value >>

Figure 4 Change in FVC* vs absolute lymphocyte levels by treatment group

Figure 4a CD3 +ve lymphocytes

<<Two-way scatter plot>>, eg:



(and similarly,

Figure 4b B lymphocytes

Figure 4c CD4 +ve lymphocytes

Figure 4d CD8 +ve lymphocytes

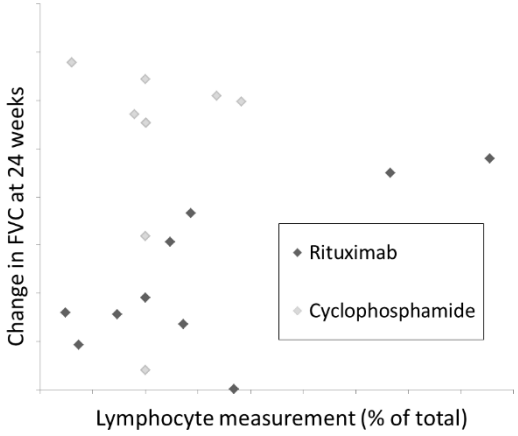
Figure 4e NK lymphocytes

Figure 4f Total lymphocytes)

Figure 5 Change in FVC* vs relative lymphocyte levels by treatment group

Figure 5a CD3 +ve lymphocytes as % of total

<<Two-way scatter plot>>, eg:



(and similarly,

Figure 5b B lymphocytes as % of total

Figure 5c CD4 +ve lymphocytes as % of total

Figure 5d CD8 +ve lymphocytes as % of total

Figure 5e NK lymphocytes as % of total

Figure 5f CD8:CD4 ratio)

*Change in FVC is here calculated as the 24 week measurement less the baseline measurement for each individual subject

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