CHEST Online Supplement

A Placebo-Controlled, Randomized Trial of Mesenchymal Stem Cells in COPD

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e-Appendix 1.

STUDY DESIGN AND OVERSIGHT

A prospective randomized, double-blind, placebo (vehicle)-controlled design was utilized. Participants were recruited from 6 different institutions in the United States (see acknowledgements section for all participating sites and personnel). The study was approved by the Institutional Review Board (IRB) for each participating center and written informed consent was obtained from each participant. The following are the names and identifying numbers for the IRB committees and protocol numbers for each of the participating sites: Copernicus Group IRB (American Health Research, Spartanburg Medical Research, Upstate Pharmaceutical Research; Principal Investigators: Spangenthal, Fogarty, and Pudi): PHA2-08-071, Los Angeles Biomedical Research Institute IRB (Principal Investigator: Casaburi): 13286-01, David Geffen School of Medicine at UCLA IRB (Principal Investigator: Taskin): 08-04-014-01, The University of Vermont Committees of Human Research (Weiss): IRB 00000485. The trial was registered on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT00683722).

The study was designed and written by the sponsor (Osiris Therapeutics Inc.). The clinical investigators reviewed the protocol, recruited the patients, and collected the data. The data was monitored, stored, and analyzed by an independent contract firm and was available to all authors for review. An independent data and safety monitoring board which approved all amendments and oversaw conduct of the trial. The first author wrote the first and final

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draft of the manuscript based on a clinical summary report from the sponsor. All the authors reviewed, contributed to, and approved all subsequent drafts and made the decision to submit the manuscript for publication. The study was conducted in accordance with the amended Declaration of Helsinki (http://www.wma.net/en/20publications/10 policies/b3/).

PATIENT SELECTION

Eligible patients were 40-80 years of age with moderate-severe COPD (GOLD Stage II or III (24)), smoking history of >10 pack years (current or former smokers), post-bronchodilator forced volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of <70%, and post-bronchodilator FEV1 between 30% and 70% of predicted value (24). All standard therapeutic regimens for COPD were permitted, including inhaled short and long acting bronchodilators, inhaled corticosteroids, theophylline, leukotriene antagonists, oral prednisone at a stable dose (<20 mg a day), and supplemental oxygen. Major exclusion criteria included asthma and other significant lung diseases apart from COPD, active infection or chronic inflammatory disease, use of immunosuppressive medications including TNFα inhibitors, active malignancy or history of malignancy within the past 5 years, or life expectancy of <6 months (Table 1). Patients who had a COPD exacerbation requiring either antibiotics, oral prednisone at a dose of >20 mg a day, or hospitalization within 4 weeks of screening, who had participated in pulmonary rehabilitation in the three months prior to screening, or who planned to do so within 6 months of enrollment, or who had a change in absolute FEV1 from screening to randomization of >20% or >225 ml were also excluded.

STUDY DRUG

The active agent was a preparation of ex-vivo cultured adult human mesenchymal stem cells, hMSCs (Osiris Therapeutics, Columbia MD), obtained from donors unrelated and not HLA–matched to recipients. The hMSCs were derived from bone marrow aspirates of donors aged 18-30 years who had been screened and tested according to FDA requirements for Blood and Tissue Based Products. The product lots were manufactured by a scaled

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adaptation of the technique according to Good Manufacturing Practices (GMP), as described previously (40,41). The process consists of cell expansion for a total of 5 passages in culture medium supplemented with 10% fetal bovine serum that has undergone extensive screening for safety and processing effectiveness. All lots passed established quality release criteria for viral pathogens, mycoplasma, sterility, endotoxin, cell identity, purity, potency and viability. The cells were formulated in Plasma-Lyte® A containing 5% human serum albumin (HSA) and 10% dimethyl sulfoxide (DMSO) and stored at ≤ 135 °C in the vapor phase of liquid nitrogen until use. The final cell dose administered was 100×106 viable cells/infusion, reconstituted with Plasma-Lyte® A in a total volume of 150 mL, for a cell concentration of 0.67 x 106 cells/ml.

STUDY TREATMENTS AND OUTCOMES

Enrolled patients were centrally randomized 1:1 to receive either non HLA-matched allogeneic MSCs (Prochymal®, Osiris Therapeutics, Inc.) or placebo (vehicle) treatment group. The vehicle contained a physiologic electrolyte solution (Baxter Plasma Lyte A®) with 50 g/L human serum albumin (HSA) and 100 mL/L dimethyl sulfoxide (DMSO). Treatment was administered on Days 0, 30, 60, and 90 (Figure 1). MSC dosing was 100×106 cells/infusion, reconstituted in a total volume of 150 mL of vehicle, and delivered at a maximum rate of 2.0×106 cells/minute, corresponding to 2-3 ml/minute. Placebo-treated patients received an infusion of vehicle of the same volume as the MSC infusion. Each infusion took approximately one hour to complete.

Participants were subsequently evaluated for safety and efficacy until death, withdrawal, or 2 years after the first study drug infusion, whichever occurred first. Safety was assessed by occurrence of adverse events during either study drug infusion or by physician assessments and laboratory evaluations (serum electrolytes, complete blood counts, liver function tests, urinalyses), echocardiograms, and electrocardiograms during the 2 year follow-up period. A record of hospitalizations, COPD exacerbations, and use of reliever medications was maintained for each patient.

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Efficacy measures included improvement from baseline in pulmonary function, exercise performance, quality of life and exacerbations in the MSC group as compared to placebo at 1 year) and 2 years. Specific outcomes included: changes in FEV1, FVC, FEV1/FVC (24), total lung capacity by plethysmography (24), single breath carbon monoxide diffusing capacity (25), six minute walk distance (26,27), dyspnea during the six minute walk test (Borg scale) (27), the St. George's Respiratory questionnaire, SGRQ total score (28,29), and global assessment of patient status by the clinical investigators. COPD exacerbations, defined as change in standard medication regimen and/or need for emergency room evaluation or hospital admission for worsening COPD symptoms, were assessed as the time to the first exacerbation and as the ratio of the rate of exacerbations between MSC and placebo treated patients. Circulating levels of TNFα, IFNγ, interleukin (IL)-2, transforming growth factor (TGF) β, IL-4, IL-5, IL-10, and C-reactive protein (CRP) were assessed as markers of systemic inflammation (30).

STATISTICAL METHODS

The number of patients was selected for initial assessment of safety and exploratory evaluation of efficacy in a Phase II investigation. The study was not powered for efficacy. The study randomized 62 patients in a 1:1 ratio of MSCs to placebo. An analysis of covariance (ANCOVA) was performed on FEV1 % predicted change from baseline at 6 months, using FEV1 % predicted at baseline as a covariate. (31). For all other endpoints, statistical analyses were performed using two-sided hypothesis tests, including t-tests, chi-square tests, Wilcoxon rank-sum tests, or Fisher's exact tests, as appropriate, at the 0.05 level of significance (31). Differences in time to first COPD exacerbation and probabilities of being exacerbation free were assessed by Kaplan-Meier methodology and log rank tests (31). Total COPD exacerbations experienced per patient, adjusted per exposure, were compared between treatment groups using a two-sided Mantel-Haenszel chi-square test for ordered categorical data (31).

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e-Appendix 2.

Participating Sites and Personnel

American Health Research
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Michelle Williams PhD, Robin Flannery. The sponsor provided funding for the investigation and was involved in the study conception and design, data interpretation, article revision and final approval of the manuscript.

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e-Table 1: Concomitant COPD Medications (Safety Set)

	PROCHYMAL (n=30)	PLACEBO (n=32)	TOTAL (n=62)
Any COPD medication	27 (90.0%)	31 (96.9%)	58 (93.5%)
COMBINATION MEDICATIONS	22 (73.3%)	25 (78.1%)	47 (75.8%)
BUDESONIDE W/FORMOTEROL FUMARATE	2 (6.7%)	6 (18.8%)	8 (12.9%)
COMBIVENT	6 (20.0%)	7 (21.9%)	13 (21.0%)
SERETIDE	17 (56.7%)	17 (53.1%)	34 (54.8%)
INHALED CORTICOSTERIOIDS	5 (16.7%)	9 (28.1%)	14 (22.6%)
BECLOMETASONE DIPROPIONATE	2 (6.7%)	3 (9.4%)	5 (8.1%)
BUDESONIDE	2 (6.7%)	2 (6.3%)	4 (6.5%)
FLUTICASONE PROPIONATE	1 (3.3%)	2 (6.3%)	3 (4.8%)
MOMETASONE FUROATE	2 (6.7%)	2 (6.3%)	4 (6.5%)
TRIAMCINOLONE ACETONIDE	1 (3.3%)	0 (0.0%)	1 (1.6%)
LEUKOTRIENE RECEPTOR ANTAGONISTS	0 (0.0%)	1 (3.1%)	1 (1.6%)
MONTELUKAST SODIUM	0 (0.0%)	1 (3.1%)	1 (1.6%)
LONG-ACTING BETA AGONISTS	6 (20.0%)	3 (9.4%)	9 (14.5%)
ARFORMOTEROL TARTRATE	0 (0.0%)	1 (3.1%)	1 (1.6%)
FORMOTEROL FUMARATE	5 (16.7%)	3 (9.4%)	8 (12.9%)
SALMETEROL XINAFOATE	1 (3.3%)	0 (0.0%)	1 (1.6%)
LONG-ACTING MUSCARINIC ANTAGONISTS	20 (66.7%)	18 (56.3%)	38 (61.3%)
TIOTROPIUM BROMIDE	20 (66.7%)	18 (56.3%)	38 (61.3%)
OTHER CORTICOSTERIOIDS	12 (40.0%)	8 (25.0%)	20 (32.3%)
METHYLPREDNISOLONE	1 (3.3%)	1 (3.1%)	2 (3.2%)
METHYLPREDNISOLONE ACETATE	0 (0.0%)	1 (3.1%)	1 (1.6%)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (3.3%)	0 (0.0%)	1 (1.6%)
PREDNISONE	12 (40.0%)	8 (25.0%)	20 (32.3%)
SHORT-ACTING BETA AGONISTS	24 (80.0%)	25 (78.1%)	49 (79.0%)
IPRATROPIUM BROMIDE	3 (10.0%)	3 (9.4%)	6 (9.7%)
LEVOSALBUTAMOL	2 (6.7%)	1 (3.1%)	3 (4.8%)
LEVOSALBUTAMOL TARTRATE	0 (0.0%)	1 (3.1%)	1 (1.6%)
SALBUTAMOL	23 (76.7%)	22 (68.8%)	45 (72.6%)
SALBUTAMOL SULFATE	2 (6.7%)	3 (9.4%)	5 (8.1%)
SHORT-ACTING MUSCARINIC ANTAGONIST	0 (0.0%)	1 (3.1%)	1 (1.6%)
IPRATROPIUM BROMIDE	0 (0.0%)	1 (3.1%)	1 (1.6%)
SUPPLEMENTAL OXYGEN	15 (50.0%)	10 (31.3%)	25 (40.3%)
OXYGEN	15 (50.0%)	10 (31.3%)	25 (40.3%)
XANTHINES	3 (10.0%)	3 (9.4%)	6 (9.7%)
THEOPHYLLINE	3 (10.0%)	3 (9.4%)	6 (9.7%)

Notes: The safety set consists of all randomized subjects who received at least one dose of study drug, analyzed according to the treatment they received, regardless of randomization.
The subject is counted only once in any medication/category.

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e-Table 2: Spirometry by Visit (Intent-to-Treat Population)

		PROCHYMAL (n=30)		PLACEBO (n=32)		
		Actual Value	Change from baseline	Actual Value	Change from baseline	P-value
Screening (Visit 1, Day -30)						
FEV_1 (L)	N	30		32		
	Mean (SD)	1.23 (0.38)		1.36 (0.59)		
	Median	1.15		1.11		
	Min, max	0.6, 2.2		0.7, 2.7		
FVC (L)	N	30		32		
	Mean (SD)	2.83 (0.70)		3.03 (1.11)		
	Median	2.63		2.81		
	Min, max	1.7, 4.4		1.7, 6.3		
FEV_1/FVC	N	30		32		
	Mean (SD)	0.43 (0.09)		0.45 (0.12)		
	Median	0.43		0.42		
	Min, max	0.3, 0.6		0.3, 0.7		
Baseline (Visit 2, Day 0)						
FEV_1 (L)	N	30		32		
	Mean (SD)	1.20 (0.37)		1.38 (0.58)		
	Median	1.14		1.21		
	Min, max	0.6, 1.9		0.7, 2.7		
FVC (L)	N	30		32		
	Mean (SD)	2.73 (0.61)		2.99 (1.06)		
	Median	2.59		2.87		
	Min, max	1.7, 4.3		1.6, 5.8		
FEV_1/FVC	N	30		32		
	Mean (SD)	0.44 (0.10)		0.46 (0.12)		
	Median	0.44		0.44		
	Min, max	0.3, 0.7		0.3, 0.7		
Hb-adjusted DLCO	N	29		32		
(mL/min/mmHg) [2]	Mean (SD)	10.73 (3.46)		12.95 (5.10)		
	Median	10.90		12.75		
	Min, max	3.53, 16.59		5.70, 22.57		
Visit 3 (Day 10)						
FEV_1 (L)	N	30	30	32	32	0.279 [1]
	Mean (SD)	1.22 (0.37)	0.020 (0.108)	1.36 (0.60)	-0.012 (0.123)	
	Median	1.17	0.000	1.16	-0.020	
	Min, max	0.6, 1.9	-0.13, 0.29	0.6, 2.7	-0.26, 0.21	
Achieved MCID≥100mL	Yes	8 (26.7%)		7 (21.9%)		0.660 [2]
	No	22 (73.3%)		25 (78.1%)		
FVC (L)	N	30	30	32	32	0.144 [1]
	Mean (SD)	2.82 (0.71)	0.091 (0.251)	2.98 (1.04)	-0.006 (0.263)	
	Median	2.77	0.06	1.76	0.04	
	Min, max	1.6, 4.3	-0.37, 0.71	1.5, 6.0	-0.95, 0.41	

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		PROCHYMAL (n=30)		PLACEBO (n=32)		
		Actual Value	Change from baseline	Actual Value	Change from baseline	P-value
FEV_1/FVC	N	30	30	32	32	0.846 [1]
	Mean (SD)	0.44 (0.10)	-0.003 (0.024)	0.46 (0.13)	-0.005 (0.038)	
	Median	0.42	-0.005	0.45	-0.004	
	Min, max	0.3, 0.6	-0.04, 0.05	0.3, 0.7	-0.09, 0.10	
Hb-adjusted DLCO	N	30	29	32	32	0.872
(mL/min/mmHg) [2]	Mean (SD)	10.47 (3.63)	-0.13 (1.75)	12.76 (5.01)	-0.20 (1.59)	
	Median	9.74	0.26	11.90	0.04	
	Min, max	2.62, 18.71	-6.18, 2.58	5.84, 24.25	-5.89, 1.94	
Visit 4 (1 month)						
FEV_1 (L)	N	30	30	32	32	0.122 [1]
	Mean (SD)	1.20 (0.40)	0.000 (0.115)	1.33 (0.58)	-0.49 (0.130)	
	Median	1.12	-0.015	1.27	-0.025	
	Min, max	0.6, 2.0	-0.27, 0.20	0.6, 2.7	-0.36, 0.14	
Achieved MCID≥100mL	Yes	8 (26.7%)		2 (6.3%)		0.029 [2]
	No	22 (73.3%)		30 (93.8%)		
FVC (L)	N	30	30	32	32	0.295 [1]
	Mean (SD)	2.73 (0.72)	0.003 (0.311)	2.91 (0.97)	-0.78 (0.289)	
	Median	2.61	-0.005	2.77	-0.015	
	Min, max	1.5, 4.3	-0.65, 1.09	1.7, 5.8	-0.84, 0.49	
FEV_1/FVC	N	30	30	32	32	0.330 [1]
	Mean (SD)	0.44 (0.10)	0.000 (0.029)	0.45 (0.12)	-0.008 (0.037)	
	Median	0.42	0.000	0.43	-0.005	
	Min, max	0.3, 0.7	-0.10, 0.06	0.3, 0.7	-0.11, 0.08	
Hb-adjusted DLCO	N	30	29	32	32	0.095
(mL/min/mmHg) [2]	Mean (SD)	9.77 (3.41)	-0.94 (1.55)	12.68 (5.00)	-0.27 (1.50)	
	Median	9.67	-0.67	12.78	-0.10	
	Min, max	2.82, 16.01	-5.20, 1.48	4.01, 22.15	-4.33, 2.48	
Visit 5 (2 months)						
FEV_1 (L)	N	30	30	32	32	0.530 [1]
	Mean (SD)	1.18 (0.40)	-0.016 (0.134)	1.34 (0.57)	-0.037 (0.133)	
	Median	1.14	-0.025	1.17	-0.025	
	Min, max	0.6, 2.2	-0.32, 0.29	0.6, 2.6	-0.35, 0.18	
Achieved MCID≥100mL	Yes	5 (16.7%)		3 (9.4%)		0.392 [2]
	No	25 (83.3%)		29 (90.6%)		
FVC (L)	N	30	30	32	32	0.731 [1]
	Mean (SD)	2.71 (0.68)	-0.023 (0.253)	2.94 (0.92)	-0.048 (0.314)	
	Median	2.68	-0.005	2.82	-0.005	
	Min, max	1.4, 4.2	-0.63, 0.70	1.4, 5.1	-1.03, 0.46	
FEV_1/FVC	N	30	30	32	32	0.478 [1]
	Mean (SD)	0.44 (0.10)	-0.001 (0.037)	0.46 (0.13)	-0.008 (0.038)	
	Median	0.41	-0.003	0.43	-0.01	
	Min, max	0.3, 0.7	-0.08, 0.08	0.3, 0.7	-0.10, 0.08	
Hb-adjusted DLCO	N	29	28	32	32	0.037
(mL/min/mmHg) [2]	Mean (SD)	9.71 (3.82)	-0.92 (1.91)	13.06 (5.27)	0.11 (1.83)	
	Median	9.24	-0.85	11.84	0.17	
	Min, max	1.86, 17.25	-7.24, 2.02	6.35, 25.57	-2.86, 3.54	

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		PROCHYMAL (n=30)		PLACEBO (n=32)		
		Actual Value	Change from baseline	Actual Value	Change from baseline	P-value
Visit 6 (3 months)						
FEV_1 (L)	N	30	30	32	32	0.309 [1]
	Mean (SD)	1.17 (0.37)	-0.033 (0.136)	1.31 (0.59)	-0.072 (0.156)	
	Median	1.14	-0.015	1.20	-0.060	
	Min, max	0.6, 1.8	-0.33, 0.34	0.7, 2.7	-0.55, 0.24	
Achieved MCID≥100mL	Yes	4 (13.3%)		2 (6.3%)		0.346 [2]
	No	26 (86.7%)		30 (93.8%)		
FVC (L)	N	30	30	32	32	0.372 [1]
	Mean (SD)	2.67 (0.67)	-0.064 (0.316)	2.85 (0.95)	-0.139 (0.343)	
	Median	2.68	-0.03	2.67	-0.035	
	Min, max	1.5, 4.0	-0.69, 0.64	1.3, 5.5	-0.98, 0.55	
FEV_1/FVC	N	30	30	32	32	0.390 [1]
	Mean (SD)	0.44 (0.11)	0.001 (0.035)	0.46 (0.12)	-0.007 (0.037)	
	Median	0.41	-0.005	0.43	-0.007	
	Min, max	0.3, 0.7	-0.06, 0.08	0.3, 0.7	-0.10, 0.08	
Hb-adjusted DLCO	N	28	27	32	32	0.082
(mL/min/mmHg) [2]	Mean (SD)	9.74 (3.78)	-1.29 (2.32)	12.61 (5.61)	-0.34 (1.77)	
	Median	7.98	-0.75	11.18	-0.17	
	Min, max	5.06, 16.86	-7.37, 2.14	4.99, 24.20	-4.31, 4.98	
Visit 7 (4 months)						
FEV_1 (L)	N	30	30	32	32	0.419 [1]
	Mean (SD)	1.18 (0.35)	-0.025 (0.155)	1.32 (0.59)	-0.054 (0.126)	
	Median	1.18	-0.035	1.11	-0.065	
	Min, max	0.6, 1.9	-0.37, 0.29	0.7, 2.7	-0.35, 0.25	
Achieved MCID≥100mL	Yes	9 (30.0%)		3 (9.4%)		0.040 [2]
	No	21 (70.0%)		29 (90.6%)		
FVC (L)	N	30	30	32	32	0.121 [1]
	Mean (SD)	2.70 (0.65)	-0.029 (0.335)	2.83 (0.96)	-0.156 (0.304)	
	Median	2.68	-0.035	2.63	-0.085	
	Min, max	1.5, 4.0	-0.58, 0.69	1.8, 5.5	-1.03, 0.29	
FEV_1/FVC	N	30	30	32	32	0.748 [1]
	Mean (SD)	0.44 (0.09)	-0.002 (0.031)	0.46 (0.12)	0.001 (0.042)	
	Median	0.41	0.000	0.45	0.000	
	Min, max	0.3, 0.7	-0.06, 0.09	0.3, 0.7	-0.10, 0.11	
Hb-adjusted DLCO	N	29	28	32	32	0.439
(mL/min/mmHg) [2]	Mean (SD)	10.05 (3.52)	-0.56 (2.08)	12.82 (5.64)	-0.13 (2.13)	
	Median	9.28	-0.29	12.16	0.19	
	Min, max	1.28, 18.22	-5.53, 3.54	4.42, 25.12	-3.47, 6.52	
Visit 8 (5 months)						
FEV_1 (L)	N	28	28	31	31	0.317 [1]
	Mean (SD)	1.17 (0.39)	-0.031 (0.125)	1.31 (0.58)	-0.070 (0.161)	
	Median	1.13	-0.025	1.08	-0.050	
	Min, max	0.6, 1.9	-0.31, 0.22	0.7, 2.7	-0.43, 0.24	

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		PROCHYMAL (n=30)		PLACEBO (n=32)		
		Actual Value	Change from baseline	Actual Value	Change from baseline	P-value
Achieved MCID≥100mL	Yes	4 (14.3%)		4 (12.9%)		0.877 [2]
	No	24 (85.7%)		27 (87.1%)		
FVC (L)	N	28	28	31	31	0.631 [1]
	Mean (SD)	2.64 (0.69)	-0.075 (0.273)	2.88 (0.94)	-0.117 (0.400)	
	Median	2.63	0.015	2.84	-0.050	
	Min, max	1.5, 4.4	-0.69, 0.31	1.4, 5.4	-1.09, 0.48	
FEV_1/FVC	N	28	28	31	31	0.328 [1]
	Mean (SD)	0.44 (0.10)	0.001 (0.039)	0.46 (0.12)	-0.009 (0.040)	
	Median	0.41	-0.005	0.41	-0.003	
	Min, max	0.3, 0.7	-0.06, 0.07	0.3, 0.7	-0.10, 0.08	
Hb-adjusted DLCO	N	27	26	31	31	0.672
(mL/min/mmHg) [2]	Mean (SD)	10.05 (3.89)	-0.29 (2.09)	13.08 (5.52)	-0.05 (2.15)	
	Median	9.57	0.14	13.03	-0.47	
	Min, max	2.54, 18.51	-5.24, 2.70	4.89, 24.95	-4.77, 6.36	
Visit 9 (6 months)						
FEV_1 (L)	N	27	27	31	31	0.639 [1]
	Mean (SD)	1.19 (0.34)	-0.28 (0.116)	1.37 (0.61)	-0.010 (0.159)	
	Median	1.14	0.010	1.25	-0.010	
	Min, max	0.6, 1.9	-0.31, 0.16	0.7, 2.9	-0.33, 0.36	
Achieved MCID≥100mL	Yes	2 (7.4%)		7 (22.6%)		0.111 [2]
	No	25 (92.6%)		24 (77.4%)		
FVC (L)	N	27	27	31	31	0.455 [1]
	Mean (SD)	2.72 (0.53)	0.004 (0.224)	30.5 (1.12)	0.055 (0.275)	
	Median	2.72	0.01	2.86	0.03	
	Min, max	1.7, 3.9	-0.50, 0.49	1.6, 6.6	-0.32, 0.76	
FEV_1/FVC	N	27	27	31	31	0.810 [1]
	Mean (SD)	0.44 (0.09)	-0.010 (0.039)	0.45 (0.13)	-0.013 (0.040)	
	Median	0.42	-0.017	0.42	-0.014	
	Min, max	0.3, 0.6	-0.08, 0.06	0.3, 0.7	-0.12, 0.06	
Hb-adjusted DLCO	N	27	26	31	31	0.338
(mL/min/mmHg) [2]	Mean (SD)	10.05 (3.62)	-0.41 (1.67)	13.28 (5.44)	0.15 (2.67)	
	Median	9.91	-0.24	13.25	-0.07	
	Min, max	2.94, 15.75	-5.73, 3.00	4.82, 24.92	-5.76, 7.17	
Visit 10 (1 year)						
FEV_1 (L)	N	23	23	28	28	0.175 [1]
	Mean (SD)	1.24 (0.39)	-0.019 (0.108)	1.35 (0.64)	-0.074 (0.173)	
	Median	1.27	-0.020	1.25	-0.060	
	Min, max	0.7, 1.9	-0.26, 0.19	0.4, 2.8	-0.46, 0.21	
Achieved MCID≥100mL	Yes	2 (8.0%)		4 (14.3%)		0.538 [2]
	No	21 (84.0%)		24 (85.7%)		

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e-Table 2: Spirometry by Visit (Intent-to-Treat Population)

		PROCHYMAL (n=30)		PLACEBO (n=32)		
		Actual Value	Change from baseline	Actual Value	Change from baseline	P-value
FVC (L)	N	23	23	28	28	0.839 [1]
	Mean (SD)	2.79 (0.67)	-0.004 (0.251)	3.04 (1.15)	0.012 (0.301)	
	Median	2.67	-0.030	2.76	-0.030	
	Min, max	1.8, 4.2	-0.40, 0.61	1.1, 5.6	-0.70, 0.60	
FEV_1/FVC	N	23	23	28	28	
	Mean (SD)	0.45 (0.11)	-0.005 (0.037)	0.44 (0.13)	-0.029 (0.043)	
	Median	0.43	0.002	0.41	-0.016	
	Min, max	0.7, 1.9	-0.33, 0.13	0.5, 3.0	-0.64, 0.52	
Hb-adjusted DLCO	N	22	21	26	26	0.179
(mL/min/mmHg) [2]	Mean (SD)	10.55 (3.83)	-0.35 (2.47)	15.57 (8.43)	1.65 (6.88)	
	Median	10.73	0.14	13.85	-0.10	
	Min, max	2.75, 18.19	-7.56, 2.92	5.63, 46.17	-1.93, 34.09	
Visit 11 (2 years)						
FEV_1 (L)	N	24	23	28	28	0.706 [1]
	Mean (SD)	1.16 (0.38)	-0.103 (0.120)	1.30 (0.67)	-0.121 (0.213)	
	Median	1.16	-0.090	1.19	-0.115	
	Min, max	0.7, 1.9	-0.33, 0.13	0.5, 3.0	-0.64, 0.52	
Achieved MCID≥100mL	Yes	1 (4.2%)		3 (10.7%)		
	No	22 (91.7%)		25 (89.3%)		
FVC (L)	N	24	23	28	28	0.729 [1]
	Mean (SD)	2.70 (0.70)	-0.080 (0.254)	2.98 (1.26)	-0.048 (0.406)	
	Median	2.60	-0.110	2.71	-0.095	
	Min, max	1.8, 4.3	-0.39, 0.72	1.1, 7.0	-0.90, 1.17	
FEV_1/FVC	N	24	23	28	28	0.260 [1]
	Mean (SD)	0.43 (0.10)	-0.024 (0.035)	0.43 (0.13)	-0.038 (0.054)	
	Median	0.41	-0.030	0.41	-0.041	
	Min, max	0.3, 0.6	-0.07, 0.05	0.2, 0.7	-0.18, 0.07	
Hb-adjusted DLCO	N	17	16	23	23	0.356
(mL/min/mmHg) [2]	Mean (SD)	10.11 (4.24)	-0.95 (2.47)	12.56 (6.07)	-0.18 (2.53)	
	Median	10.55	-0.99	11.42	-0.47	
	Min, max	2.07, 18.99	-6.71, 3.91	3.19, 24.71	-3.46, 6.11	

The intent-to-treat (ITT) population consisted of all randomized subjects analyzed in the group to which they were randomized, regardless of actual treatment received.

Abbreviations:

FEV_1 = forced expiratory volume in 1 second

FVC = forced vital capacity

Min = minimum

Max = maximum

MCID = minimum clinically important difference

SD = standard deviation

[1] Probability comparing changes from baseline from 2-sided t-test.

[2] Probability from 2-sided chi-square test.

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e-Table 3: Oxygen Saturation Pre- and Post-Six-Minute Walk Test by Visit (ITT Set)

	PROCHYMAL (n=30)					PLACEBO (n=32)				
SaO_2 (%)	Pre-Test	End of test	15 min post	30 min post	45 min post	Pre-Test	End of test	15 min post	30 min post	45 min post
Baseline (Visit 2, Day 0) [1]										
n	30	30	30	29	28	32	32	32	32	32
Mean (SD)	95.1 (2.52)	90.3 (5.28)	95.1 (3.22)	95.3 (2.71)	95.6 (2.71)	94.5 (2.05)	91.8 (3.80)	94.5 (3.04)	95.3 (2.51)	95.0 (2.68)
Median	95.5	91.0	96.0	96.0	96.0	94.0	92.0	95.0	95.0	94.5
Min, max	90, 98	75, 98	83, 99	90, 99	91, 100	90, 99	85, 98	89, 100	91, 99	91, 100
Visit 3 (Day 10)										
n	30	30	30	30	30	32	32	32	32	32
Mean (SD)	94.5 (2.42)	90.7 (4.68)	94.2 (3.02)	95.2 (2.25)	95.2 (2.60)	94.1 (2.49)	90.5 (5.05)	94.1 (2.76)	94.3 (2.43)	94.7 (2.02)
Median	94.0	91.0	94.5	95.5	95.0	94.0	91.0	94.0	94.0	95.0
Min, max	91, 99	81, 98	88, 99	91, 99	90, 99	90, 99	78, 98	87, 100	90, 99	91, 98
Visit 4 (1 month)										
n	30	30	30	30	29	32	32	32	32	32
Mean (SD)	94.1 (1.92)	89.7 (4.35)	94.1 (2.35)	94.9 (2.66)	94.4 (2.89)	94.4 (2.17)	91.8 (3.70)	95.0 (3.04)	95.1 (2.72)	95.2 (2.90)
Median	94.0	90.0	94.0	95.0	95.0	94.0	91.5	95.0	95.0	95.0
Min, max	90, 98	80, 97	90, 100	90, 100	90, 100	90, 98	84, 98	88, 100	90, 100	89, 100
Visit 5 (2 months)										
n	30	30	30	30	30	32	32	32	32	32
Mean (SD)	94.2 (2.27)	89.9 (4.35)	94.9 (2.68)	95.6 (2.66)	94.6 (2.83)	94.4 (2.21)	90.3 (5.37)	94.6 (2.41)	95.2 (2.57)	95.3 (2.36)
Median	93.5	90.5	94.5	95.5	95.0	94.0	91.0	94.0	95.0	95.5
Min, max	91, 98	80, 96	89, 99	91, 100	88, 100	91, 100	71, 98	90, 99	90, 100	90, 100
Visit 6 (3 months)										
n	30	30	30	30	30	32	32	32	32	32
Mean (SD)	94.2 (3.20)	90.3 (4.55)	95.1 (3.14)	95.0 (2.47)	95.6 (2.51)	94.7 (2.39)	91.0 (4.45)	95.5 (2.33)	95.3 (3.25)	95.3 (4.04)
Median	95.0	90.0	96.0	95.0	96.0	95.0	91.5	96.0	95.5	95.5
Min, max	92, 98	77, 98	89, 100	90, 100	90, 100	91, 99	82, 98	90, 99	83, 100	78, 100
Visit 7 (4 months)										
n	30	30	30	30	30	32	32	32	32	32
Mean (SD)	94.5 (2.45)	89.2 (4.85)	94.7 (2.80)	94.5 (3.27)	95.3 (2.96)	94.4 (1.95)	91.3 (5.17)	94.6 (2.42)	94.6 (1.72)	94.5 (2.69)
Median	94.5	90.0	95.0	95.0	95.5	94.5	91.5	94.0	94.5	94.5
Min, max	88, 98	79, 98	88, 99	84, 99	86, 100	91, 98	76, 100	90, 99	91, 99	86, 99
Visit 8 (5 months)										
n	27	27	27	27	27	30	30	30	30	30
Mean (SD)	94.1 (2.28)	91.3 (4.36)	94.0 (5.40)	94.0 (5.40)	94.5 (3.64)	94.6 (2.74)	91.7 (4.66)	95.0 (2.24)	94.9 (2.80)	94.8 (2.88)
Median	94.0	91.0	95.0	95.0	94.0	94.5	93.0	95.0	95.0	95.0
Min, max	90, 99	81, 99	70, 99	70, 99	81, 99	88, 99	81, 98	90, 99	84, 99	84, 99
Visit 9 (6 months)										
n	27	27	27	27	27	31	31	31	31	31
Mean (SD)	95.1 (2.25)	89.4 (6.28)	94.4 (3.30)	95.5 (2.28)	95.4 (2.31)	94.9 (2.19)	91.2 (4.15)	95.2 (2.73)	95.2 (2.54)	95.8 (2.66)
Median	95.0	91.0	95.0	96.0	96.0	95.0	91.0	95.0	96.0	96.0
Min, max	91, 99	75, 98	86, 99	90, 99	91, 99	90, 98	84, 99	87, 99	86, 98	85, 100
Visit 10 (1 year)										
n	22	22	22	22	22	26	26	26	26	26
Mean (SD)	94.9 (2.29)	91.8 (5.19)	93.9 (4.81)	94.5 (2.69)	95.1 (2.97)	95.0 (2.05)	92.1 (4.90)	94.3 (3.09)	93.9 (3.93)	94.5 (3.59)
Median	94.5	91.5	94.0	94.0	95.0	95.0	93.0	94.0	95.0	95.5
Min, max	91, 98	81, 98	76, 100	86, 98	86, 100	91, 98	78, 98	84, 99	82, 98	83, 98
Visit 11 (2 years)										
n	20	20	20	20	20	27	27	27	27	27
Mean (SD)	96.0 (2.20)	89.9 (4.56)	96.0 (2.48)	95.1 (2.45)	95.6 (2.09)	95.5 (2.31)	90.6 (4.23)	94.3 (2.92)	94.5 (2.05)	95.0 (1.91)
Median	96.5	90.0	97.0	95.5	96.5	96.0	92.0	95.0	95.0	95.0
Min, max	90, 99	77, 96	89, 99	90, 98	91, 98	92, 98	82, 97	85, 97	90, 98	90, 97

Notes: The intent-to-treat (ITT) set consistes of all randomized subjects analyzed in the group to which they were randomized, regardless of actual treatment received.

Min=minimum; max=maximum; min=minutes; SaO_2=oxygen saturation; SD=standard deviation

[1] Baseline is immediately pre-dose.

e-Table 4: Cytokine and C-reactive Protien Assays by Visit (Intent-to-Treat Population)

		PROCHYMAL (n=30)		PLACEBO (n=32)		
		Actual Value	Change from baseline	Actual Value	Change from baseline	P-value [1]
Baseline (Visit 2, Day 0)						
C-reactive protien (hs)	N	30		32		
	Mean (SD)	7.55 (12.83)		6.38 (7.90)		
	Median	2.59		5.20		
	Min, max	0.6, 62.9		0.4, 43.2		
Visit 3 (Day 10)						
C-reactive protien (hs)	N	30	30	32	32	0.886
	Mean (SD)	6.87 (13.23)	-0.68 (15.69)	6.17 (6.32)	-0.20 (9.50)	
	Median	2.92	-0.04	4.51	0.09	
	Min, max	0.6, 72.1	-41.4, 63.2	0.4, 25.0	-41.7, 19.0	
Visit 4 (1 Month)						
C-reactive protien (hs)	N	30	30	32	32	0.307
	Mean (SD)	4.97 (3.95)	-2.58 (10.80)	6.58 (7.63)	0.20 (10.45)	
	Median	3.23	-0.13	4.44	0.23	
	Min, max	0.7, 13.6	-49.9, 12.8	0.3, 32.4	-41.7, 24.5	
Visit 5 (2 Months)						
C-reactive protien (hs)	N	30	30	32	32	0.929
	Mean (SD)	5.57 (8.09)	-1.98 (8.09)	4.68 (4.31)	-1.70 (8.15)	
	Median	2.80	-0.32	3.61	-0.12	
	Min, max	0.3, 38.6	-58.1, 37.9	0.3, 17.8	-39.9, 11.0	
Visit 6 (3 Months)						
C-reactive protien (hs)	N	30	30	32	32	0.968
	Mean (SD)	4.94 (5.06)	-2.61 (13.16)	3.88 (3.01)	-2.50 (7.77)	
	Median	2.78	-0.09	3.59	-0.23	
	Min, max	05, 23.8	-58.4, 21.7	0.5, 12.9	-41.1, 3.1	
Visit 7 (4 Months)						
C-reactive protien (hs)	N	29	29	32	32	0.934
	Mean (SD)	6.68 (13.63)	-0.99 (7.20)	5.22 (4.91)	-1.16 (8.60)	
	Median	3.03	-0.18	3.47	0.00	
	Min, max	04, 74.3	-34.0, 11.4	0.2, 20.3	-40.1, 15.3	
Visit 8 (5 Months)						
C-reactive protien (hs)	N	28	28	31	31	0.253
	Mean (SD)	4.24 (3.98)	-3.58 (13.17)	7.03 (13.82)	0.75 (15.38)	
	Median	3.03	-0.10	3.50	-0.02	
	Min, max	0.6, 17.7	-59.6, 5.0	0.3, 76.3	-41.4, 68.2	
Visit 9 (6 Months)						
C-reactive protien (hs)	N	27	27	31	31	0.686
	Mean (SD)	9.76 (12.77)	2.03 (19.01)	6.56 (12.45)	0.28 (13.58)	
	Median	4.39	-0.16	4.00	-0.06	
	Min, max	0.4, 44.4	-53.7, 42.9	0.3, 68.9	-41.6, 60.7	
Visit 10 (1 Year)						
C-reactive protien (hs)	N	25	25	28	28	0.908
	Mean (SD)	5.63 (5.97)	-2.53 (13.34)	3.42 (3.12)	-2.88 (8.34)	
	Median	2.90	0.22	2.12	-0.74	
	Min, max	0.4, 21.7	-53.7, 19.3	0.3, 11.2	-41.3, 3.5	
Visit 11 (2 Years)						
C-reactive protien (hs)	N	19	19	26	26	0.732
	Mean (SD)	5.68 (5.20)	-3.38 (13.11)	4.26 (5.07)	-2.22 (9.32)	
	Median	4.82	-0.07	2.44	-0.61	
	Min, max	0.5, 20.4	-42.5, 9.7	0.2, 22.2	-41.0, 14.7	

Notes: The intent-to-treat (ITT) set consists of all randomized subjects analyzed in the group to which they were randomized, regardless of actual treatment received.
Min = minimum; max = maximum; SD = standard deviation; TGF = transforming growth factor.
[1] Probability comparing changes from baseline from two-sided t-tests.

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