Reduction of PRO-C3 and PRO-C6 fibrogenesis biomarkers in connective tissue disease-associated interstitial lung disease: results from the Phase IIb RECITAL trial

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Background

- Interstitial lung disease (ILD) is a major cause of morbidity and mortality in connective tissue disease (CTD)
- While cyclophosphamide is often an effective treatment for **CTD-ILD**, its use is limited by side effects
- Rituximab was tested as an alternative in the **RECITAL phase IIb trial** (NTC1862926)
- Both drugs **improved 24- and 48-week lung function** with **rituximab showing fewer adverse events** (Maher et. al, 2022. Lancet Resp Med)

Cyclophosphamide
- Effective treatment in CTD-ILD
- Side effects

Rituximab
- Rescue therapy in CTD-ILD
- Alternative?

Severe or progressive CTD-ILD

- Systemic sclerosis
- Idiopathic inflammatory myositis
- Mixed CTD

Rituximab
(1000 ng at weeks 0 and 2)

Cyclophosphamide
(600 mg/m^2 body surface area every 4th week for 6 doses)

Aim & Methods

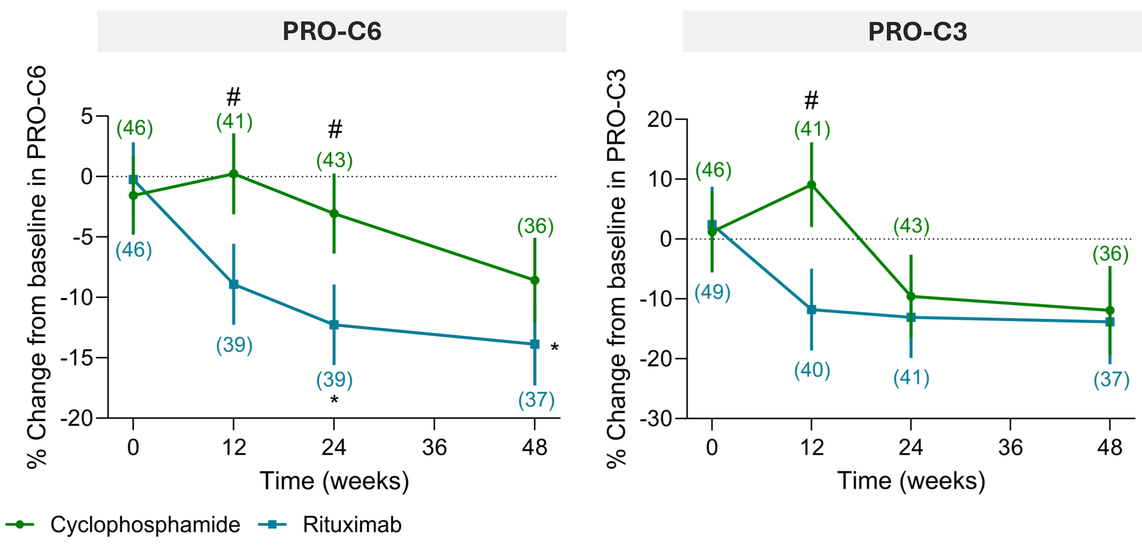
Evaluate the effect of cyclophosphamide and rituximab on fibrogenesis in CTD-ILD

Measure fibrogenesis biomarkers in serum from subjects enrolled in RECITAL at baseline, 12, 24 and 48 weeks after treatment

Biomarker	Description	Target
nordicPRO-C3™	Fibrillar collagen formation	Type III collagen pro-peptide
nordicPRO-C6™	Collagen formation (fibrogenesis)	Type VI collagen C-terminal (endotrophin)

Results

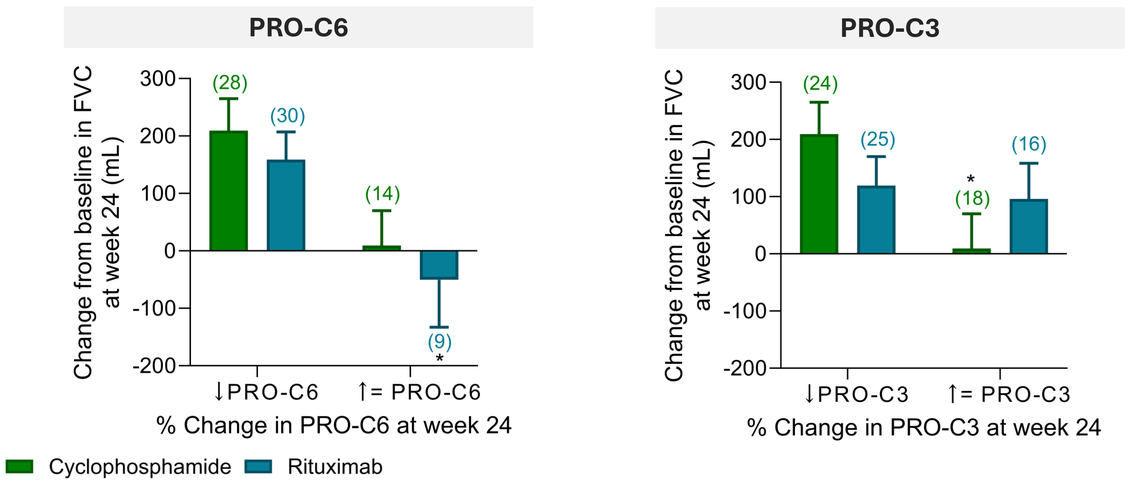
Longitudinal change of fibrogenesis biomarkers



Data were analysed by linear mixed models adjusted for age, sex and diagnosis and are shown as mean ± standard error.
* Indicates significant difference compared to week 0, # indicates significant difference compared to rituximab arm (p-value < 0.05).

Rituximab **reduced PRO-C6** levels at weeks 24 and 48

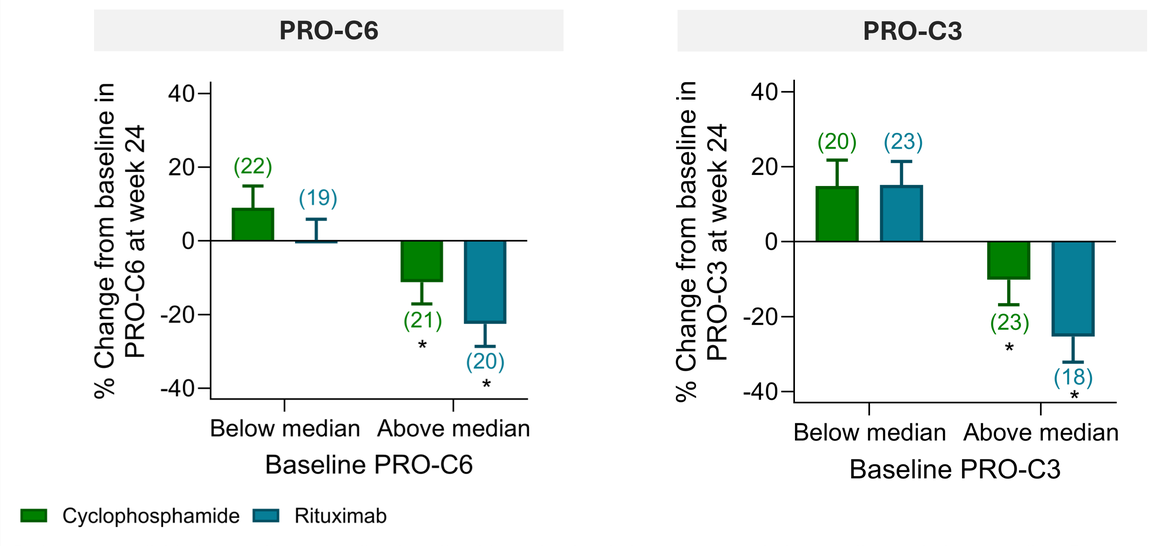
Change of fibrogenesis biomarkers and FVC at week 24



Patients were divided according to the % change from baseline (% CFB) in the biomarker level at week 24: ↓ PRO-C6/C3 (% CFB <0), ↑= PRO-C6/C3 (% CFB ≥ 0). Data were analysed by linear models adjusted for age, sex and diagnosis and are shown as mean ± standard error. * Indicates significant difference compared to ↓ PRO-C6/C3 group (p-value < 0.05). FVC: Forced Vital Capacity

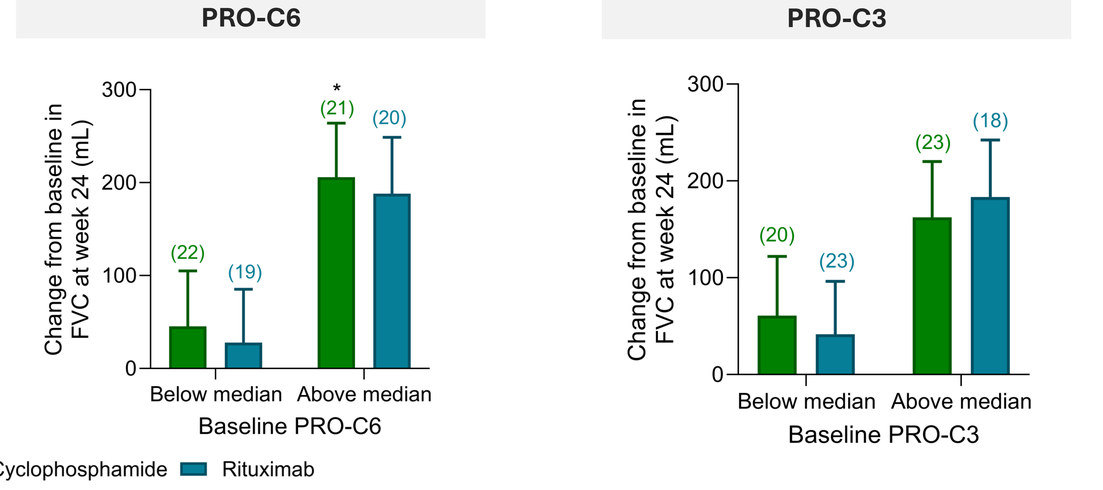
A **decrease** in **PRO-C6** and **PRO-C3** is associated with an **improvement in FVC** at week 24

Baseline fibrogenesis biomarkers and FVC response at week 24



Patients were divided according to median baseline biomarker levels in two groups: below median and above median. Data were analysed by linear models adjusted for age, sex and diagnosis and are shown as mean ± standard error. * Indicates significant difference compared to "Below median" group for the respective treatment

Patients having higher **baseline PRO-C3** and **PRO-C6** display a **greater biomarker reduction** at week 24



Patients were divided according to median baseline biomarker levels in two groups: below median and above median. Data were analysed by linear models adjusted for age, sex and diagnosis and are shown as mean ± standard error. * Indicates significant difference compared to "Below median" group for the respective treatment

A higher **baseline PRO-C3** and **PRO-C6** is associated with a **higher FVC increase** at week 24

Key Messages

- The decrease in PRO-C6 and PRO-C3 suggest that, besides their immunomodulatory effects, these drugs may also reduce fibrogenesis
- PRO-C3 and PRO-C6, measured at baseline and as % change from baseline, are associated with an FVC response

These findings highlight PRO-C3 and PRO-C6 as promising biomarkers for CTD-ILD

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Disclosures: FILS, JSA, MAK, and DJL are employed at Nordic Bioscience and may be shareholders