Supplemental Online Content

Martinez FJ, Yow E, Flaherty KR, et al; the CleanUP-IPF Investigators of the Pulmonary Trials Cooperative HE. Effect of antimicrobial therapy on respiratory hospitalization or death in adults with idiopathic pulmonary fibrosis: the CleanUP-IPF Randomized Clinical Trial. *JAMA*. doi:10.1001/jama.2021.4956

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Detailed inclusion and exclusion criteria.

Inclusion Criteria

1. ≥ 40 years of age
2. Diagnosed with IPF by enrolling investigator
3. Signed informed consent

Exclusion Criteria

1. Received antimicrobial therapy in the past 30 days for treatment purposes (antibiotic prophylaxis for procedures do not meet criteria, nor do antivirals)
2. Contraindicated for antibiotic therapy, including but not exclusive to:
    a. Allergy or intolerance to BOTH tetracyclines AND trimethoprim, sulfonamides or their combination
    b. Allergy or intolerance to tetracyclines AND known potassium level > 5 mEq/L in the past 90 days.
        i. If the enrolling physician feels the potassium level has normalized, documentation to that effect must be provided.
    c. Allergy or intolerance to tetracyclines AND concomitant use of angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), potassium sparing diuretic, dofetilide, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide
    d. Allergy or intolerance to tetracyclines AND known glucose-6-phosphate dehydrogenase deficiency
    e. Allergy or intolerance to tetracyclines AND untreated folate or B12 deficiency
    f. Allergy or intolerance to tetracyclines AND known renal insufficiency (defined as a GFR < 30 ml/min within the previous 90 days)
        i. If the enrolling physician feels the renal dysfunction has resolved, documentation to that effect must be provided.
    g. Seizure disorder on antiepileptic therapy.
3. Pregnant (as determined by urine dipstick pregnancy test at randomization), or anticipate becoming pregnant
4. Use of an investigational study agent for IPF therapy within the past 30 days, or an IV infusion with a half-life of four (4) weeks
5. Concomitant immunosuppression with azathioprine, mycophenolate, cyclophosphamide, or cyclosporine.

eTable 2. Pre-specified secondary endpoints.

- Time to death from any cause
- Time to first non-elective, respiratory hospitalization
- Time to first non-elective, all-cause hospitalization
- Total number of non-elective respiratory hospitalizations
- Total number of non-elective all-cause hospitalizations
- Change in FVC from randomization to 12 months
- Change in DLCO from randomization to 12 months
- Total number of respiratory infections
- UCSD-Shortness of Breath Questionnaire at 12 months
- Fatigue Severity Scale score at 12 months
- Leicester Cough Questionnaire score at 12 months
- EQ-5D score and SF-12 score at 12 months
- ICEpop CAPability measure for Older people score at 12 months

eTable 3. Statistical power assuming a sample size of 500 randomized patients

Usual care plus antimicrobial therapy event rate*	Usual care event rate	One-year Event Rate Reduction	Power
16.8%	24%	30%	78%
21.0%	30%	30%	87%
25.2%	36%	30%	93%
16.0%	24%	33.3%	86%
20.0%	30%	33.3%	93%
24.0%	36%	33.3%	97%
15.6%	24%	35%	89%
19.5%	30%	35%	95%
23.4%	36%	35%	98%

*12-month event rates. Calculations assume a 2-sided Type-I error rate of 0.05. The minimum follow-up is planned to be 12 months and the maximum follow-up is 42 months. Drop-out rates are assumed to be approximately 2% per year. Power calculations were based on a log-rank test with assumed event rates were exponentially distributed. Calculations were computing using nQuery 7.0 software.

eTable 4. Primary endpoint and its components as a function of Clinical Endpoint Committee (CEC) Adjudication or Clinical Site determination.

Event	Usual care plus antimicrobial therapy strategy (n=254)	Usual Care (n=259)	Hazard Ratio with 95% Confidence Intervals
Primary endpoint (CEC)			
Death or first non-elective, respiratory hospitalization, n (%)	52 (20.5%)	56 (21.6%)	1.04 (0.71, 1.53)
Primary endpoint (Site Investigator)			
Death or first non-elective, respiratory hospitalization, n (%)	52 (20.5%)	55 (21.2%)	1.06 (0.72, 1.56)
Primary endpoint components (CEC)			
Death, n (%)	37 (14.6%)	37 (14.3%)	1.11 (0.70, 1.78)
First non-elective, respiratory hospitalization, n (%)	36 (14.2%)	30 (11.6%)	1.11 (0.70, 1.78)
Primary endpoint components (Site Investigator)			
Death, n (%)	37 (14.6%)	37 (14.3%)	1.39 (0.85, 2.27)
First non-elective, respiratory hospitalization, n (%)	38 (15.0%)	29 (11.2%)	1.49 (0.91, 2.43)

eTable 5. Total events and event rates for the primary endpoint and its components as a function of the Clinical Event Adjudication Committee, clinical site and best available determination.

Event	Clinical Adjudication Committee	Clinical Site	Best Available
Composite Primary Endpoint			
Total number of events	108	107	108
Follow-up (years)	559.3	560.6	559.1
Rate, events/year	0.118	0.191	0.193
Primary endpoint Components			
Death			
Total number of events	74	74	74
Follow-up (years)	593.6	593.6	593.6
Rate, events/year	0.125	0.125	0.125
Non-elective respiratory hospitalization			
Total number of events	66	67	67
Follow-up (years)	559.3	560.6	559.1
Rate, events/year	0.118	0.120	0.120

eTable 6. Multivariable modelling using best available data and multiple imputation for the primary composite and its components.

Composite endpoint or its component	Hazard Ratio Estimate (95% CI)	P-value
Time to death or 1st nonelective respiratory hospitalization		
Antimicrobial therapy + usual care vs usual care*	1.04 (0.71, 1.53)	0.83
Age (per 10 years)	1.06 (0.80, 1.42)	0.69
Female	0.85 (0.51, 1.42)	0.53
Baseline DL_{co} %pred (per 10 percentage points)	0.69 (0.57, 0.82)	<0.001
Baseline FVC %pred (per 10 percentage points)	0.86 (0.75, 0.98)	0.002
NAC use at enrollment	1.93 (1.03, 3.63)	0.04
Pirfenidone at enrollment	1.14 (0.68, 1.91)	0.62
Nintedanib at enrollment	1.23 (0.74, 2.04)	0.43
Pre-randomization co-trimoxazole cohort	0.88 (0.59, 1.31)	0.53
Time to death		
Antimicrobial therapy + usual care vs usual care	1.11 (0.70, 1.78)	0.65
Age (per 10 years)	1.10 (0.78, 1.58)	0.56
Female	0.78 (0.41, 1.50)	0.46
Baseline DL_{co} %pred (per 10 percentage points)	0.65 (0.53, 0.81)	<0.001
Baseline FVC %pred (per 10 percentage points)	0.87 (0.75, 1.02)	0.08
NAC use at enrollment	1.73 (0.78, 3.81)	0.18
Pirfenidone at enrollment	1.04 (0.55, 1.97)	0.90
Nintedanib at enrollment	1.10 (0.59, 2.05)	0.78
Pre-randomization co-trimoxazole cohort	0.91 (0.56, 1.46)	0.69
Time to 1st nonelective respiratory hospitalization		
Antimicrobial therapy + usual care vs usual care	1.34 (0.82, 2.17)	0.25
Age (per 10 years)	1.11 (0.77, 1.59)	0.58
Female	0.75 (0.38, 1.48)	0.40
Baseline DL_{co} %pred (per 10 percentage points)	0.73 (0.58, 0.91)	0.006
Baseline FVC %pred (per 10 percentage points)	0.88 (0.75, 1.03)	0.11
NAC use at enrollment	1.40 (0.56, 3.59)	0.48
Pirfenidone at enrollment	1.10 (0.58, 2.11)	0.77
Nintedanib at enrollment	1.18 (0.62, 2.23)	0.62
Pre-randomization co-trimoxazole cohort	0.93 (0.56, 1.53)	0.77

NAC – N-acetylcysteine

*A sensitivity analysis using the robust sandwich estimate of Lin and Wei (1989) for the covariance matrix resulted in an adjusted hazard ratio of 1.05, 95%CI 0.72, 1.54.for antimicrobial therapy + usual care vs. usual care alone.

eTable 7. Total events and event rates for the primary endpoint by GAP score as a function of the Clinical Event Adjudication Committee, Site Investigator, and Best Available determination.

Event	Clinical Adjudication Committee	Clinical Site	Best Available
GAP I (n=114)			
Total number of events	11	12	11
Follow-up (years)	133.2	133	133.2
Rate, events/year	0.083	0.09	0.083
GAP II (n=257)			
Total number of events	49	51	49
Follow-up (years)	292.1	289.76	291.9
Rate, events/year	0.168	0.176	0.168
GAP III (n=113)			
Total number of events	39	37	39
Follow-up (years)	309.3	113.6	111.8
Rate, events/year	0.349	0.326	0.349

eTable 8. Multivariable modelling using multiple imputations for the change from baseline to 12 months in secondary endpoints.

Physiological endpoint	Estimate (95% CI)	P-value
FVC (L)		
Antimicrobial therapy + usual care vs usual care	0.04 (-0.02, 0.10)	0.22
Age (per 10 years)	0.01 (-0.04, 0.05)	0.85
Female	0.02 (-0.06, 0.10)	0.63
Baseline DL_{CO} %pred (per 10 percentage points)	0.01 (-0.01, 0.04)	0.31
Baseline FVC %pred (per 10 percentage points)	-0.03 (-0.05, -0.00)	0.02
NAC use at enrollment	-0.07 (-0.13, 0.04)	0.32
Pirfenidone at enrollment	-0.04 (-0.13, 0.04)	0.32
Nintedanib at enrollment	0.02 (-0.07, 0.11)	0.61
Pre-randomization co-trimoxazole cohort	0.05 (-0.12, 0.01)	0.12
DLCO corrected for hemoglobin (mL/min/mmHg)		
Antimicrobial therapy + usual care vs usual care	0.35 (-0.53, 1.05)	0.33
Age (per 10 years)	0.14 (-0.63, 0.35)	0.57
Female	0.08 (-0.73, 0.88)	0.86
Baseline DL_{CO} %pred (per 10 percentage points)	0.25 (-0.52, 0.03)	0.08
Baseline FVC %pred (per 10 percentage points)	0.21 (-0.03, 0.44)	0.08
NAC use at enrollment	1.86 (-3.21, -0.50)	0.007
Pirfenidone at enrollment	0.54 (-0.57, 1.37)	0.27
Nintedanib at enrollment	0.40 (-0.57, 1.37)	0.42
Pre-randomization co-trimoxazole cohort	0.65 (-1.36, 0.06)	0.07
UCSD Shortness of Breath Questionnaire		
Antimicrobial therapy + usual care vs usual care	-0.59 (-4.62, 3.43)	0.77
Age (per 10 years)	0.57 (-2.38, 3.52)	0.70
Female	-3.02 (-8.05, 2.02)	0.24
Baseline DL_{CO} %pred (per 10 percentage points)	-0.33 (-2.02, 1.37)	0.70
Baseline FVC %pred (per 10 percentage points)	-0.89 (-2.22, 0.43)	0.19
NAC use at enrollment	-0.09 (-8.09, 7.91)	0.98
Pirfenidone at enrollment	4.68 (-0.77, 10.12)	0.09
Nintedanib at enrollment	1.43 (-4.01, 6.87)	0.61
Pre-randomization co-trimoxazole cohort	1.58 (-2.57, 5.73)	0.46
Fatigue Severity Score		
Antimicrobial therapy + usual care vs usual care	0.10 (-0.26, 0.46)	0.59
Age (per 10 years)	0.01 (-0.25, 0.28)	0.93
Female	0.07 (-0.38, 0.51)	0.78
Baseline DL_{CO} %pred (per 10 percentage points)	0.03 (-0.11, 0.18)	0.65
Baseline FVC %pred (per 10 percentage points)	-0.89 (-2.22, 0.43)	0.63
NAC use at enrollment	0.58 (-0.12, 1.29)	0.98
Pirfenidone at enrollment	-0.09 (-0.57, 0.40)	0.72
Nintedanib at enrollment	0.08 (-0.41, 0.56)	0.61
Pre-randomization co-trimoxazole cohort	-0.13 (-0.50, 0.24)	0.49
Leicester Cough Questionnaire		
Antimicrobial therapy + usual care vs usual care	0.01 (-0.82, 0.80)	0.98

Physiological endpoint	Estimate (95% CI)	P-value
Age (per 10 years)	0.17 (-0.77, 0.43)	0.58
Female	0.32 (-0.70, 1.34)	0.54
Baseline DL_{CO} %pred (per 10 percentage points)	0.06 (-0.40, 0.28)	0.73
Baseline FVC %pred (per 10 percentage points)	0.08 (-0.18, 0.35)	0.54
NAC use at enrollment	0.25 (-1.36, 1.85)	0.77
Pirfenidone at enrollment	0.69 (-1.78, 0.40)	0.21
Nintedanib at enrollment	0.59 (-1.67, 0.50)	0.29
Pre-randomization co-trimoxazole cohort	0.03 (-0.80, 0.87)	0.94
EuroQol Index Score		
Antimicrobial therapy + usual care vs usual care	0.007 (-0.04, 0.05)	0.75
Age (per 10 years)	-0.003 (-0.03, 0.03)	0.87
Female	0.002 (-0.05, 0.68)	0.94
Baseline DL_{CO} %pred (per 10 percentage points)	0.003 (-0.02, 0.02)	0.78
Baseline FVC %pred (per 10 percentage points)	0.019 (0.005, 0.03)	0.008
NAC use at enrollment	0.01 (-0.08, 0.10)	0.79
Pirfenidone at enrollment	-0.01 (-0.07, 0.05)	0.68
Nintedanib at enrollment	0.003 (-0.06, 0.06)	0.93
Pre-randomization co-trimoxazole cohort	0.006 (-0.04, 0.05)	0.80
SF12 mental score		
Antimicrobial therapy + usual care vs usual care	0.46 (-1.45, 2.37)	0.64
Age (per 10 years)	-0.17 (-1.57, 1.23)	0.82
Female	-1.37 (-3.75, 1.02)	0.26
Baseline DL_{CO} %pred (per 10 percentage points)	0.37 (-0.41, 1.15)	0.35
Baseline FVC %pred (per 10 percentage points)	0.33 (-0.30, 0.96)	0.31
NAC use at enrollment	0.18 (-3.70, 4.06)	0.93
Pirfenidone at enrollment	-2.60 (-5.16, -0.03)	0.05
Nintedanib at enrollment	-1.87 (-4.44, 0.71)	0.16
Pre-randomization co-trimoxazole cohort	-0.73 (-2.70, 1.24)	0.47
SF14 physical score		
Antimicrobial therapy + usual care vs usual care	0.46 (-1.18, 2.10)	0.58
Age (per 10 years)	0.49 (-0.72, 1.69)	0.43
Female	-0.19 (-2.23, 1.85)	0.85
Baseline DL_{CO} %pred (per 10 percentage points)	0.24 (-0.44, 0.91)	0.49
Baseline FVC %pred (per 10 percentage points)	0.09 (-0.45, 0.64)	0.74
NAC use at enrollment	-1.50 (-4.83, 1.82)	0.38
Pirfenidone at enrollment	1.30 (-0.89, 3.51)	0.24
Nintedanib at enrollment	1.81 (-0.39, 4.02)	0.11
Pre-randomization co-trimoxazole cohort	-1.59 (-3.28, 0.11)	0.07
ICECAP-O		
Antimicrobial therapy + usual care vs usual care	0.01 (-0.03, 0.05)	0.64
Age (per 10 years)	-0.03 (-0.06, 0.001)	0.06
Female	-0.03 (-0.08, 0.03)	0.34
Baseline DL_{CO} %pred (per 10 percentage points)	-0.002 (-0.019, 0.015)	0.85
Baseline FVC %pred (per 10 percentage points)	-0.01 (-0.02, 0.01)	0.32
NAC use at enrollment	-0.02 (-0.10, 0.06)	0.60

Physiological endpoint	Estimate (95% CI)	P-value
Pirfenidone at enrollment	0.003 (-0.05, 0.06)	0.91
Nintedanib at enrollment	-0.03 (0.08, 0.03)	0.39
Pre-randomization co-trimoxazole cohort	-0.01 (-0.05, 0.03)	0.71

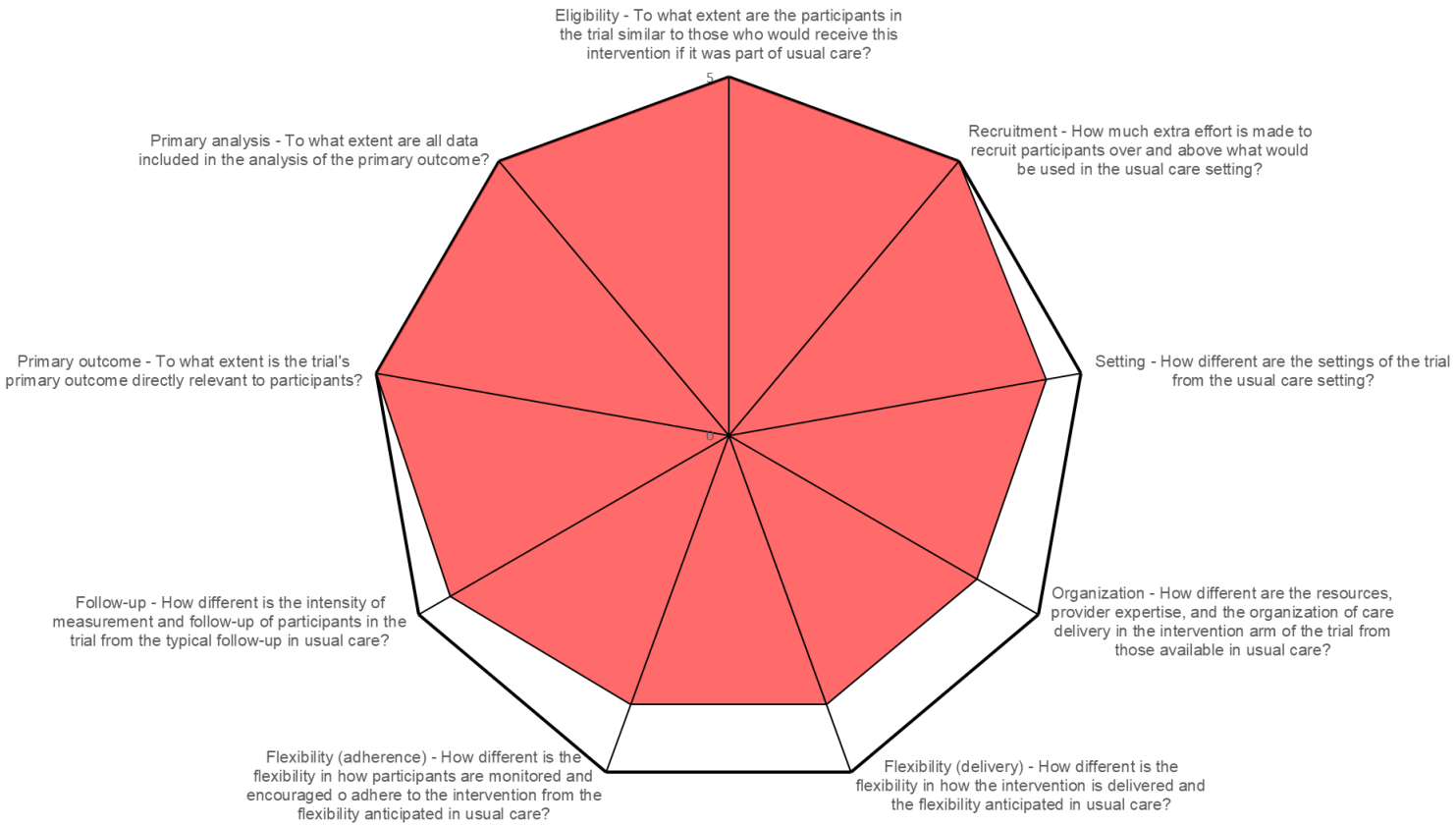
NAC – N-acetylcysteine

eTable 9. Serious adverse events and adverse events of special interest by pre-randomization cohort.

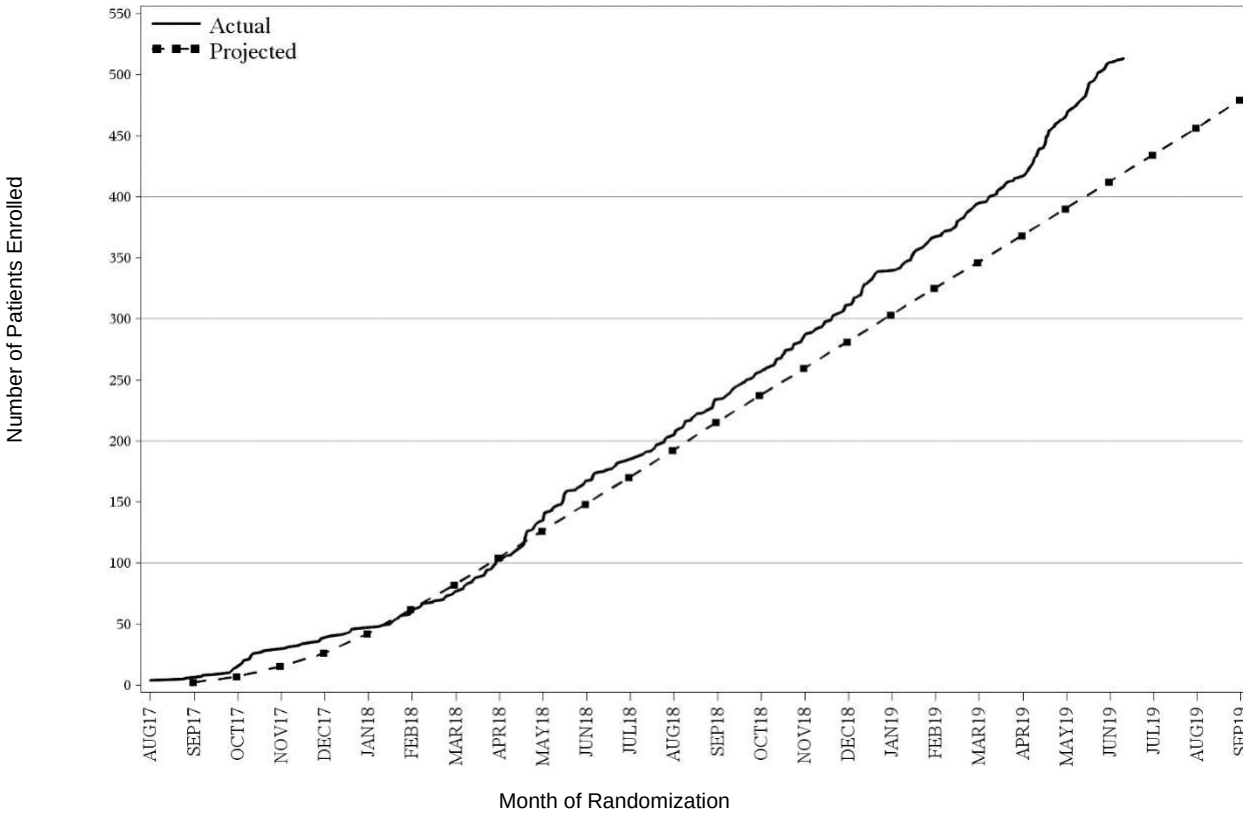
	Pre-randomization Co-trimozazole Cohort		Pre-randomization Doxycycline Cohort	
Serious Adverse Events*	**Antimicrobial Therapy + Ususal Care (n=128)**	**Usual Care (n=144)**	**Antimicrobial Therapy + Ususal Care (n=126)**	**Usual Care (n=115)**
Any SAE	36 (28.1%)	37 (25.7%)	35 (27.8%)	28 (24.3%)
Respiratory, thoracic and mediastinal	22 (17.2%)	15 (10.4%)	20 (15.9%)	11 (9.6%)
Idiopathic Pulmonary Fibrosis	12 (9.4%)	4 (2.8%)	4 (3.2%)	1 (0.9%)
Dyspnea	1 (0.8%)	1 (0.7%)	4 (3.2%)	1 (0.9%)
Respiratory failure	4 (3.1%)	3 (2.1%)	1 (0.8%)	1 (0.9%)
Cardiovascular	5 (3.9%)	5 (3.5%)	6 (4.8%)	6 (5.2%)
Infections	2 (1.6%)	12 (8.3%)	5 (4.0%)	5 (4.3%)
Pneumonia	2 (1.6%)	5 (3.5%)	3 (2.4%)	2 (1.7%)
Nervous System	1 (0.8%)	2 (1.4%)	7 (5.6%)	1 (0.9%)
Syncope	0 (0%)	0 (0%)	3 (2.4%)	0 (0%)
Loss of consciousness	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)
Gastrointestinal	0 (0%)	3 (2.1%)	3 (2.4%)	1 (0.9%)
Metabolism and nutrition	1 (0.8%)	3 (2.1%)	1 (0.8%)	1 (0.9%)
Adverse Events of Special Interest				
Arrhythmia	1 (0.8%)	2 (1.4%)	1 (0.8%)	3 (2.6%)
Vomiting	6 (4.7%)	1 (0.7%)	6 (4.8%)	1 (0.9%)
Hyperkalemia	9 (7.0%)	2 (1.4%)	1 (0.8%)	0 (0%)
Rash	11 (8.6%)	0 (0%)	6 (4.8%)	0 (0%)
Diarrhea	8 (6.3%)	3 (2.1%)	18 (14.3%)	5 (4.3%)

*Specific SAEs occurring in more than 1% of the population are reported.

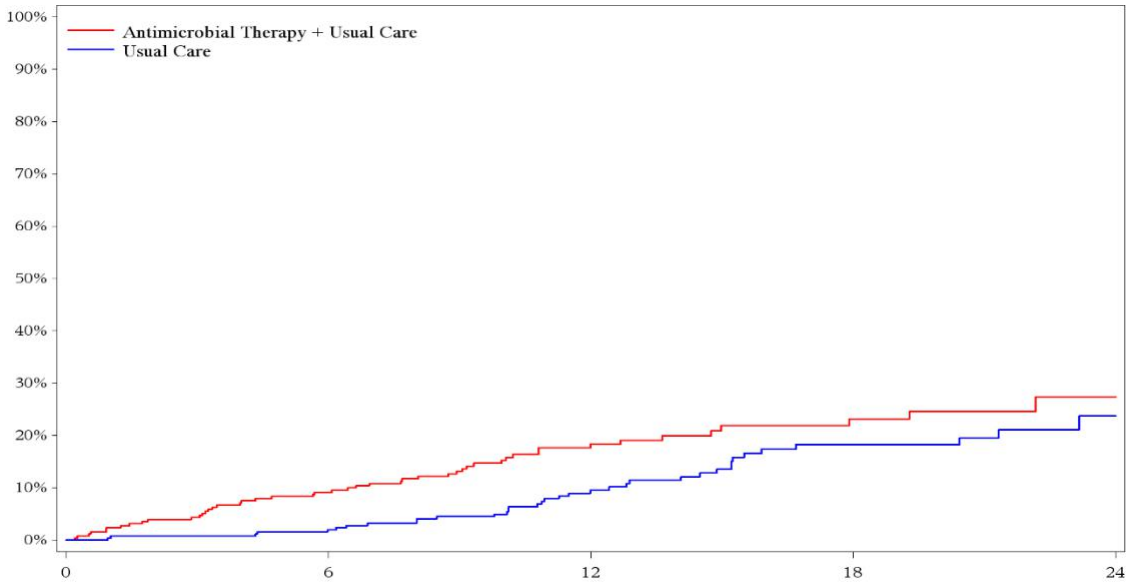
eFigure 1. PRECIS-2 diagram



eFigure 2. Enrollment (Actual vs. Projection).



eFigure 3. Time to withdrawal from study.

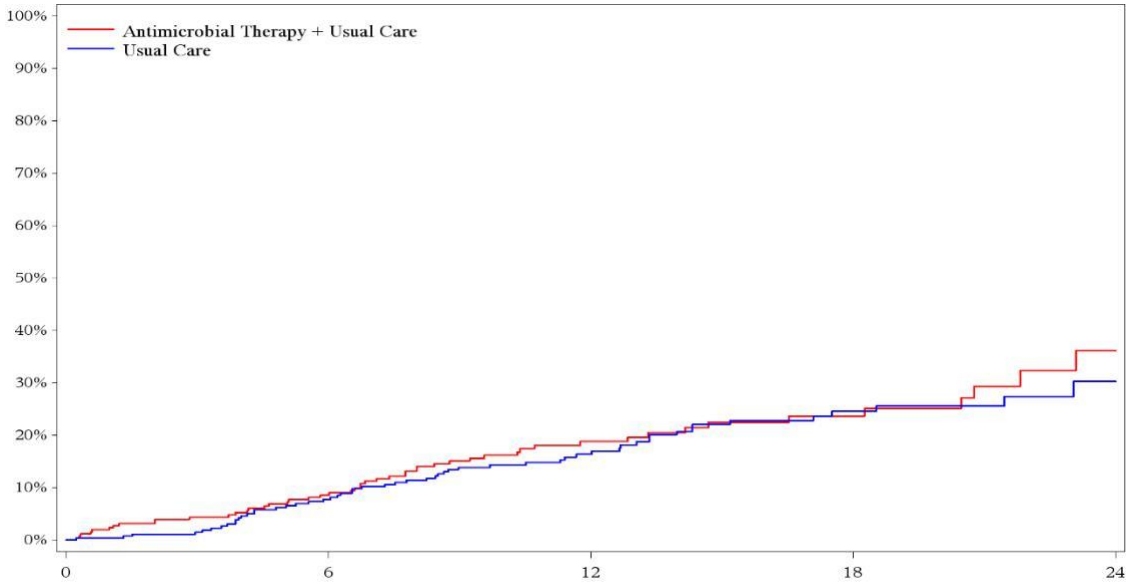


Months since randomization

AT	254	221	116	59	15
SC	259	239	154	85	23

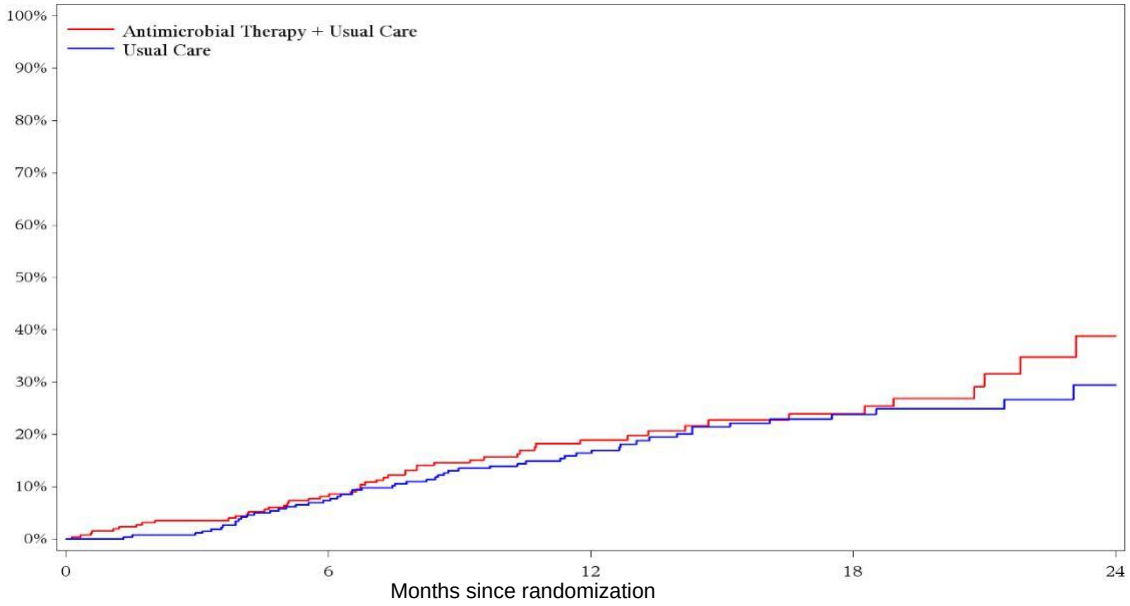
eFigure 4. Time to first non-elective respiratory hospitalization or death using the Clinical Endpoint Committee adjudicated (Panel A) and Site Investigator (Panel B) determined outcomes.

A.



AT	254	213	108	53	13
SC	259	232	147	77	17

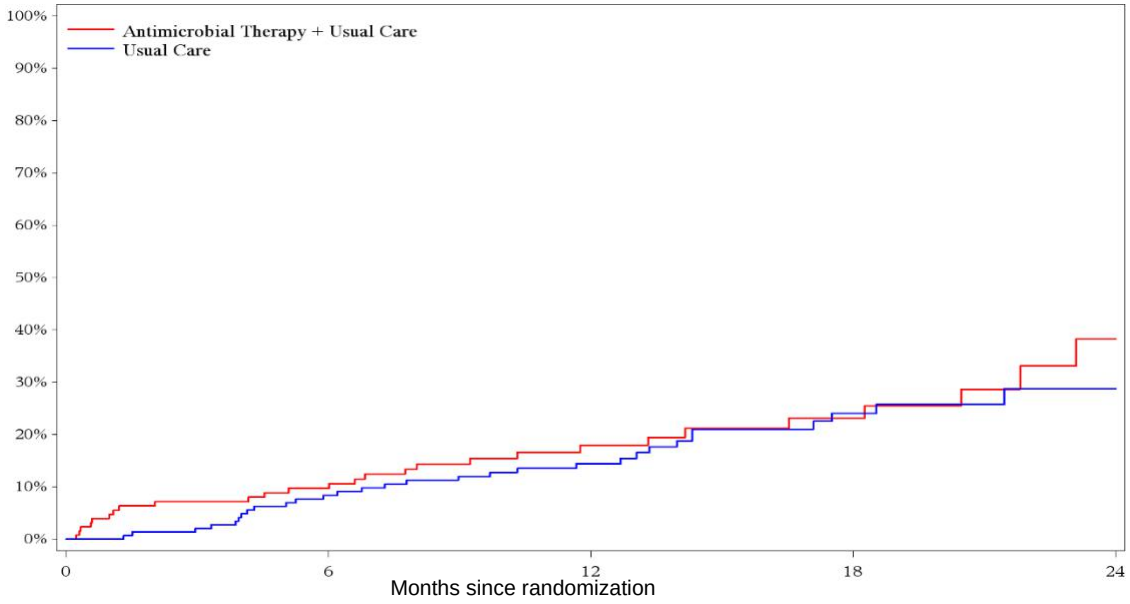
B.



AT	254	215	108	53	11
SC	259	233	148	78	18

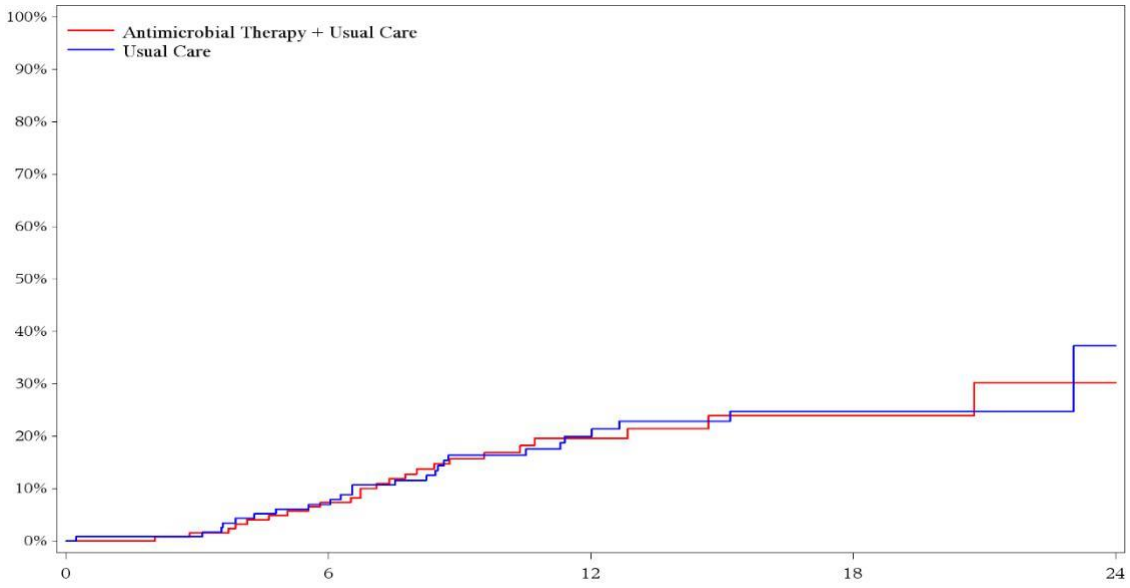
eFigure 5. Time to first non-elective respiratory hospitalization or death for the Pre-Randomization Co-trimoxazole (Panel A) or Doxycycline (Panel B) Cohorts.

A.



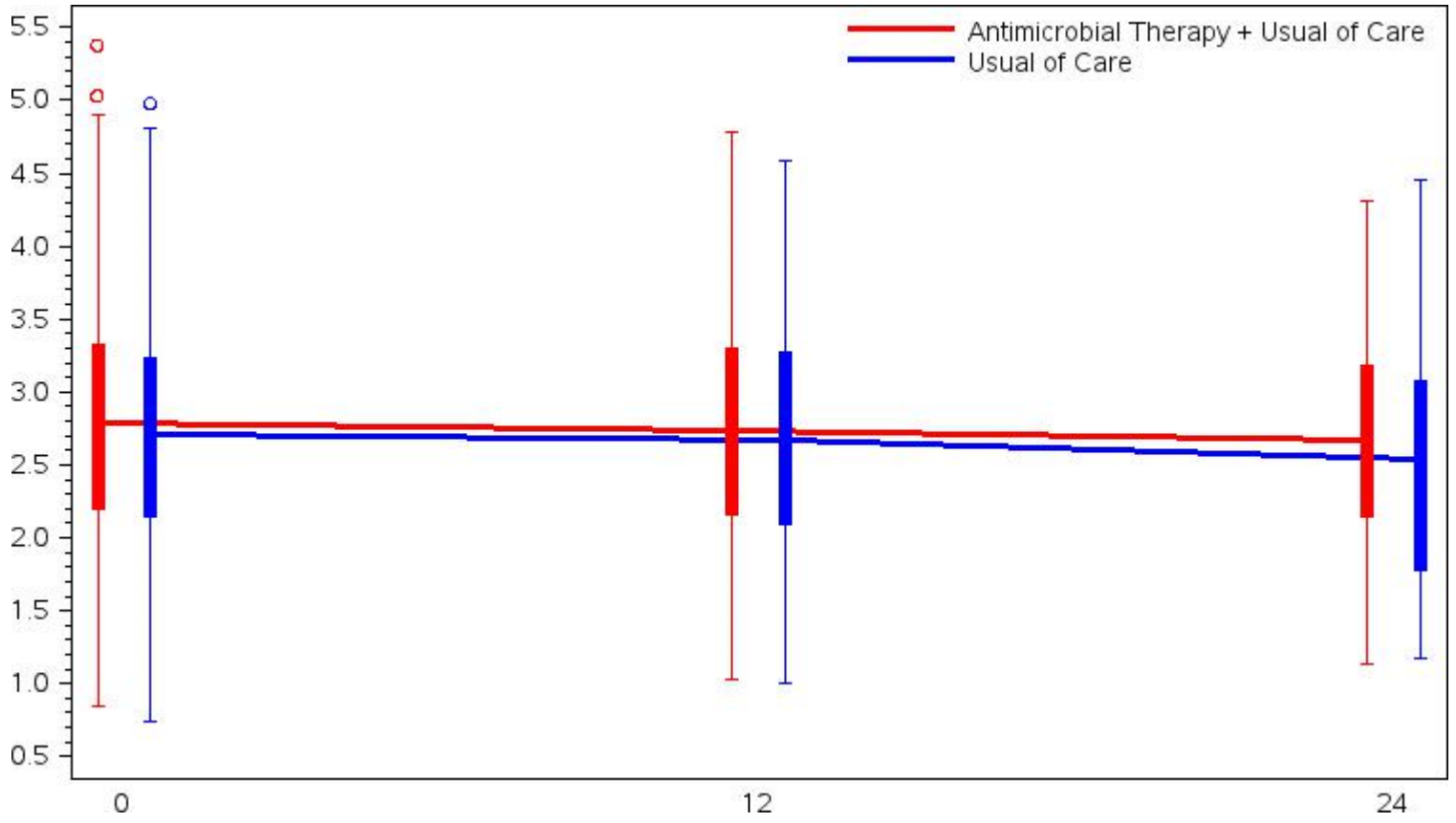
AT	128	104	59	33	10
SC	144	129	91	46	13

B.



AT	126	109	49	20	3
SC	115	103	55	31	4

eFigure 6. Boxplots of FVC at each Study Visit



Number of Patients

AT	247	148	53
SC	255	168	69

Supplemental Appendix 4

DSMB Communications

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

December 19, 2019

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Dear Drs. Martinez and Anstrom:

The purpose of this letter is to document formally the National Heart, Lung, and Blood Institute's (NHLBI) decision for early termination of the Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP-IPF) within the Pulmonary Trials Cooperative (PTC). This decision was informed by the recommendation of the Data and Safety Monitoring Board (DSMB) and subsequent NHLBI review as described below.

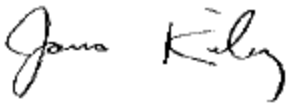
The DSMB met on December 18, 2019 to review the first planned efficacy analysis for CleanUp-IPF, and unanimously voted to terminate the study early for futility and to proceed with an orderly close-out. This determination was based on the low likelihood of the study demonstrating a statistically significant positive effect of the intervention. Although no clear harm signal was seen, the DSMB also noted a trend toward a higher rate of the primary outcome (non-elective respiratory hospitalization or all-cause mortality), mortality, and SAEs in the intervention arm, further supporting its recommendation to proceed to early orderly close-out. The DSMB recommends that the last study visit occur within 3 months (by mid-March) and patients may complete their course of study agent until their next (and last) visit.

The NHLBI carefully reviewed the DSMB recommendations. On December 19, 2019, Dr. Lora Reineck notified you of the intent of the Institute to concur with the DSMB recommendation for early termination.

The NHLBI is hopeful that we can achieve our shared goal of maximizing the information and generalizable knowledge gained from the study.

Thank you for your leadership on this important study.

Sincerely,



James P. Kiley, Ph.D.
Director, Division of Lung Diseases
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cc:
Dr. Frank Sciurba
Dr. Stephen Wisniewski
Dr. Tony Punturieri
Ms. Lisa Viviano
Mr. Andre Walker
Dr. Tom Croxton
Dr. Lora Reineck
Dr. Amy Patterson
Dr. Nakela Cook

Operations Memo CL023

TO: CleanUP IPF Clinical Site Principal Investigators and Lead Coordinators

FROM: NEMO and CleanUP IPF PLG

DATE: December 20, 2019

RE: End of Study Operations; Trial Card

CleanUP *Operations Memos are posted on the PTC website under* Documents – CleanUP Documents*. Recipients are encouraged to download and file these memos for ready reference.*

The purpose of this memo is to inform you that the CleanUP-IPF Data Safety Monitoring Board met on December 18, 2019 to review the first planned efficacy analysis for the trial, and unanimously voted to terminate the study early for futility and to proceed with an orderly study close-out. This determination was based on the low likelihood of the study demonstrating a statistically significant positive effect of the intervention. Although no clear harm signal was seen, the DSMB also noted a trend toward a higher rate of the primary outcome (non-elective respiratory hospitalization or all-cause mortality), mortality, and SAEs in the intervention arm, further supporting its recommendation to proceed to early orderly close-out.

The study PIs recommend contacting the individual patients on antimicrobial therapy to discontinue study treatment as soon as possible. All study patients, including those on standard of care, should be contacted by January 31 for a safety check and requested to have a final study visit scheduled and completed by March 13, 2020. Any visits scheduled prior to January 31 can be scheduled as end of study visits. A letter for the participants with more details will be sent in early January 2020.

Trial Card vouchers will be deactivated January 31, 2020.

A copy of the DSMB recommendation is included on pages two and three of this memo. ***This memo is not a close out letter***. Your official close out letter will come on completion of all study visits and data queries.

Please submit this memo and the DSMB letter to your local IRB in the next two weeks. Once you have submitted to your IRB, please e-mail the NEMO at pulmonarytrials@edc.pitt.edu to let us know. You will also need to send a copy of your IRB's response letter to the same e-mail address

Please submit a Help Desk Ticket on the PTC website (https://www.pulmonarytrials.org) with any questions or concerns.