Meta-Analysis of Lung Capacity and Skin Thickening in Interstitial Lung Disease

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ILD Meta-analysis overview

Interstitial Lung Disease (ILD) is a group of disorders that cause lung inflammation and scarring, making it difficult to breathe and get oxygen into the bloodstream.

Goal: To determine the efficacy of currently approved or in pipeline ILD drugs for drug development benchmarking

Literature Search → PICOS

- Both monotherapy and drugs in combination studies were included in the search. Clinical trials were selected relating to the use of nintedanib, tociluzumab, rituximab, lenabasum, prednisolone, pirfenidone, cyclophosphamide, and mycophenolate mofetil. Only Phase 2/3 randomized, placebo or active controlled studies were included in the search.

PICOS		
Population	Demographics	Adults; mixed connective tissue diseases. Exclude pulmonary hypertension
	Disease	Interstitial lung disease (ILD)with mixed connective tissue disease. Excluding exposure
	Sub Populations	RA, Scleroderma, Mixed Connective Tissue Disease, Polymyositis, Dermatomyositis,
	Covariates	corticosteroids, methotrexate, rituximab, mycophenolate mofetil, cyclophosphamide,
Interventions	Primary	corticosteroids, methotrexate, mycophenolate mofetil, cyclophosphamide,
	Secondary	oxygen
	Background	
	Prior	
	Post Search Interventions	
Comparators	Placebo/SoC/Drug of Interest	Placebo, SoC, nintedanib, MEDI-551, BIBF 1120, actemra, tociluzumab, rituximab,
Outcomes	Main Outcomes	(FVC or "forced vital capacity" or mRSS or "modified Rodnan Skin Score" or DLCO or "diffusing capacity of the lung for carbon monoxide" or CRP or C-reactive protein or hsCRP or hs-CRP or "High-sensitivity C-reactive protein" or ESR or "erythrocyte sedimentation rate" or survival or "Kaplan Meier plot").mp
	Primary Endpoints	serum surfactant protein-D, serum KL-6, tissue biopsy, FACIT-Fatigue, HAQ-DI
	Secondary Endpoints	ACR-CRISS, St. George's Respiratory Questionnaire, high resolution CT scan changes,
Study Designs		Phase 2 and 3, randomized, double-blind, placebo controlled

Important endpoints in ILD

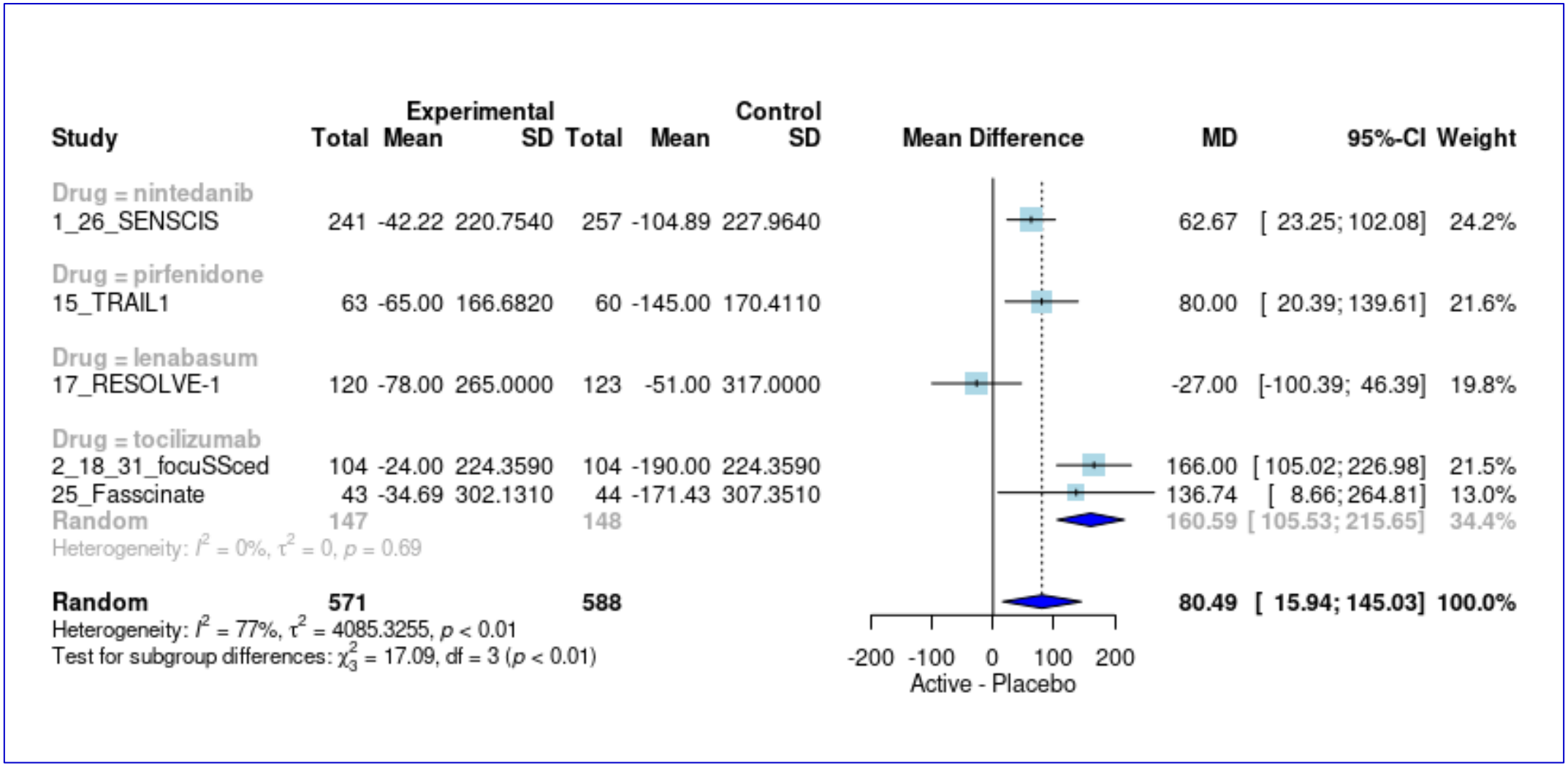
- **FVC**
  - Forced vital capacity (FVC) is the amount of air that can be forcibly exhaled from your lungs after taking the deepest breath possible (measured in milliliters (mL) of air). An increase in FVC is considered beneficial.
- **mRSS**
  - Skin thickness is quantified using the modified Rodnan measurement method (mRSS), with a scale that ranges from 0 (no skin involvement) to a maximum of 51. The reported skin score is determined by a clinical assessment of skin thickness, which is performed by a trained reader, and represents the sum of individual assessments that are made in each of 17 body areas. Each area is given a score in the range of 0-3 (0 = normal; 1= mild thickness; 2 = moderate; 3 = severe thickness). A higher score represents more severe skin involvement, meaning a decrease in mRSS is considered beneficial.
- **DLCO**
  - The DLCO measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries (measured in % change from baseline). An increase in DLCO is considered beneficial.

Literature search results

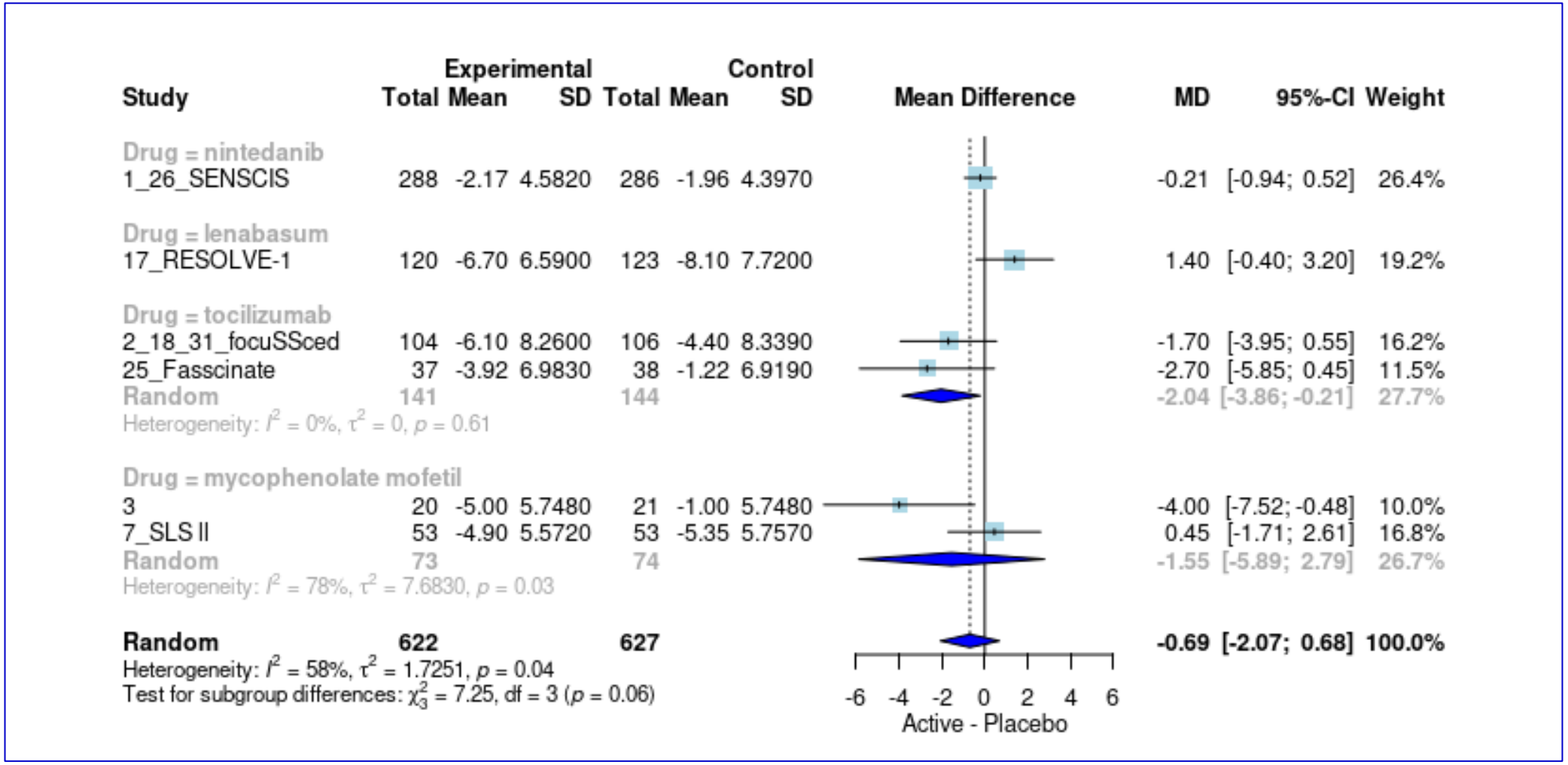
- 62 manuscripts were identified in the literature search. However, after systematic review, **19** studies representing **2070** subjects and **7** mixed connective tissue disorder subpopulations were included in the meta-analysis.

- Given the limited number of studies investigating ILD at the clinical trial level, the overall dataset was sparse but novel in its findings.

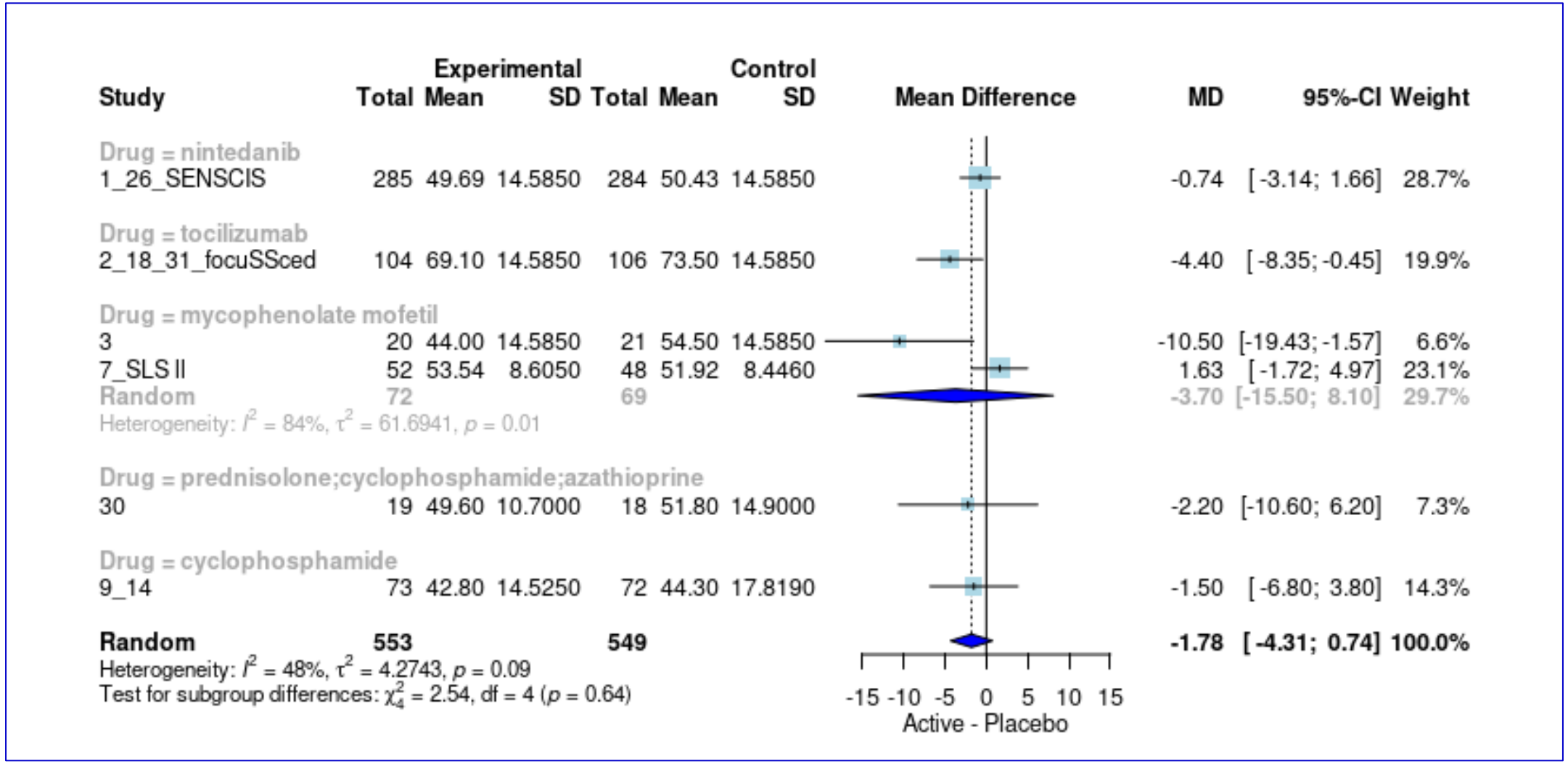
Results-FVC


Study
Experimental
Total Mean SD
Control
Total Mean SD
Mean Difference
MD 95%-CI Weight
Drug = nintedanib
1_26_SENSCIS 241 -42.22 220.7540 257 -104.89 227.9640 62.67 [23.25; 102.08] 24.2%
Drug = pirfenidone
15_TRAIL1 63 -65.00 166.6820 60 -145.00 170.4110 80.00 [20.39; 139.61] 21.6%
Drug = lenabasum
17_RESOLVE-1 120 -78.00 265.0000 123 -51.00 317.0000 -27.00 [-100.39; 46.39] 19.8%
Drug = tocilizumab
2_18_31_focuSSced 104 -24.00 224.3590 104 -190.00 224.3590 166.00 [105.02; 226.98] 21.5%
25_Fasscinate 43 -34.69 302.1310 44 -171.43 307.3510 136.74 [8.66; 264.81] 13.0%
Random 147 148 160.59 [105.53; 215.65] 34.4%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.69
Random 571 588 80.49 [15.94; 145.03] 100.0%
Heterogeneity: I^2 = 77%, τ^2 = 4085.3255, p < 0.01
Test for subgroup differences: χ^2_3 = 17.09, df = 3 (p < 0.01)
-200 -100 0 100 200
Active - Placebo

Results- mRSS



Results- DLCO



Conclusion

- For both FVC and mRSS, **tocilizumab showed the greatest magnitude of efficacy** with a mean difference in FVC of 160.59 ml (95% CI 105.53, 215.65) and a mean difference in skin thickening score points of -2.04 (95% CI -3.86, -0.21). In contrast, **lenabasum studies showed a negative change** in FVC and mRSS, suggesting poor patient outcomes in these areas.

- Although study information on ILD drugs is sparse, results from this meta-analysis provide a novel overview of the current drug landscape in ILD studies.

- **Overall, ILD drugs show clinically relevant improvement for FVC. However, impact on dermatological endpoints and oxygen transfer endpoints is marginal.**

- These findings suggest that there is marked room for improvement in ILD drug efficacy relating to FVC, mRSS and DLCO. Benchmarks identified for ILD endpoints are a valuable resource in the decision-making process for future drug development and clinical trial design.

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