Safety and Efficacy of Inhaled GM-CSF (Molgramostim) in Autoimmune Pulmonary Alveolar Proteinosis
- The IMPALA Trial -
Baseline Data and Blinded Treatment Period Results

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Disclosures

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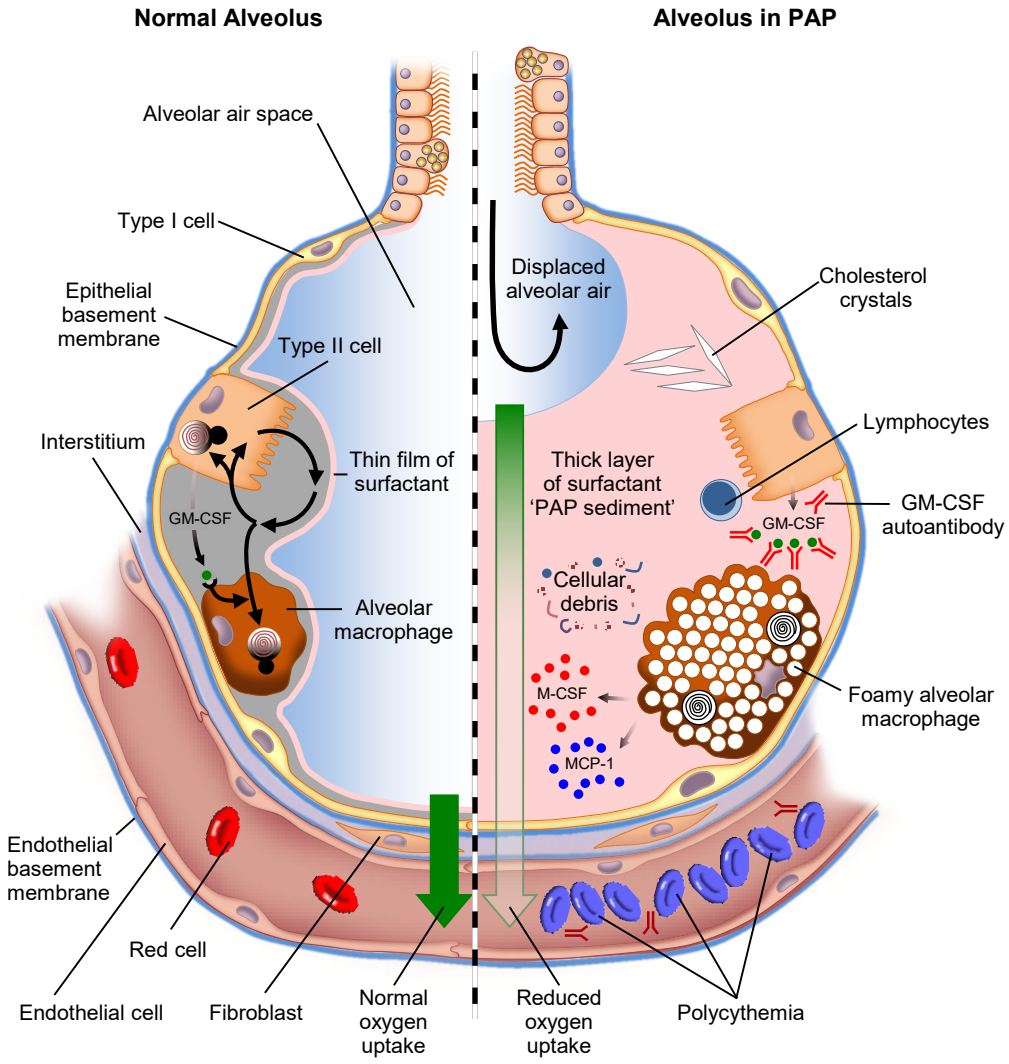
- I receive grant funding from the US National Institutes of Health
- I have consulted for: Boehringer Ingelheim, CSL Behring, Genzyme, Gilead, Grifols, GSK, Kiniksa, Medimmune, Merck, Savara, Sanofi, Takeda

Background: Autoimmune Pulmonary Alveolar Proteinosis (aPAP)

- aPAP is characterized by:
  - Pulmonary surfactant accumulation
  - Progressive hypoxemic respiratory failure
  - Increased PAP biomarkers
  - Polycythemia (systemic response to lung disease)
  - Increased infection risk (uncommon)
  - Pulmonary fibrosis (uncommon)
- GM-CSF is required to regulate alveolar macrophage
  - Differentiation
  - Functions
  - Population size
- GM-CSF autoantibodies cause aPAP by blocking stimulation of alveolar macrophages, which reduces their ability to clear surfactant



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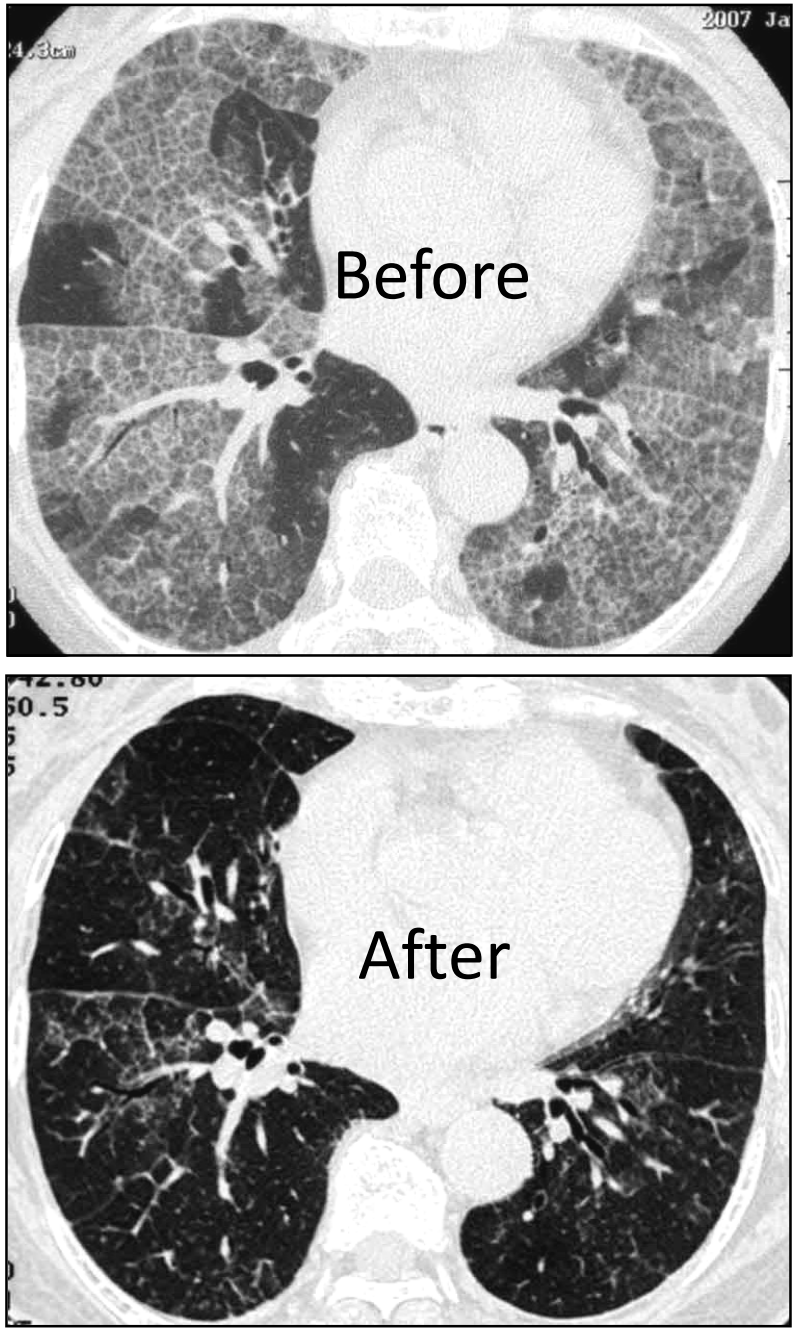
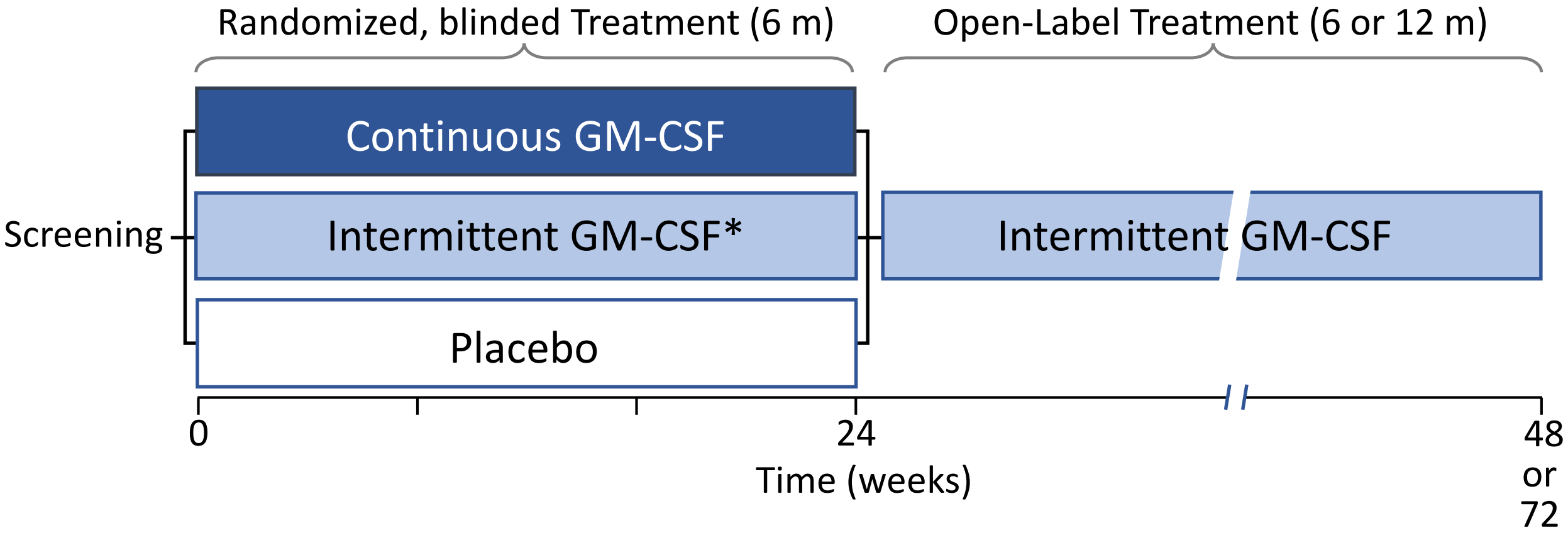
Background: Inhaled GM-CSF Therapy of aPAP

- 1996, Seymour: First patient treated with GM-CSF (SQ)
- 2000, Kavuru: 4 patients treated (SQ)
- 2001, Seymour: 14 patients treated (SQ)
- 2004, Aria: 1 patient treated (Inhaled)
- 2005, Tazawa: 3 patients treated (Inhaled)
- 2006, Wylam: 12 patients treated (Inhaled)
- 2005, Venkateshiah: 25 patients treated (SQ)
- 2010, Tazawa: 39 Patients treated (inhaled)
- 2014, Papiris: 6 Patients treated (inhaled)
- 2019, Tazawa: 64 Patients treated (inhaled)
- IMPALA Trial, 138 patients treated (inhaled)



Tazawa... 2010

Study Design of the IMPALA Trial



Study Groups

Continuous – Daily administration of inhaled GM-CSF (300 µg) (n=46)

Intermittent – Daily administration of GM-CSF (300 µg) every other week* (n=45)

Placebo – Daily administration (n=47)

*Placebo administered on 'off' weeks

Study Design: Endpoints

- **Safety**: Number of adverse events (AE) and serious adverse events (SAE)
- **Efficacy**: Change from baseline at 24 weeks in the following endpoints:

Disease element	Variable
• Pathology	• Chest CT ground glass opacification (GGO) score • Serum PAP biomarkers
• Physiology	• Alveolar-arterial difference in oxygen conc. (A-aDO_2)* • DLCO
• Health status & Function	• Saint Georges Respiratory Questionnaire (SGRQ) ** • Six-minute walk test - Distance**
• Rescue therapy requirement (Whole lung lavage - WLL)	• Time to first WLL** • Number of patients with WLL, Number of WLL
• Systemic response to chronic lung disease (polycythemia)	• Hemoglobin concentration

* = Primary end point, ** = Key Secondary end point

Baseline Characteristics: Demographics

Characteristic	Continuous	Intermittent	Placebo
Age, years	54.0 ± 13.3	49.2 ± 14.0	46.1 ± 14.8
Gender (Male), %	60.9	57.8	53.2
Smoking history, %			
Never smoker	28.3	35.6	34.0
Ex smoker	58.7	44.4	42.6
Current smoker	13.0	20.0	23.4
Geographic region, %			
Europe	34.8	46.7	70.2
Japan	43.5	22.2	21.3
USA	4.3	4.4	0
Other	17.4	26.7	8.5

Baseline Characteristics: Disease Severity

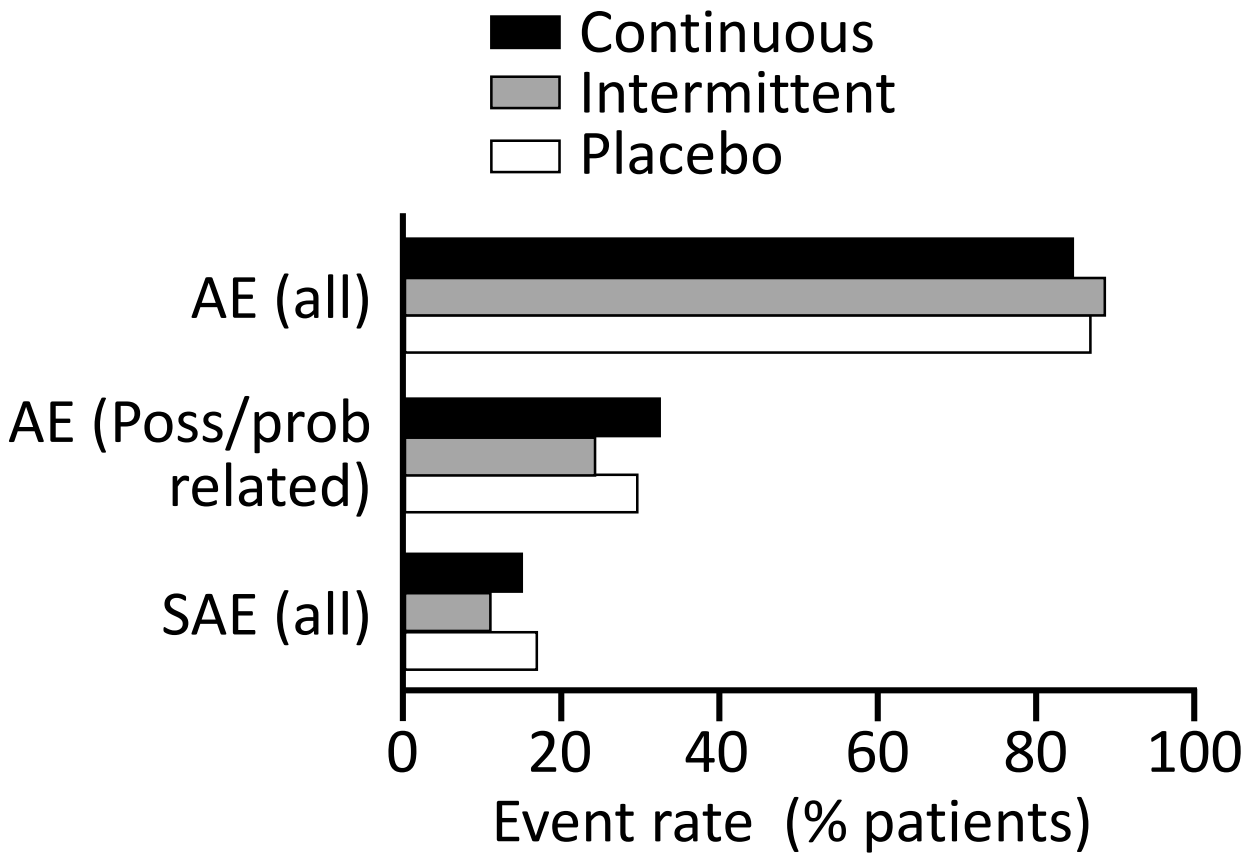
Characteristic	Continuous	Intermittent	Placebo
A-aDO_2*, mm Hg (FAS)	40.5 ± 19.6	40.9 ± 20.2	40.2 ± 14.3
DLCO, % predicted	52.1 ± 18.6	46.1 ± 14.5	49.6 ± 14.3
Disease severity score (DSS), %			
DSS 1 (Mild)	8.7	11.1	6.4
DSS 2	26.1	31.1	34.0
DSS 3	37.0	28.9	29.8
DSS 4	10.9	20.0	21.3
DSS 5 (Severe)	17.4	6.7	8.5
SGRQ Total score**	47.2 ± 20.4	44.4 ± 21.4	44.1 ± 21.7
6MWT-Distance**, m	412 ± 144	447 ± 117	447 ± 125
Vital capacity, % predicted	78.6 ± 32.2	74.8 ± 19.5	74.1 ± 18.6

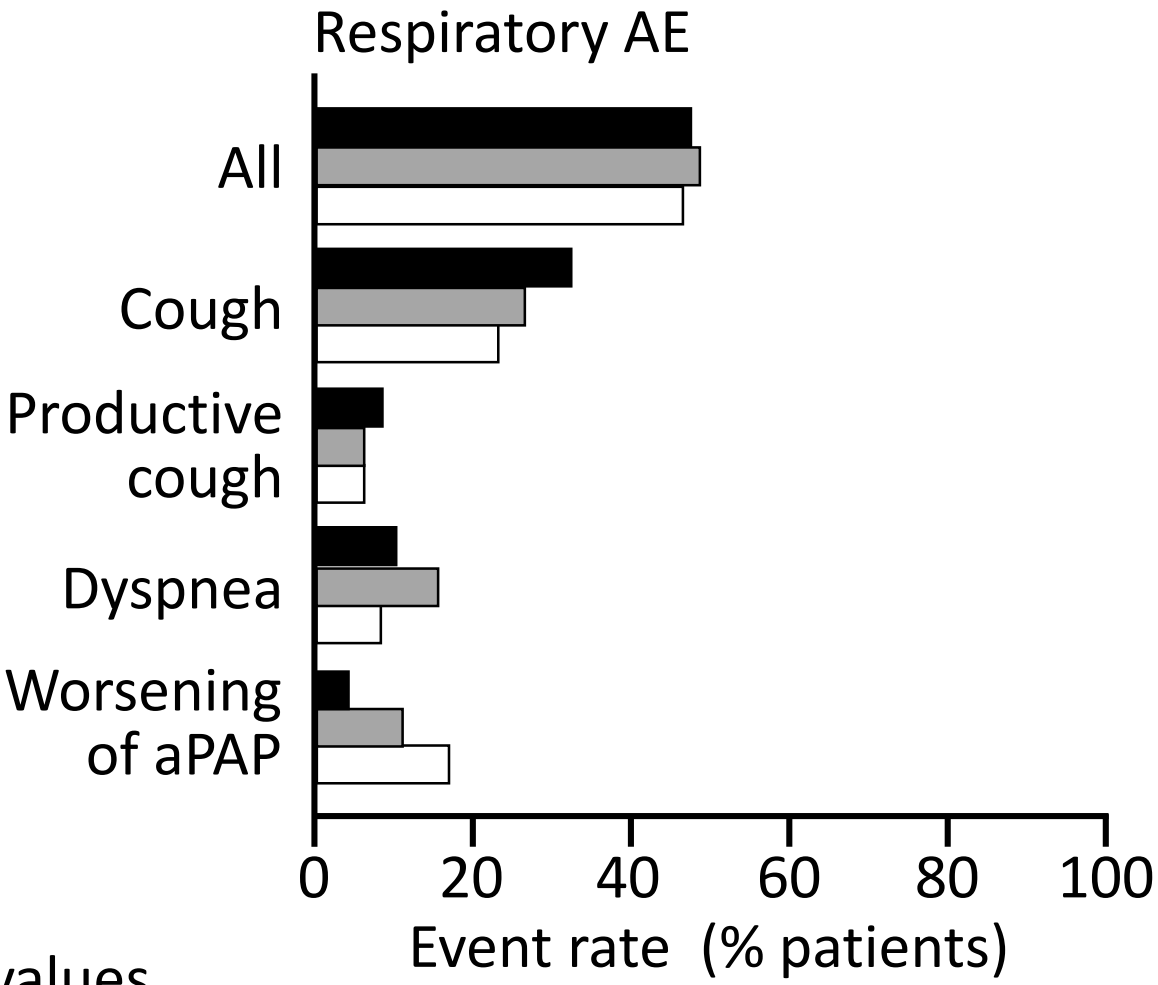
* = Primary end point, ** = Key Secondary end point

Baseline Characteristics: Previous Therapies

Characteristic	Continuous	Intermittent	Placebo
Supplemental oxygen use, %	32.6	26.7	23.4
Whole lung lavage			
Prior use of WLL (any), %	47.8	68.9	63.8
Total Number of WLLs	3.3 ± 2.2	3.3 ± 3.0	2.8 ± 3.0
Time since last WLL, m	25.0 ± 53.7	19.7 ± 27.4	17.7 ±20. 7
GM-CSF therapy (any), %	13.0	15.6	12.8

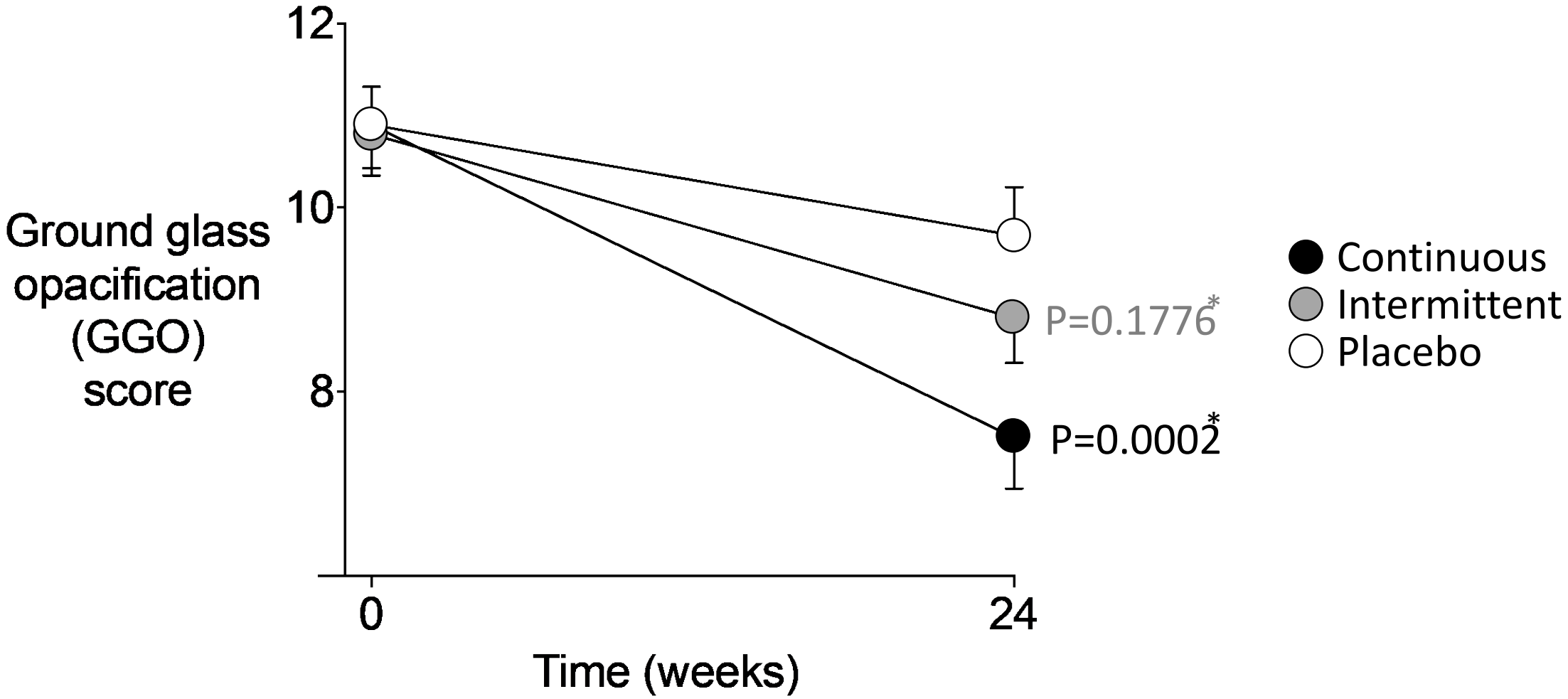
Safety: AE, SAE, and Respiratory AE Occurring in at least 5% of Patients





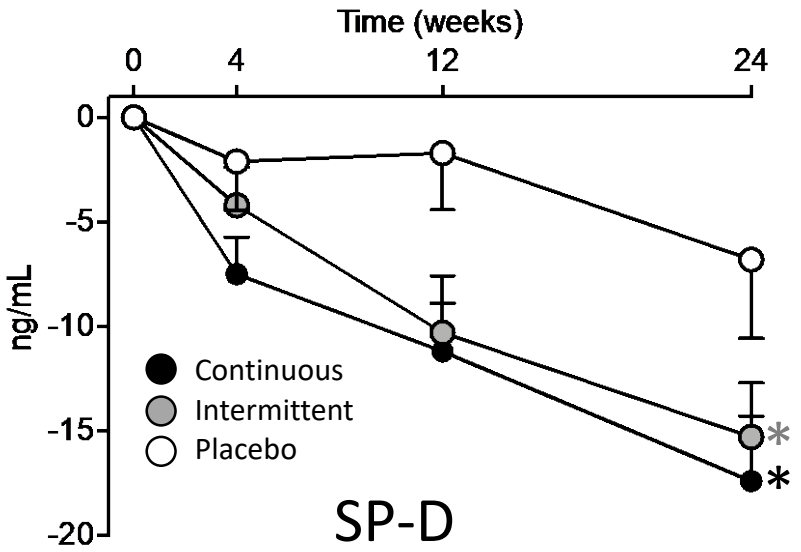
- No clinically significant changes in laboratory values
- No evidence of anti-drug antibody development
- Study completion: Continuous: 97.8%, Intermittent: 97.8%, Placebo: 91.5%

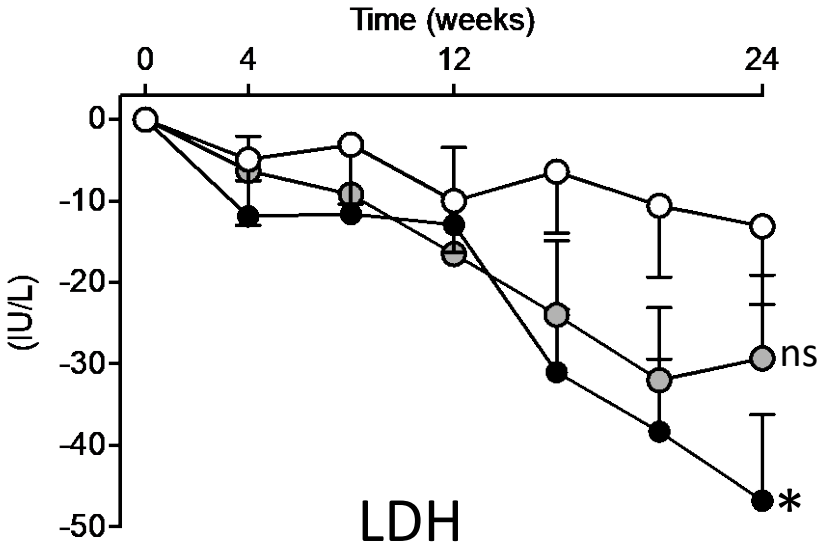
Pathology: GM-CSF Improved Chest CT GGO Score

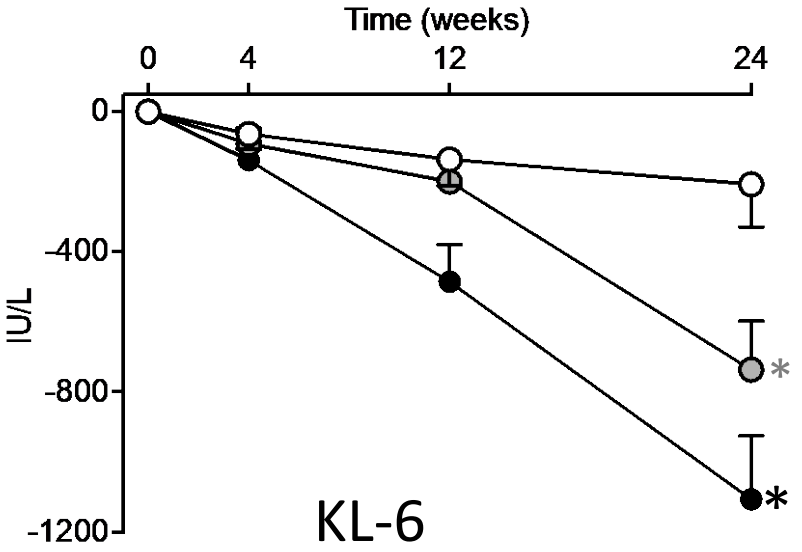


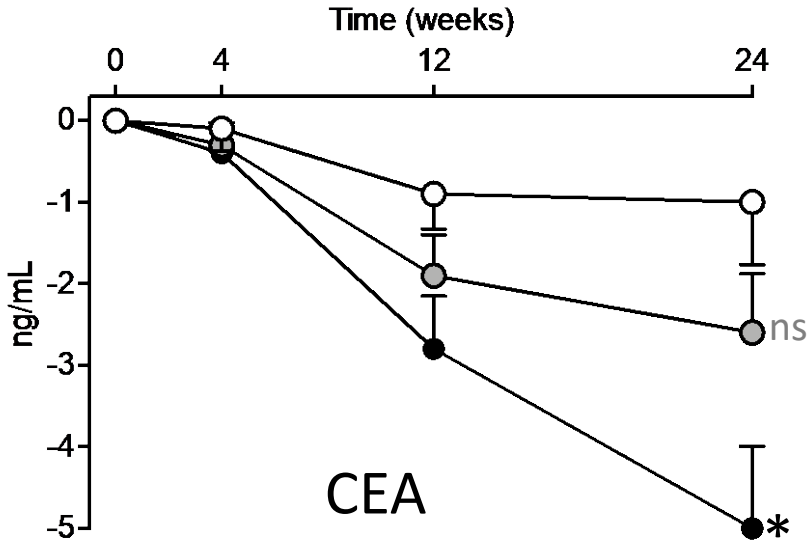
*Comparison to Placebo

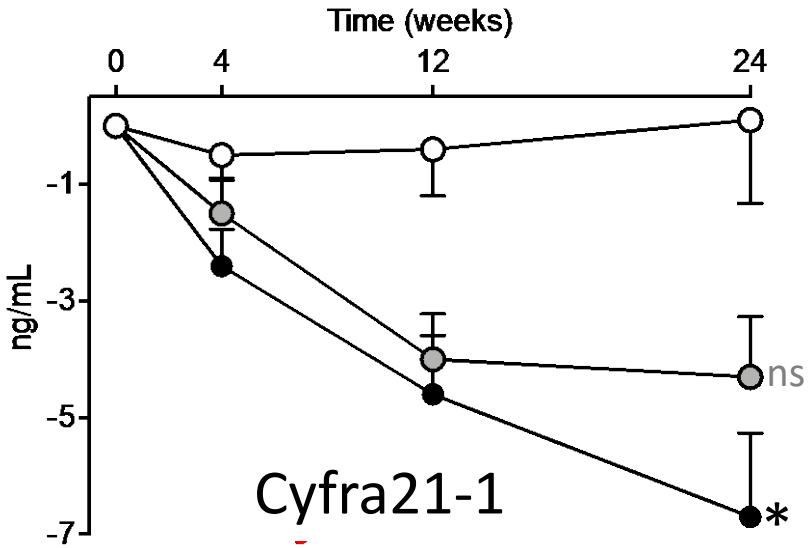
Pathology: GM-CSF Improved Serum Biomarkers

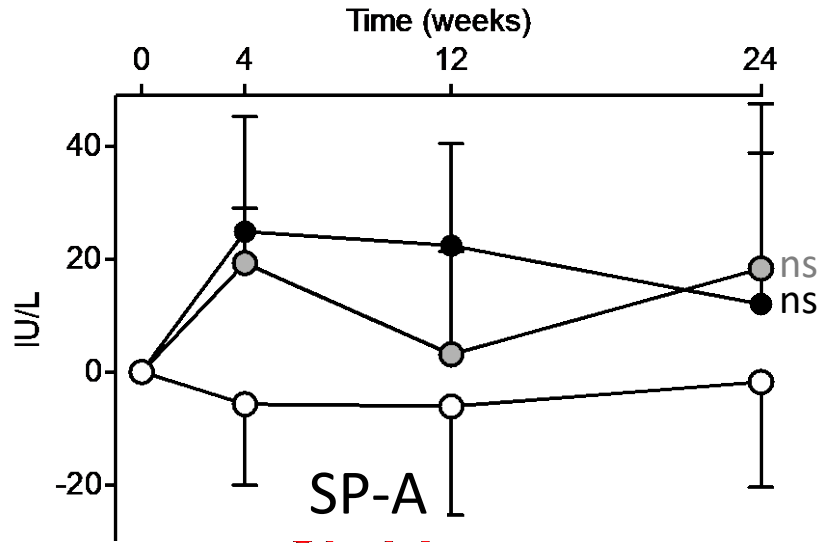






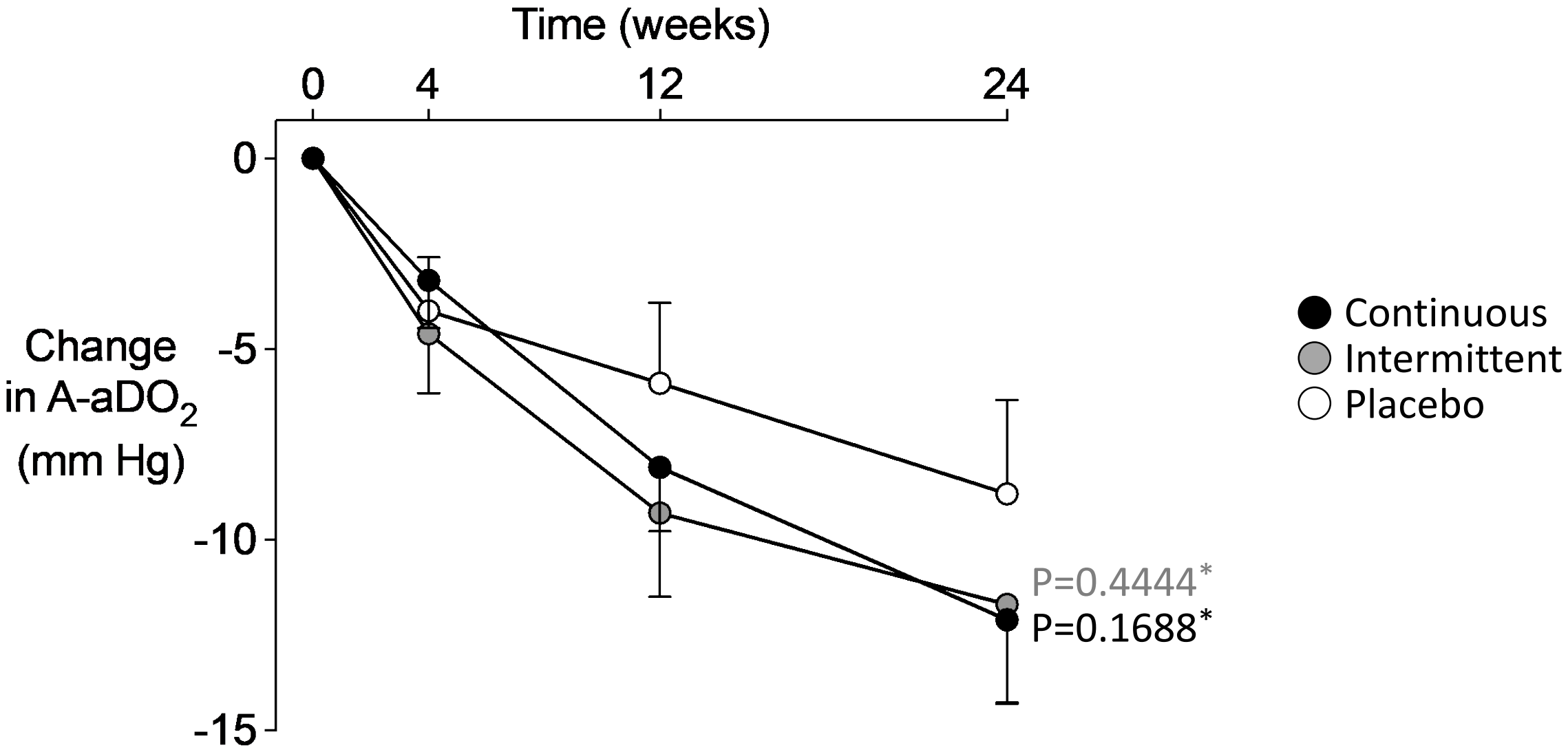






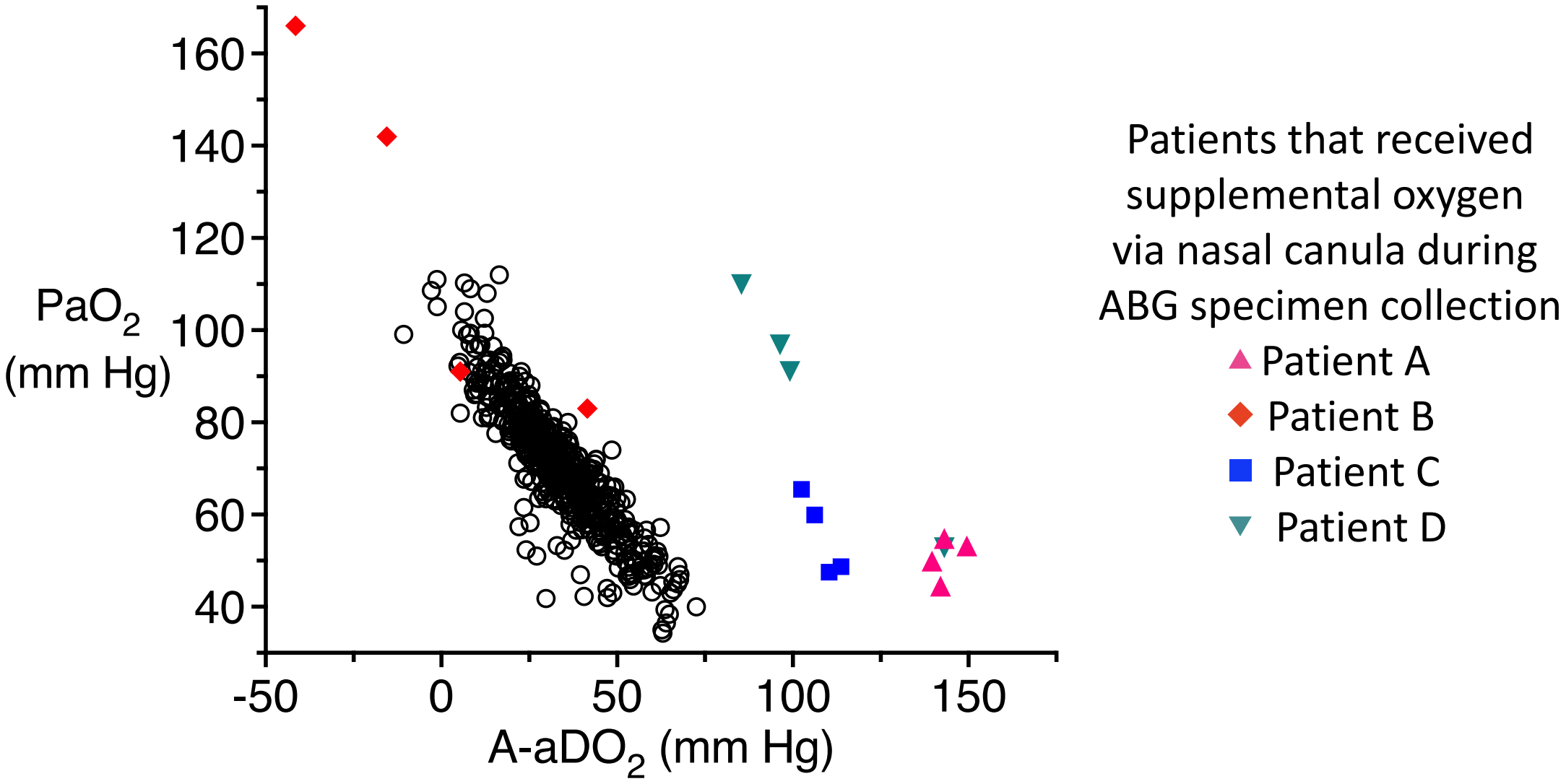
* = P<0.05, ns = P>0.05, comparison to Placebo

Physiology: GM-CSF Trended Towards Improvement in the Primary End Point ($A\text{-}aDO_2$) – Full Analysis Set (FAS)

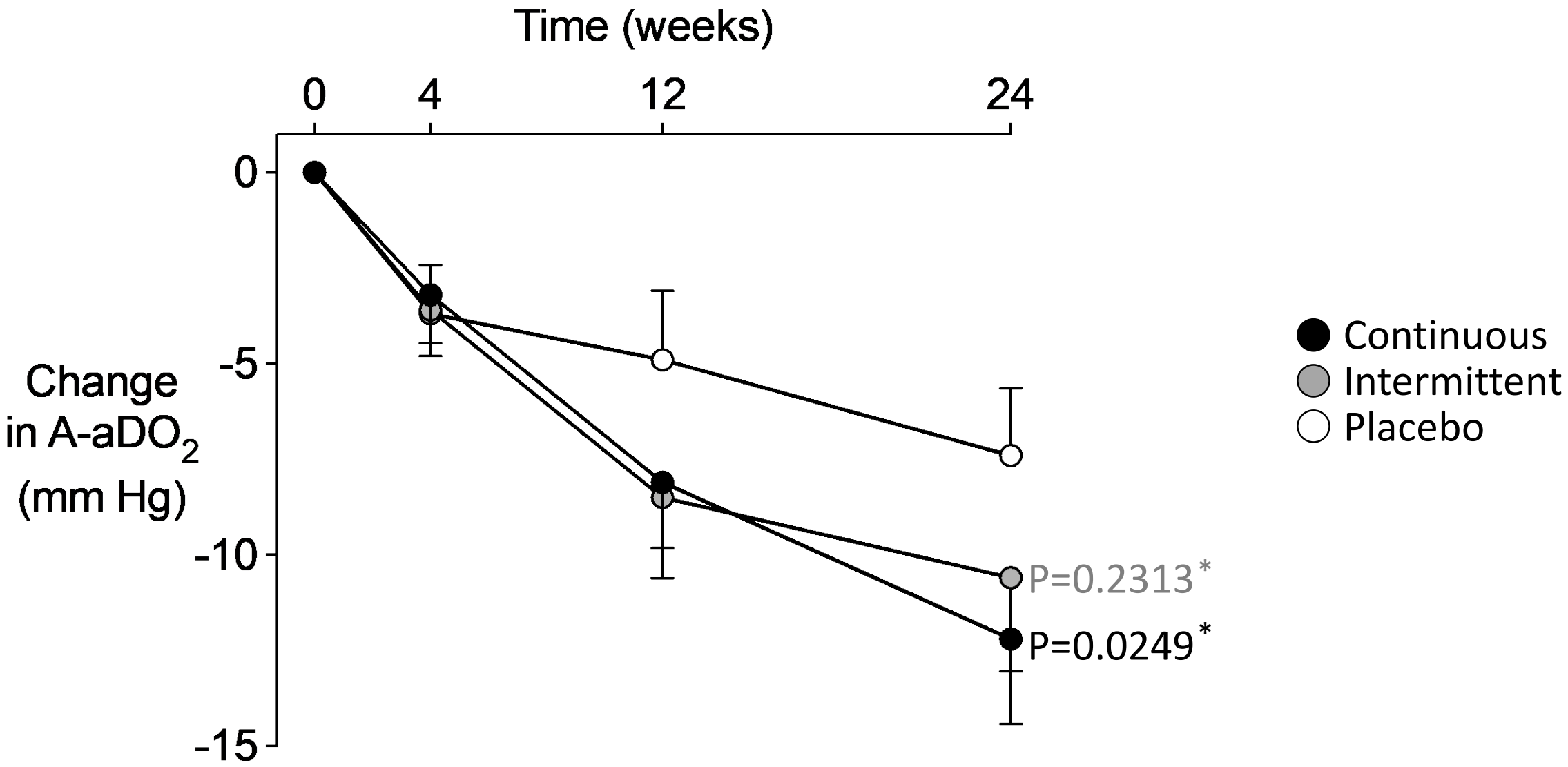


*Comparison to Placebo

Correlation of PaO_2 and A-aDO_2 Identifies Patients Who Received Oxygen Therapy During Blood Collection as Outliers

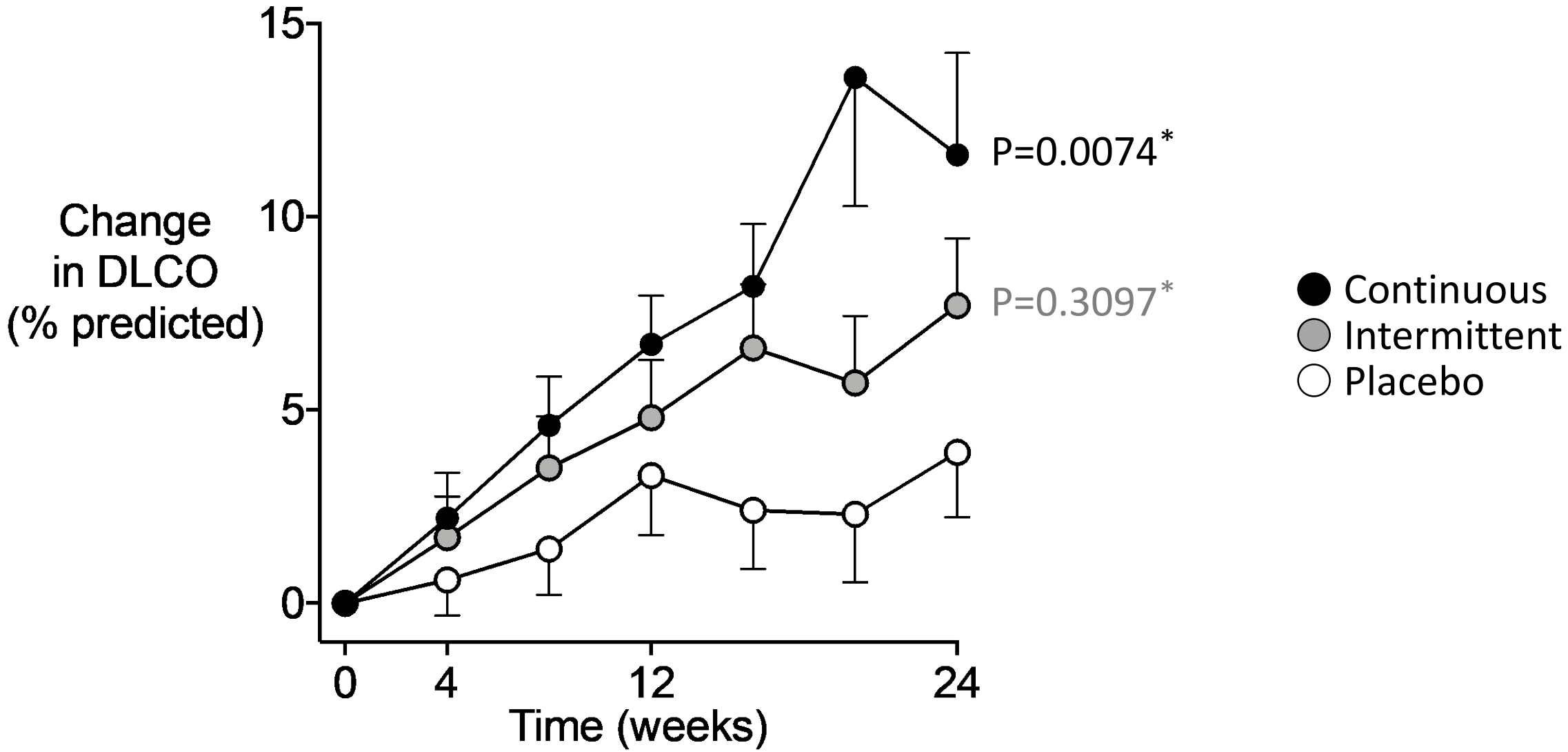


Exclusion of Data for Patients On Oxygen Therapy During Arterial Blood Collection Significantly Influenced the Primary Endpoint (A-aDO_2 – Revised)



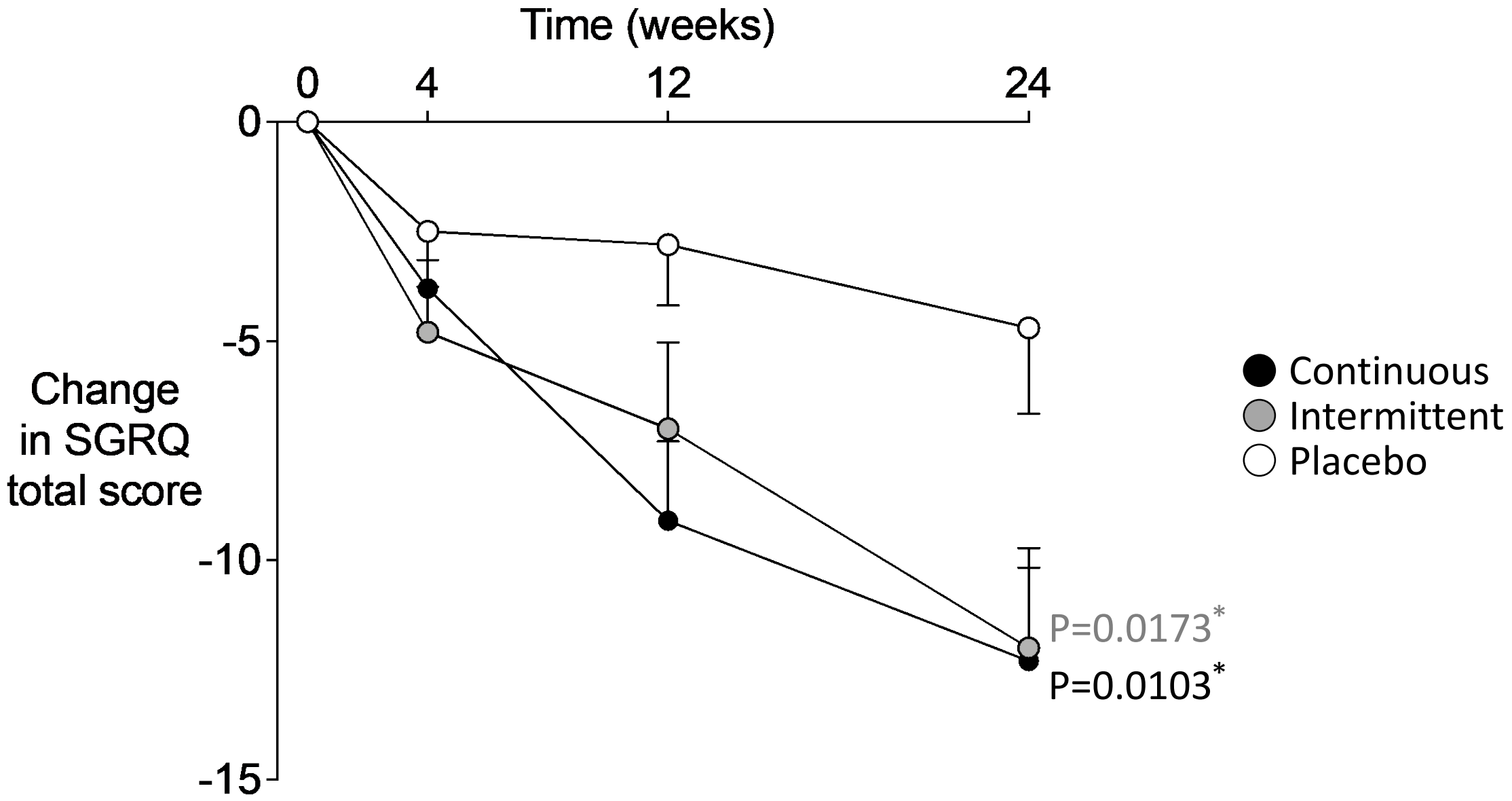
*Comparison to Placebo

Physiology: GM-CSF Improved DLCO



*Comparison to Placebo

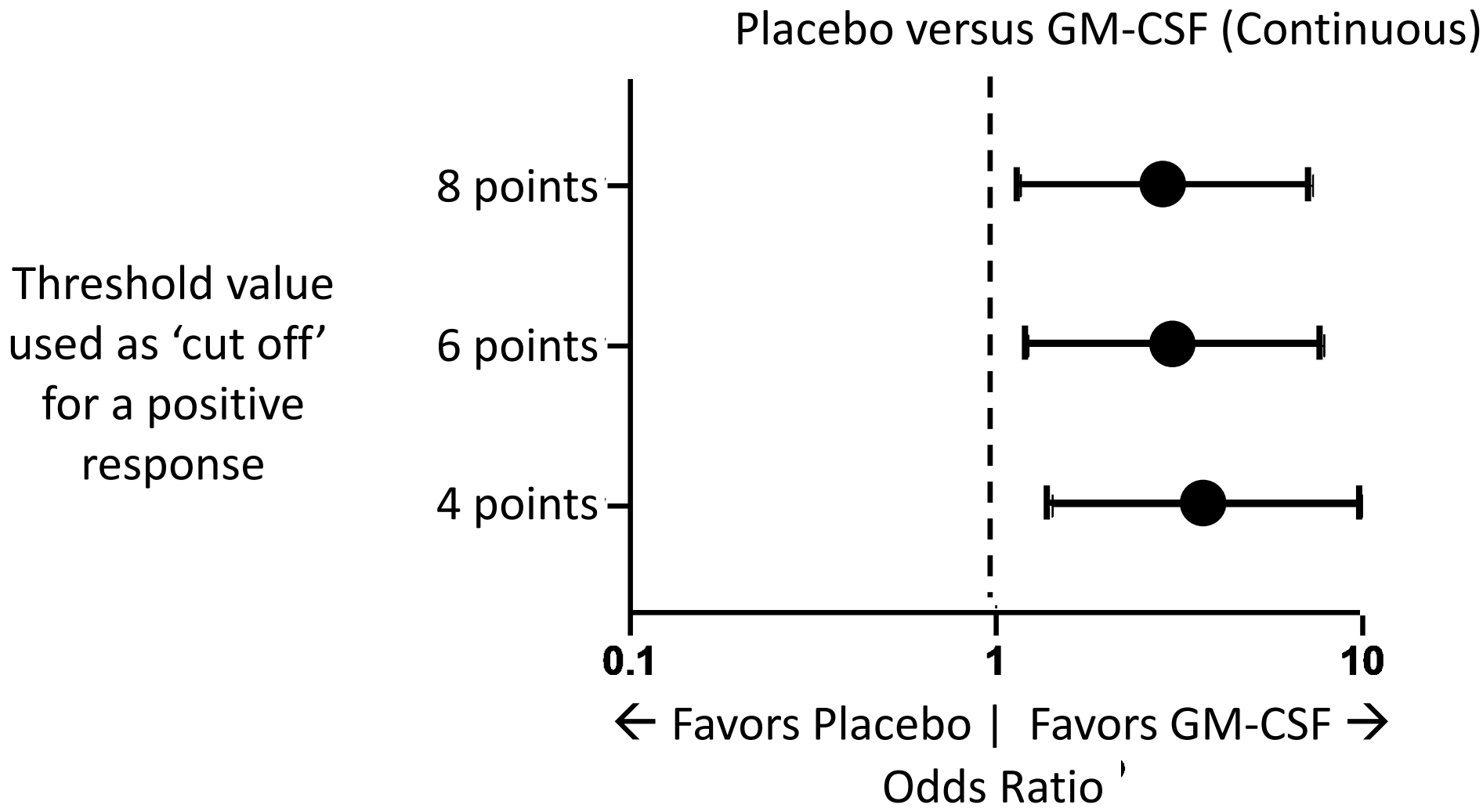
Health Status: GM-CSF Improved SGRQ Total Score



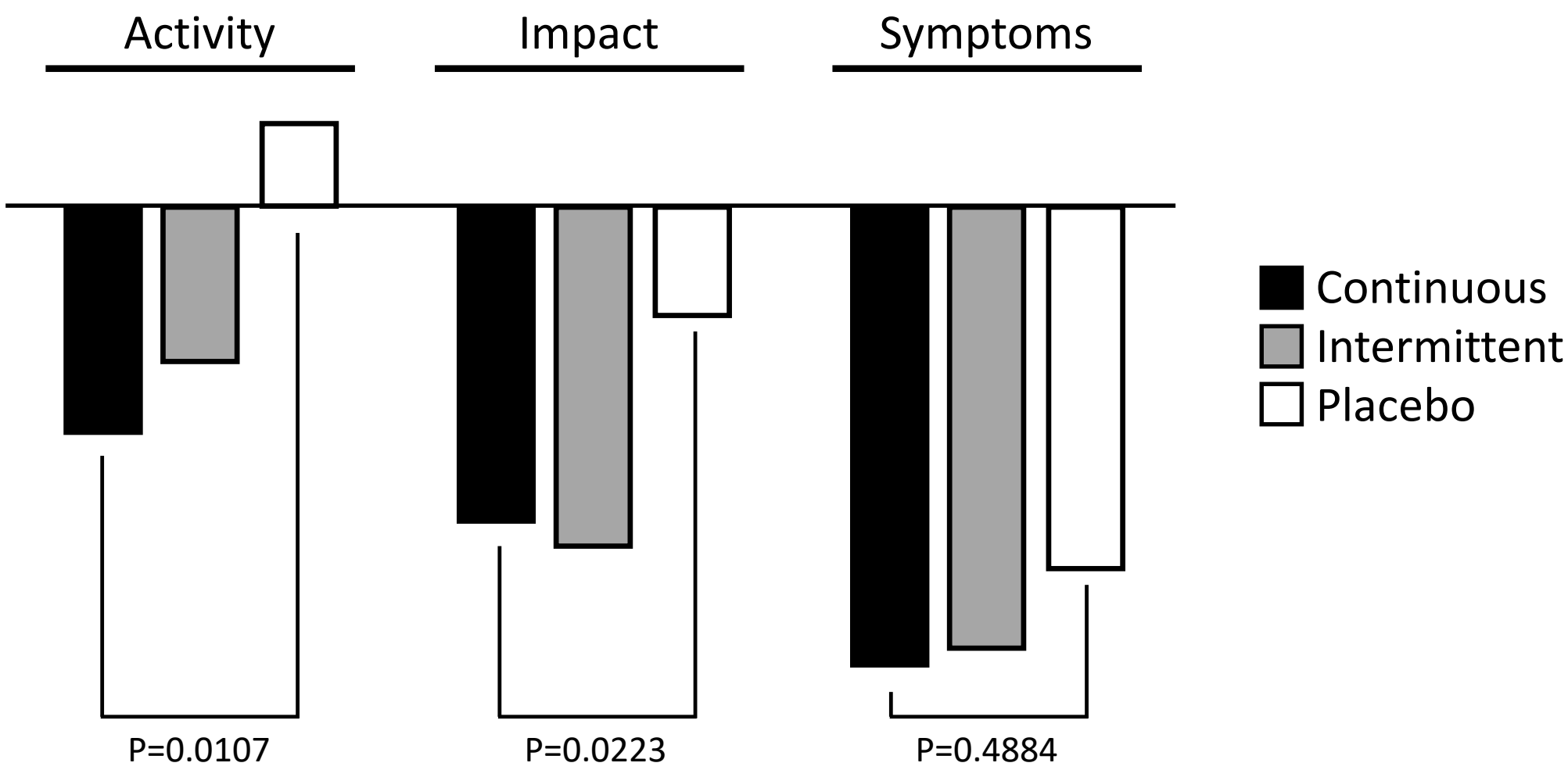
+ MCID is 4 Points in COPD patients

*Comparison to Placebo

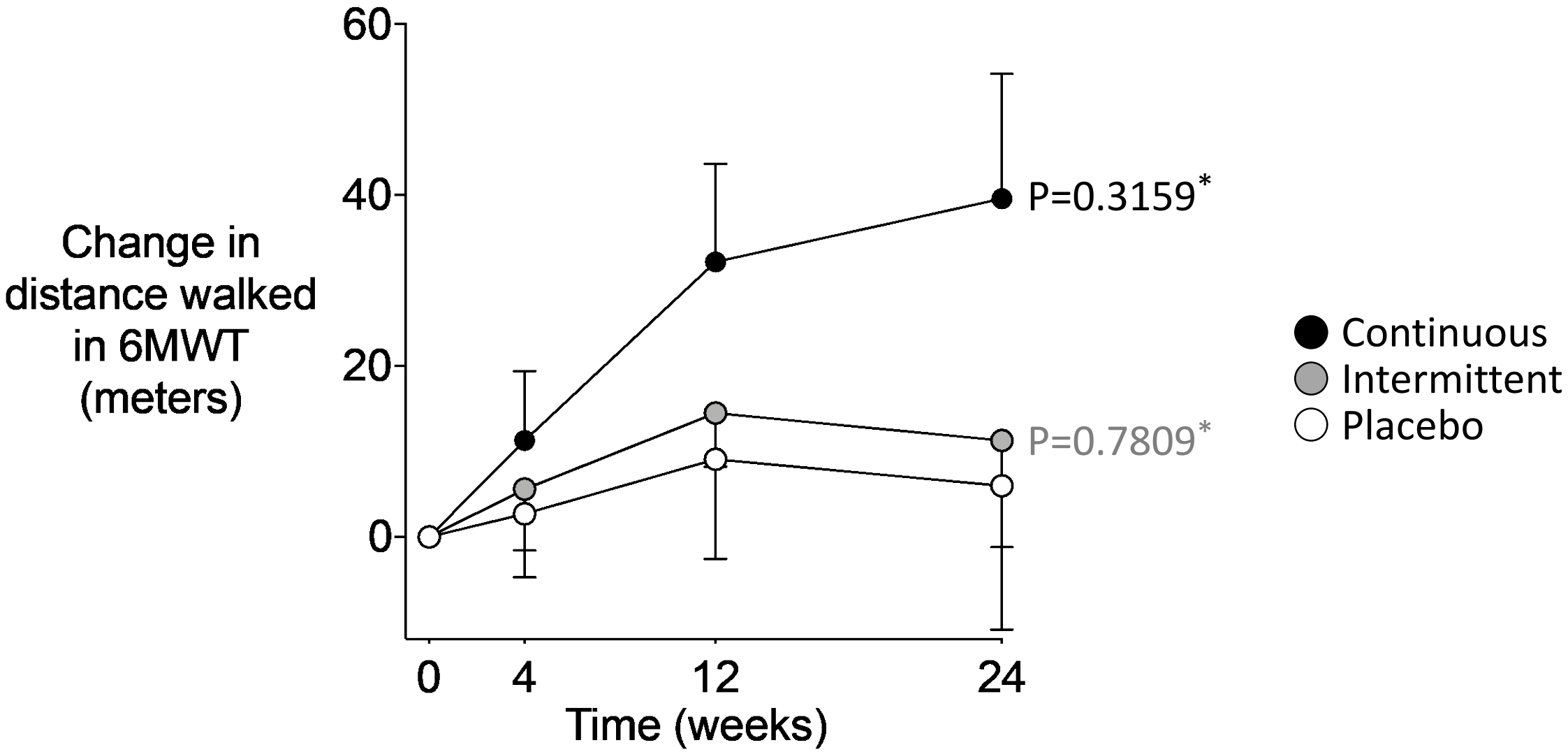
The Improvement in SGRQ was Robust as Shown by Responder Analysis



A Pattern of Improvement was Seen Across all SGRQ Domains

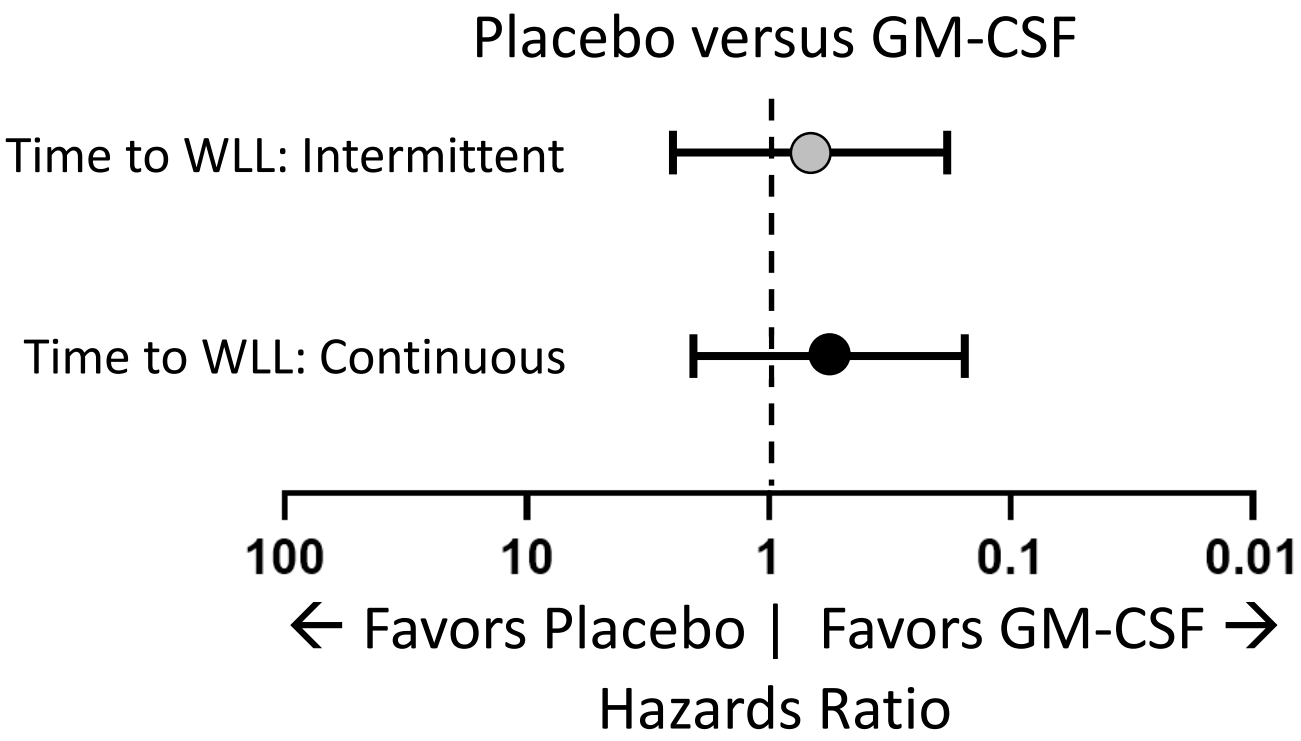


Function: GM-CSF Trended Towards Improved 6MWT-Distance



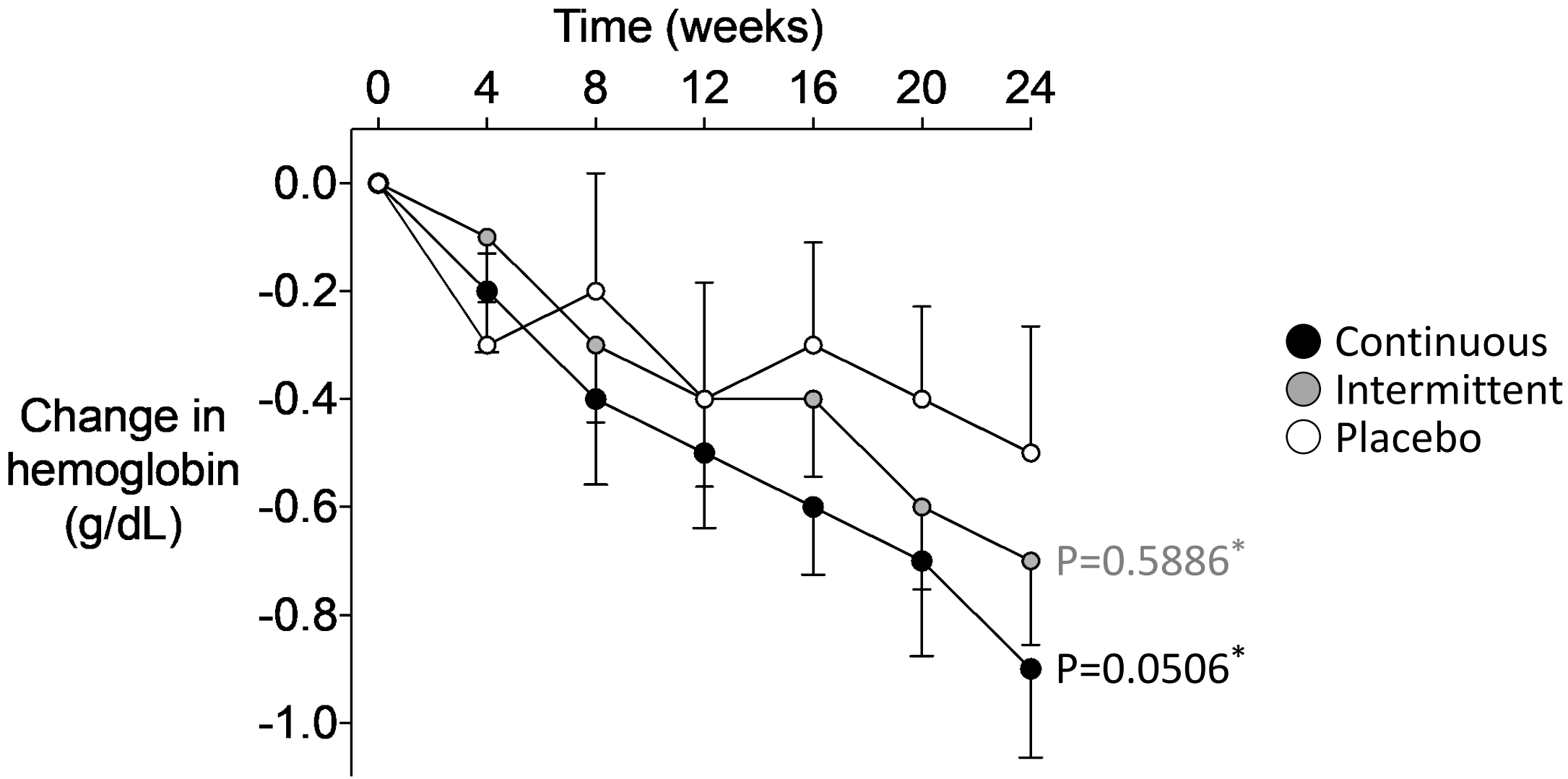
*Comparison to Placebo

Rescue Therapy: GM-CSF Trended Towards a Reduction in WLL



	WLL Therapy Requirement		
Group	# patients	# treatments	Rate Ratio vs Placebo
Continuous (n=46)	4	9	0.284
Intermediate (n=45)	4	7	0.367
Placebo (n=47)	6	17	-

Systemic Response: GM-CSF Trended Towards Reduced Hemoglobin Levels



*Comparison to Placebo

Totality of Outcome Data Favors Continuous GM-CSF over Placebo

Disease element	Endpoint	Units	Treatment effect	P-value
• Pathology	Chest CT – GGO	Score	-2.4	0.0002
	Serum LDH, KL-6, SP-D, CEA, Cyfra 21-1	IU/L pg/ml	All favor GM-CSF	<0.05
• Physiology	A-aDO_2* – FAS	mm Hg	-4.6	0.1688
	A-aDO_2* – Revised	mm Hg	-6.5	0.0249
	DLCO	% predicted	7.9	0.0074
• Health status & Function	SGRQ**	total score	-7.6	0.0103
	6MWT-Distance**	m	20.6	0.3159
• Rescue therapy	Time to WLL**	Hazard ratio	0.59	0.4204
	WLL frequency	Rate ratio	0.28	0.1918
• Systemic response	Hemoglobin	(g/dL)	-0.5	0.0506

* = Primary end point, ** = Key Secondary end point

Conclusions

- Baseline clinical features of aPAP
  - A large, global cohort of adult aPAP patients was identified and carefully characterized
  - Study groups were well-balanced for demographics and disease severity
- Clinical trial observations
  - The Placebo group experienced an unexpected degree of improvement in A-aDO_2
  - Inhaled recombinant human GM-CSF therapy (molgramostim) of aPAP is:
    - ➢ Safe and well-tolerated
    - ➢ Effective as shown by changes in lung pathology, physiology, health status, function, and the systemic response to chronic lung disease
    - ➢ More effective when administered continuously than on alternating weeks

Acknowledgments

We are grateful to and thank:

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