

**SUPPLEMENT ANNEX TO:****Mycophenolate and Azathioprine for interstitial lung disease: a systematic review and meta-analysis**

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**Supplemental Document 1 – PICO question**

Our PICO question is: “Does Mycophenolate or Azathioprine improve lung function in patients with interstitial lung disease?”

Population:

Patients with:

- Interstitial lung disease (ILD)
- Idiopathic Pulmonary Fibrosis (IPF)
- Connective tissue disease with ILD (CTD-ILD)

Intervents:

- Mycophenolate mofetil (MMF)
- Mycophenolic acid
- Enteric-coated mycophenolate sodium
- Azathioprine (AZA)

Comparators:

- Placebo, standard of care or other interventional drugs
- Change from baseline (FVC, DLco)

Outcome:

- Lung function
- Pulmonary function test (PFT)
- Forced vital capacity (FVC)
- Diffusion Lung capacity for carbon monoxide (DLco)

**Supplemental Document 2 – Search Strategy**

## Medline

1. exp Lung Diseases, Interstitial/
2. sarcoidosis/ or sarcoidosis, pulmonary/
3. (pulmonar\* adj (fibros\* or fibrot\*)).tw
4. (lung\* adj (fibros\* or fibrot\*)).tw.
5. (Interstitial Lung Disease\* or Pulmonary Fibrosis or Diffuse Lung Parenchymal Disease\* or Sarcoidosis or Sarcoid or ILD or fILD or IPF or PFILD or PPF or DLPD or DLPDs).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Connective Tissue Diseases/
8. scleroderm\*.tw.
9. systemic sclerosi\*.tw.
10. (CTD or LES or RA or SS or SSc).tw.
11. 7 or 8 or 9 or 10
- 12. 6 or 11**
13. Mycophenolic Acid/
14. (Mycophenolate Mofetil or Mycophenolic Acid or Morpholinoethyl Ester or Cellcept or Mycophenolate Sodium or Sodium Mycophenolate or Myfortic or Mycophenolate Mofetil Hydrochloride or MMF).tw
15. 13 or 14
16. Azathioprine/
17. (Imurel or Imuran or Immuran or Azathioprine Sodium or Sodium, Azathioprine or Azathioprine Sodium Salt or Azathioprine Sulfate or AZA).tw
18. 16 or 17
- 19. 15 or 18**
20. exp Respiratory Function Tests
21. (Vital Capacit\* or Lung capacit\* or Diffusing capacit\*).tw.
22. (Lung function or Pulmonary function or Respiratory function).tw.
23. (FVC or DLco or TLco or Kco).mp.
- 24. 20 or 21 or 22 or 23**
- 25. 12 and 19 and 24**

## Embase

1. exp interstitial lung disease/
2. exp lung sarcoidosis/
3. (pulmonar\* adj (fibros\* or fibrot\*)).tw.
4. (lung\* adj (fibros\* or fibrot\*)).tw.
5. (Interstitial Lung Disease\* or Pulmonary Fibrosis or Diffuse Lung Parenchymal Disease\* or Sarcoidosis or Sarcoid or ILD or fILD or IPF or PFILD or PPF or DLPD or DLPDs).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp connective tissue diseases/
8. scleroderm\*.tw.
9. systemic sclerosi\*.tw.
10. (connective tissue disease\* or CTD or systemic lupus erythematosus or LES or rheumatoid arthritis or RA or myositis or Sjogren's syndrome or SS).tw.
11. 7 or 8 or 9 or 10
12. **6 or 11**
13. exp mycophenolic acid/
14. (Mycophenolate Mofetil or Mycophenolic Acid or Morpholinoethyl Ester or Cellcept or Mycophenolate Sodium or Sodium Mycophenolate or Myfortic or Mycophenolate Mofetil Hydrochloride or MMF).tw
15. 13 or 14
16. exp azathioprine/
17. (Imurel or Imuran or Immuran or Azathioprine Sodium or Sodium, Azathioprine or Azathioprine Sodium Salt or Azathioprine Sulfate or AZA).tw
18. 16 or 17
19. **15 or 18**
20. exp lung function test/
21. (Vital Capacit\* or Lung capacit\* or Diffusing capacit\*).tw.
22. (Lung function or Pulmonary function or Respiratory function).tw.
23. (FVC or DLco or TLco or Kco).mp.
24. **20 or 21 or 22 or 23**
25. 12 and 19 and 24

### Supplemental Document 3 – Ongoing trials

#### **Mycophenolate Mofetil in Systemic Sclerosis With Subclinical Interstitial Lung Disease (SSc-mILD)**

**[NCT05785065]**: phase II pilot RCT to evaluate the feasibility of a phase III trial to assess the effectiveness of MMF in subclinical SSc-ILD. It is not recruiting yet. They calculated a sample size of 35 patients, randomized 1:1 to MMF or placebo. The rate of FVC% decline is a secondary outcome.

#### **Clinical Study of MMF in Treatment of IIM-ILD and Its Effect on Peripheral Blood Treg Cells**

**[NCT05129410]**: pilot phase IV interventional open-label study to assess the effect of MMF on IIM-ILD and Treg cells. FVC% change will be evaluated as primary outcome at 12 months follow up.

#### **An RCT of Mycophenolate Mofetil (MMF) in Fibrotic Hypersensitivity Pneumonitis (MYCOHYPE)**

**[NCT05626387]**: a randomized open label phase IV trial to assess the safety and the efficacy of MMF and prednisolone in fibrotic HP. 144 patients will be randomized 1:1 to intervention vs prednisolone alone. The primary outcome is the annual rate of FVC decline.

#### **MPA AUC Monitoring in Patients Receiving MMF for Diffuse Cutaneous or Pulmonary Involvement in Systemic Sclerosis (SCLERAMAC) [NCT04244916]**

**[NCT04244916]**: cohort study that is recruiting 50 patients to define the value AUC MPA to improve the skin disease and the lung function in SS. Change in FVC after 1 year of treatment is a secondary outcome.

Supplemental Table 1 – Characteristics of excluded full texts

Author	Title	Year	Type of study	Treatment	Overall population	# record	Reason of exclusion
<b>Bejan-Angoulvant</b>	Evaluation of efficacy and safety of rituximab in combination with mycophenolate mofetil in patients with nonspecific interstitial pneumonia non-responding to a first-line immunosuppressive treatment (EVER-ILD): A double-blind placebo-controlled randomized trial	2020	Protocol registration	MMF + (rituximab or placebo)	122	54	It was incomplete because it is a protocol registration. The complete study, by Mankikian and al., has been published after our last search. It was included after checking new relevant papers (see PRISMA flowchart) and is cited as reference 12 in our manuscript.
<b>Cegla</b>	Therapy of the idiopathic fibrosis of the lung. Experiences with three therapeutic principles: corticosteroids in combination with azathioprine, D penicillamine and K paraaminobenz oate	1975	Pilot study	Corticosteroids + (AZA or penicillamine or paraaminebenz oate)	27	272 1	High doses of steroid were administered.
<b>Fischer</b>	Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease	2013	Retrospective study	MMF	125	144	Retrospective selection of patients already treated (median duration of treatment: 897 days).

<b>Hoyles</b>	A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma	2006	Randomized double-blind trial	Prednisolone + cyclophosphamide + AZA	45	186	High doses of steroids and cyclophosphamide were administered
<b>Karampitsakos</b>	Safety and Effectiveness of Mycophenolate Mofetil in Interstitial Lung Diseases: Insights from a Machine Learning Radiographic Model	2022	Observational study	MMF	55	34 and 714	Retrospective selection of patients treated at least for 1 year.
<b>Pavlov-Dolijanovic</b>	Long-term effects of immunosuppressive therapy on lung function in scleroderma patients	2018	Open label trial	Prednisolone + cyclophosphamide.  AZA or MMF or methotrexate as maintenance therapy	30	87	High doses of steroids were administered. MMF or AZA are administered as maintenance therapy and there is not a comparative group.
<b>Raghu</b>	Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial	1991	Randomized double-blind controlled trial	Prednisone + (AZA or placebo)	27	216	High doses of steroids were administered.

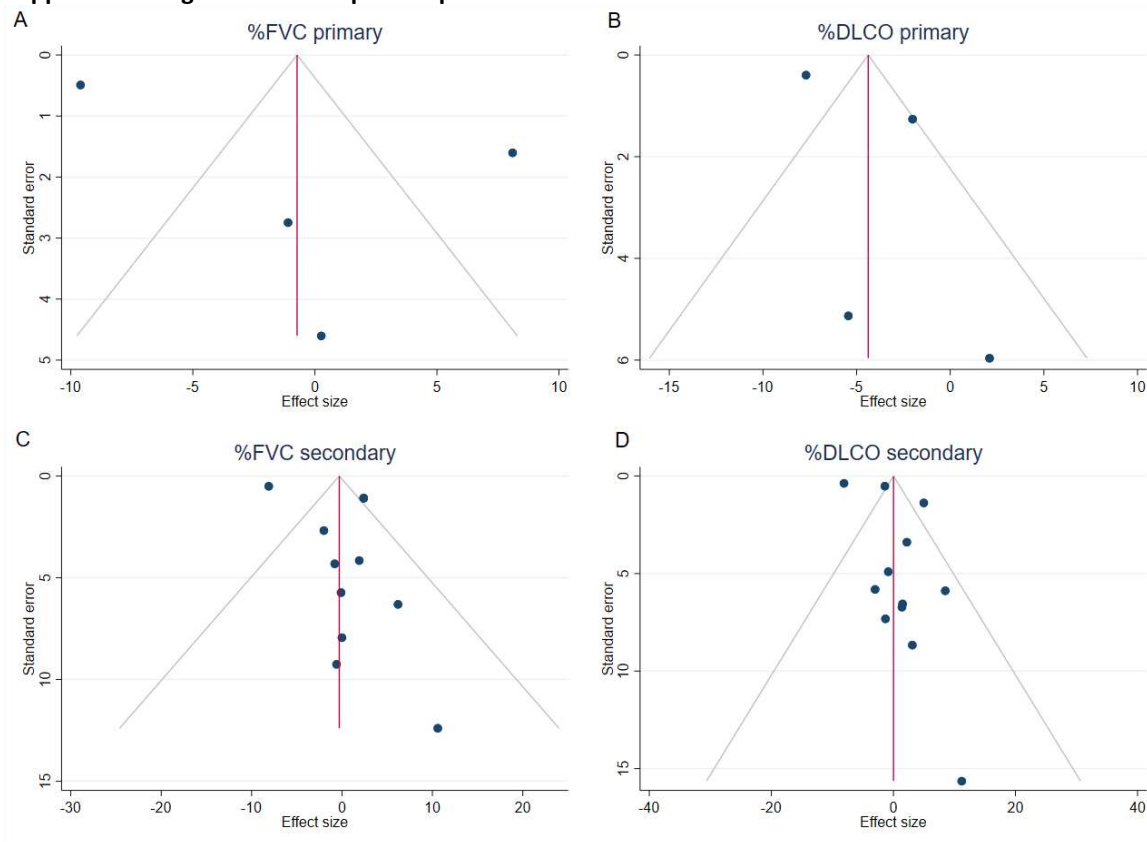


<b>Stratton</b>	Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma	2001	Pilot study	Anti-thymocyte globulin + MMF	13	203	The clear effect of MMF alone is not available or evaluable.
<b>Tashkin</b>	Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial	2016	Randomized double-blind controlled trial	MMF versus CYC	142	113	We included the post-hoc analysis of Volkmann (reference #19) which compares MMF arm (SLS II) and placebo arm (SLS I). Tashkin study was excluded to avoid issues in independence of observations.  This study has been noted as "incomplete" in PRISMA flowchart as a more updated dataset was available.
<b>Vanthuyne</b>	A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis	2007	Pilot study	MMF + intravenous methylprednisolone + glucocorticoids	16	2416	High dose of steroids were administered.
<b>Volkmann</b>	Treatment With Mycophenolate and Cyclophosphamide Leads to Clinically Meaningful Improvements in Patient-Reported Outcomes in Scleroderma Lung Disease: Results of Scleroderma Lung Study II	2020	Post hoc analysis	Cyclophosphamide + MMF	142	21	Evaluated patient reported outcomes in combination therapy, excluded due lack of measurement of interest

**Supplemental Table 2 - Newcastle – Ottawa Quality assessment scale for cohort studies**

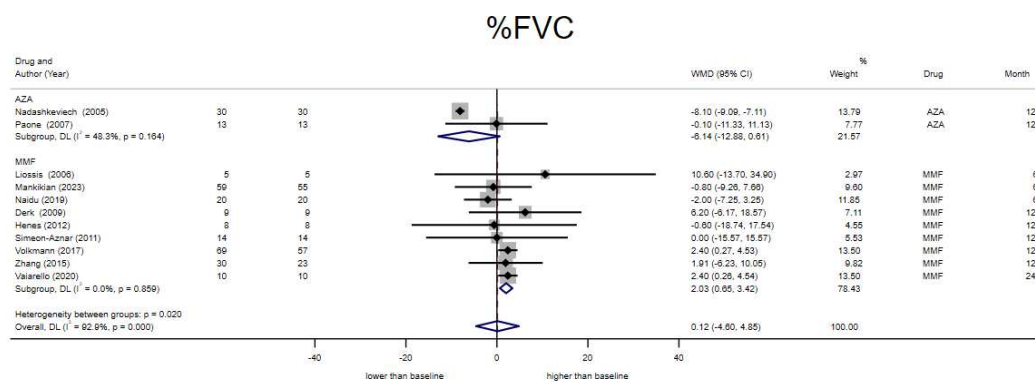
	Selection Bias				Comparability		Outcome		TOT	
	Representativeness of cohort	Selection of the non exposed	Ascertainment of exposure	Outcome not present at the start	Main factors	Additional factors	Assessment	Follow-up length		Adequacy of FU cohort
Derk (2009)	*	*	*	*	*	*	*	*	-	8
Henes (2012)	*	*	-	*	*	*	*	*	-	7
Liossis (2006)	*	-	-	*	*	*	*	-	*	6
Mendoza (2012)	-	*	-	*	*	*	*	*	-	6
Paone (2007)	*	*	-	*	*	*	*	*	*	8
Simeon-Aznar (2011)	*	*	-	*	*	*	*	*	*	8
Vaiarello (2020)	*	*	-	*	*	*	*	*	*	8

**Supplemental Figure 1 - Funnel plot for publication bias inclusive of all MMF and AZA studies**

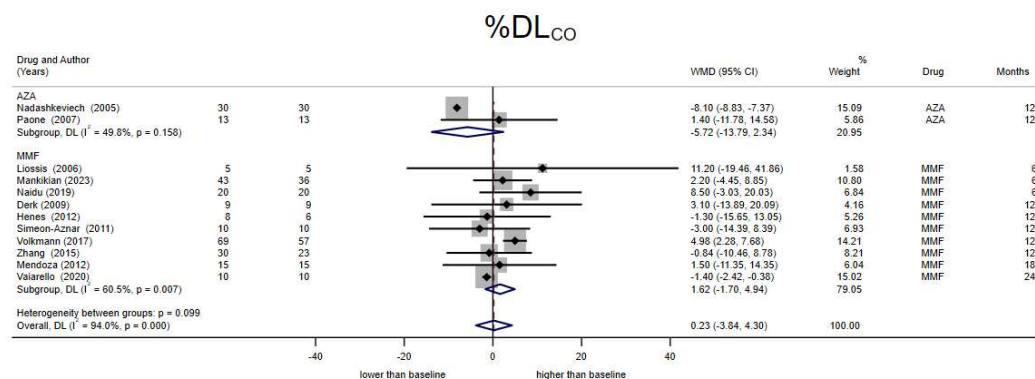


**Supplemental Figure 2 - Secondary endpoint analysis of efficacy on pulmonary function compared to baseline with summary estimate by drug subgroup**

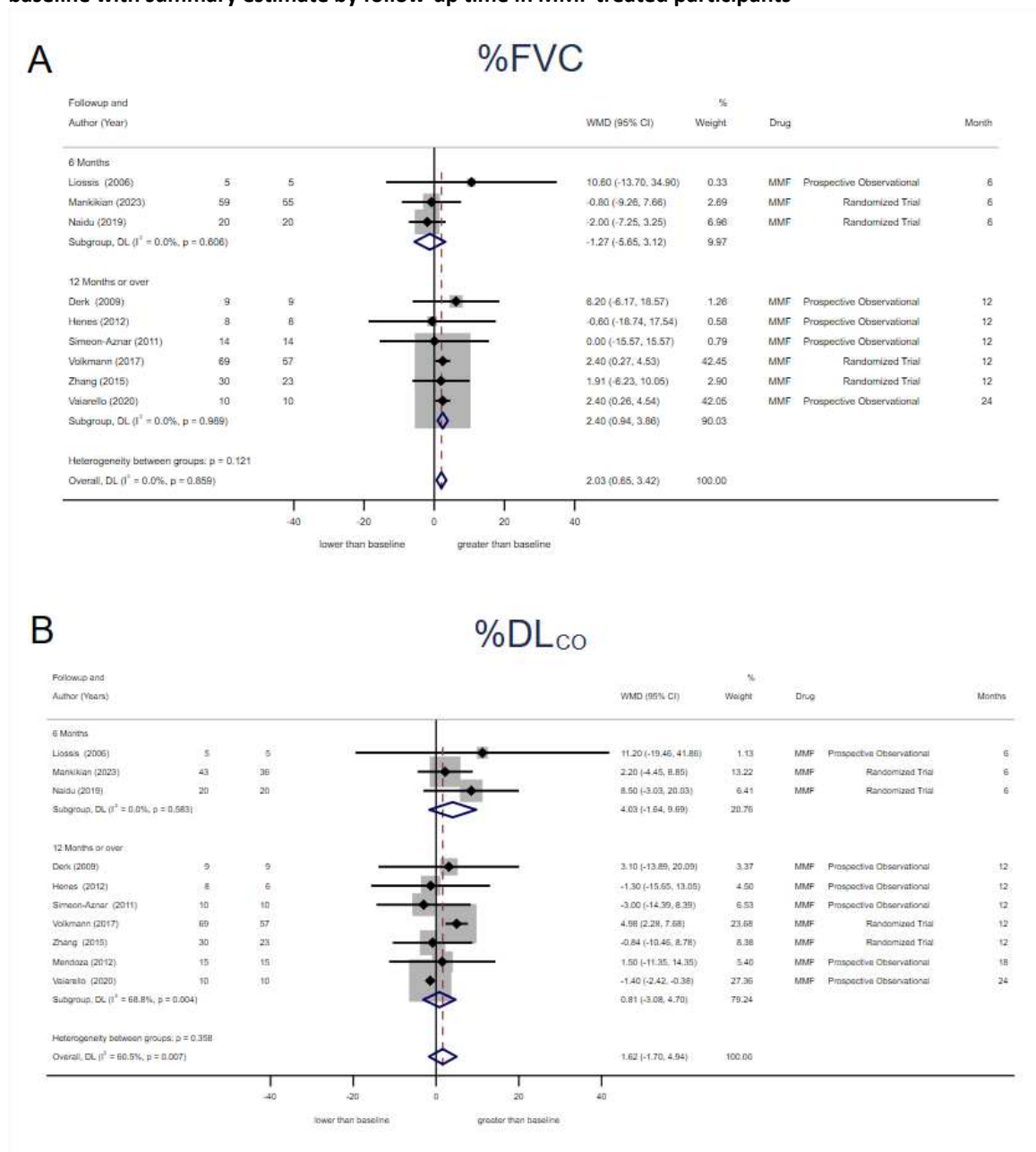
**A**



**B**



**Supplemental Figure 3 - Secondary endpoint analysis of efficacy on pulmonary function compared to baseline with summary estimate by follow-up time in MMF treated participants**



**Supplemental Table 3 – Table of adverse events**

Author	Diarrhoea	Nausea/ Vomit	Dyspepsia	Skin infection	Pansinusitis	Pneumonia	Pleuritis	UTRI	Non infectious respiratory tract disorder	Cardiac disorder	Lympho penia/Le ukopeni a	Anaemia	Otitis media	Hematuria	UTI	Oral Candidosis
Derk	2			3		1										
Henes		3			1											
Liopsis							1									
Mankikian									12	2						
Mendoza	3							3			2				2	
Nadashkevich		3	2								2		1			
Naidu	15			4		2		5				1			2	
Paone																
Rolg											2					
Simeon-Aznar						1										
Vaiarello																
Volkman						5					4	8		3		
Zhang				2		10		2							1	1

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