Statistical Analysis Plan

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Table of Contents

I. Overview

CleanUP-IPF is a randomized, unblinded, multi-center clinical trial of patients with a diagnosis of idiopathic pulmonary fibrosis (IPF). A total of approximately 500 patients will be enrolled in the trial. Eligible patients will be randomized to the following treatment strategies:

- Standard care
- Standard care + oral antimicrobial therapy

Patients randomized to receive antimicrobial therapy will be given co-trimoxazole unless they have an allergy, contraindication to co-trimoxazole, renal insufficiency (GFR < 30 ml), are hyperkalemic (potassium > 5 mEq/L), or are concomitantly taking an angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or potassium sparing diuretic in which case they will receive doxycycline.

II. Study Design

Randomization

Eligible patients will be randomized 1:1 to either receive or not receive a prescription drug voucher for oral antimicrobial therapy in the form of one double strength 160mg trimethoprim/800mg sulfamethoxazole (double strength co-trimoxazole) twice daily plus folic acid 5 mg daily OR doxycycline 100mg once daily if weight < 50 kilograms or 100mg twice daily if weight > 50 kilograms.

Data Sources

A database of case report form and biomarker core lab data will be created in eClincalOS (eCOS), and the data then transferred to SAS for analysis. The randomized treatment assignment will be provided through data collected by the eCOS system.

III. Analysis Population and Missing Data

The primary analysis will be based on intention to treat. All randomized patients will be included in the analysis population for assessing the primary and secondary endpoints. Extensive efforts being made in connection with the clinical sites to ensure data quality and completeness, it is expected that exclusion of patients for any endpoint analysis will be minimal.

For the primary endpoint patients without any observed non-elective, respiratory hospitalization or all-cause mortality will be censored at their last visit or lung transplantation. For the adjustment variables in the primary model the imputation method will be dictated by the amount of missingness. If all the adjustment variables

have a missing data rate of 2% or below (approximately 10 or less out of 500) then a simple imputation mehod will implemented. If any one of the adjustment variables has a missing data rate over 2% (approximately more than 10 out of 500) then multiple imputation mehod will implemented. For the simple approach categorical adjustment variables will be imputed to the mode and continuous adjustment variables will be imputed to the median value. For the multiple imputation the full conditional specification method (FCS) method wil be used and assume an arbitrary missing data pattern [Berglund and Heeringa 2014]. The multiple imputation scenario (20 planned iterations) will be constructed which includes the treatment group indicator variable and the adjustment variables planned for the primary model.

IV. General Methodology

Definition of Statistical Significance: The statistical plan will test non-directional hypotheses, i.e., all tests will be 2-sided. The level of significance for all efficacy and safety analyses will be 0.05.
Statistical Tests: For situations were one observation per patient is observed, (e.g. safety comparisons at individual time points), a general analysis convention will be used unless otherwise specified. For continuous and ordinal variables, treatment group differences will be tested using the Wilcoxon rank-sum test for two groups and Kruskal-Wallis one-way analysis of variance for comparisons of more than two groups. For censored data, like time to event, treatment group differences will be tested using the log rank test. For discrete variables, treatment group differences will be tested using the chi-square test. In the situation of low cell counts the treatment group differences will be tested using Fisher's exact method.
Descriptive Statistics: For continuous and ordinal variables the number of observations, number of missing values, mean, standard deviation, median, twenty-fifth percentile, and seventy-fifth percentile will be given. For binary (e.g. yes/no), categorical, and/or ordinal variables a simple count and percent will be provided. Other statistics may be considered if necessary.
Descriptive Plots: Descriptive plots may replace or produced in addition to descriptive statistics if deemed appropriate. If deemed necessary plots of descriptive statistics such as spaghetti, mosaic, box, cumulative distribution, and loess curves will be provided.
Study Listings: Study data will be listed by treatment group, visit if applicable, and patient where appropriate.
Software and Validation Procedures: All data presented in interim and final analyses will be generated and validated under the guidance of the DCRI Clinical Trials Statistical SOPs.

V. Primary Endpoint

The primary endpoint of this study will be the comparison of "Standard care + oral antimicrobial therapy" and "Standard care" for the time to first non-elective, respiratory hospitalization or all-cause mortality.

VI. Secondary Endpoints

Secondary goals of this study are to assess differences between treatment groups for the following:

1. Time to death from any cause
2. Time to first non-elective respiratory hospitalization
3. Time to first non-elective all-cause hospitalization
4. Total number of non-elective respiratory hospitalizations
5. Total number of non-elective all-cause hospitalizations
6. Change in FVC from randomization to 12 months
7. Change in DLCO from randomization to 12 months
8. Total number of respiratory infections
9. Change in UCSD-Shortness of Breath Questionnaire from randomization to 12 months
10. Change in Fatigue Severity Scale score from randomization to 12 months
11. Change in Leicester Cough Questionnaire score from randomization to 12 months
12. Change in EQ-5D score and SF-12 score from randomization to 12 months
13. Change in ICEpop CAPability measure for Older people (ICECAP-O) score from randomization to 12 months

VII. Endpoint Descriptions

Primary Endpoint

Endpoint Description: Time to first non-elective, respiratory hospitalization or all-cause mortality.

Response Variable Definition: Time to first respiratory hospitalization or all-cause mortality (primary endpoint) will be defined as the time to first observed event respiratory hospitalization or all-cause mortality. All patients will have some information regarding mortality and last visit of follow-up. Patients without any observed respiratory hospitalization or death event at the time of analysis will be censored at their last visit or lung transplantation. The respiratory hospitalizations will be reviewed and adjudicated by a clinical events committee (CEC).

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization. Note that the baseline DLCO and baseline FVC will be added to regression models using the % predicted versions for all endpoints.

Handling of Dropouts and Missing Data:
The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection of restricted cubic spline plots. If a departure is observed then a suitable transformation

will be explored. In addition the proportional hazard assumptions will be explored by inspection of Martingale residuals plots for all model covariates. If a major departure is observed then the variable will added to the model as a stratification variable.

Statistical Tests: The Cox proportional hazards regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the time to first non-elective, respiratory hospitalization or all-cause mortality with model terms for treatment arm, baseline measurement, and covariates. Hazard ratios and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For Cox regression models a hazard ratio below 1.00 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A hazard ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Alternative Analysis: To explore therapy crossovers an alternative analysis scenario with be constructed. Therapy crossover will be defined as patients assigned "Standard care" and receiving after randomization "oral antimicrobial therapy". The previous presented primary analysis model will be used and moditified. Specifucally the response variable definition for the "Standard care" assigned patients (with crossover) will be changed such that the time to event and event indicator variables will be censored at the time of therapy crossover. The same statistical model and interpretation will be used as the primary analysis.

VIII. Secondary Endpoint Descriptions

Secondary Endpoint #1

Endpoint Description: Time to death from any cause.

Response Variable Definition: Time to death will be defined as the time to all-cause mortality. All patients will have some information regarding mortality and last visit of follow-up. Patients without any observed death at the time of analysis will be censored at their last visit or lung transplantation.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection of restricted cubic spline plots. If a departure is observed then a suitable transformation will be explored. In addition the proportional hazard assumptions will be explored by

inspection of Martingale residuals plots. If a major departure is observed then the variable will added to the model as a stratification variable.

Statistical Tests: The Cox proportional hazards regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the time to death from any cause with model terms for treatment arm, baseline measurement, and covariates. Hazard ratios and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For Cox regression models a hazard ratio below 1 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A hazard ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #2

Endpoint Description: Time to first non-elective respiratory hospitalization

Response Variable Definition: Time to first non-elective respiratory hospitalization will be defined as the time to first non-elective respiratory hospitalization. The hospitalizations will be reviewed and adjudicated by a CEC as non-elective respiratory hospitalizations. All patients will have some information regarding mortality and last visit of follow-up. Patients without any observed event at the time of analysis will be censored at their last visit, death, or lung transplantation.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection of restricted cubic spline plots. If a departure is observed then a suitable transformation will be explored. In addition the proportional hazard assumptions will be explored by inspection of Martingale residuals plots. If a major departure is observed then the variable will added to the model as a stratification variable.

Statistical Tests: The Cox proportional hazards regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the time to first non-elective respiratory hospitalization with model terms for treatment arm, baseline measurement, and covariates. Hazard ratios and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For Cox regression models a hazard ratio below 1.00 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A

hazard ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #3

Endpoint Description: Time to first non-elective all-cause hospitalization

Response Variable Definition: Time to first non-elective hospitalization will be defined as the time to first non-elective hospitalization. The hospitalizations will be reviewed and adjudicated by a CEC as non-elective all-cause hospitalizations. All patients will have some information regarding mortality and last visit of follow-up. Patients without any observed event at the time of analysis will be censored at their last visit, death, or lung transplantation.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection of restricted cubic spline plots. If a departure is observed then a suitable transformation will be explored. In addition the proportional hazard assumptions will be explored by inspection of Martingale residuals plots. If a major departure is observed then the variable will added to the model as a stratification variable.

Statistical Tests: The Cox proportional hazards regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the time to first non-elective all-cause hospitalization with model terms for treatment arm, baseline measurement, and covariates. Hazard ratios and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For Cox regression models a hazard ratio below 1.00 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A hazard ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #4

Endpoint Description: Total number of non-elective respiratory hospitalizations

Response Variable Definition: The hospitalizations will be reviewed and adjudicated by a clinical events committee (CEC) as non-elective respiratory hospitalizations.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: All patients will have some information regarding mortality and last visit of follow-up. Lung transplantation will be additional censoring variable in this analyses. The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: A Poisson regression model will be used to estimate outcome ratio between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the total number of non-elective respiratory hospitalizations with model terms for treatment arm, baseline measurement, and covariates. Rates and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For poisson regression models a ratio below 1.00 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A hazard ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #5

Endpoint Description: Total number of non-elective all-cause hospitalizations

Response Variable Definition: The hospitalizations will be reviewed and adjudicated by a CEC as non-elective all-cause hospitalizations.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: All patients will have some information regarding mortality and last visit of follow-up. Lung transplantation will be additional censoring variable in this analyses. The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting

modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The Poisson regression model will be used to estimate outcome ratio between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the total number of non-elective all-cause hospitalizations with model terms for treatment arm, baseline measurement, and covariates. Rates and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For Poisson regression models a ratio below 1.00 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #6

Endpoint Description: Change in FVC (L) from randomization to 12 months

Response Variable Definition: The FVC data will be collected at baseline and 12 months. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: All patients will have some information regarding mortality and last visit of follow-up. Lung transplantation will be additional censoring variable in this analyses. The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #7

Endpoint Description: Change in DLCO from randomization to 12 months

Response Variable Definition: The DLCO data will be collected at baseline and 12 months. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data:
All patients will have some information regarding mortality and last visit of follow-up. Lung transplantation will be additional censoring variable in this analyses. The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: “Standard care + oral antimicrobial therapy” and “Standard care”. The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for “Standard care + oral antimicrobial therapy” arm. A difference above 0.00 will indicate increase in score for “Standard care + oral antimicrobial therapy” arm.

Secondary Endpoint #8

Endpoint Description: Total number of respiratory infections

Response Variable Definition: all lower respiratory tract infection(s) treated with antibiotic treatment will be collected in follow-up.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: A Poisson regression model will be used to estimate outcome ratio between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the total number of respiratory infections with model terms for treatment arm, baseline measurement, and covariates. Rates and 95% confidence intervals will summarize the differences between treatment arms.

Interpretation of Results: For Poisson regression models a ratio below 1.00 will indicate a reduction in events for "Standard care + oral antimicrobial therapy" arm. A ratio above 1.00 will indicate increase in events for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #9

Endpoint Description: Change in UCSD-Shortness of Breath Questionnaire from randomization to 12 months

Response Variable Definition: The UCSD-Shortness of Breath Questionnaire data will be collected at baseline and 12 months. For the collect questionnaire data the UCSD-Shortness of Breath score will be calculated. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data:
The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial

therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #10

Endpoint Description: Change in Fatigue Severity Scale score from randomization to 12 months

Response Variable Definition: The Fatigue Severity Scale Questionnaire data will be collected at baseline and 12 months. For the collect questionnaire data the Fatigue Severity Scale score will be calculated. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #11

Endpoint Description: Change in Leicester Cough Questionnaire score from randomization to 12 months

Response Variable Definition: The Leicester Cough Questionnaire data will be collected at baseline and 12 months. For the collect questionnaire data the Leicester Cough Questionnaire score will be calculated. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data:
The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #12

Endpoint Description: Change in EQ-5D score and SF-12 score from randomization to 12 months

Response Variable Definition: The SF-12 questionnaire data will be collected at baseline and 12 months. The EQ-5D questionnaire data will be collected at baseline and 12 months. For the collect questionnaire data the EQ-5D score and SF-12 score will be calculated. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data:
The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

Secondary Endpoint #13

Endpoint Description: Change in ICEpop CAPability measure for Older people (ICECAP-O) score from randomization to 12 months

Response Variable Definition: The ICECAP-O questionnaire data will be collected at baseline and 12 months. For the collect questionnaire data the ICECAP-O score will be calculated. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

IX. Safety endpoints

Serious adverse events

Endpoint Description: Frequency and types of serious adverse events (SAEs) during the following-up period of the trial.

Response Variable Definition: SAEs will be identified by the site PI and coded into the MEDRA medical dictionary.

Statistical Tests: The number of patients with one or move SAEs will be tabulated along with the total number of distinct SAEs. Comparison of the "Standard care + oral antimicrobial therapy" and "Standard care" arms will be done with a chi-square test, i.e. the number of patient with one or more events. Other groupings of SAEs maybe generated as deemed necessary.

Interpretation of Results: For cases where "Standard care + oral antimicrobial therapy" rate is less than "Standard care" rate will indicate a reduction for "Standard care + oral antimicrobial therapy" arm. For cases where "Standard care + oral antimicrobial therapy" rate is greater than "Standard care" rate will indicate an increase for "Standard care + oral antimicrobial therapy" arm.

Concomitant Medication

Endpoint Description: Frequency and types of concomitant medication usage during the following-up period of the trial.

Response Variable Definition: Concomitant medication will be collected each visit and phone contact with the site.

Statistical Tests: The number of patients with one or more given concomitant medication will be tabulated. Shift tables from baseline will be generate also. Comparison of the "Standard care + oral antimicrobial therapy" and "Standard care" arms will be done with a chi-square test, i.e. the number of patient with one or more occurrences. Other groupings of concomitant medication maybe generated as deemed necessary.

Interpretation of Results: For cases where "Standard care + oral antimicrobial therapy" rate is less than "Standard care" rate will indicate a reduction for "Standard care + oral antimicrobial therapy" arm. For cases where "Standard care + oral antimicrobial therapy" rate is greater than "Standard care" rate will indicate an increase for "Standard care + oral antimicrobial therapy" arm.

X. Trial conduct

Compliance

Endpoint Description: Rates of thearpy distribution and adherence within the assigned testing strategy: Standard care + oral antimicrobial therapy.

Response Variable Definition: Data related to the distribution (payment system for prescriptions called TRIALCARD) of the assigned therapy will be collected during patient follow-up. Patient response to thearpy adherence in weeks prior to contact will be collect at 6 months intervals

Statistical Tests: No statistical tests are planned. The rates of thearpy distribution and adherence are to be estimated at 6 and 12 months for the Standard care + oral antimicrobial therapy assigned patients.

Therapy crossover

Endpoint Description: Rates of oral antimicrobial therapy crossover for the "Standard care" assigned patients.

Response Variable Definition: Time to first crossover will be defined as the time to first oral antimicrobial therapy usage in the patients randomized to "Standard care"

Statistical Tests: No statistical tests are planned. Kaplan-meier event rates will be calculated at representative intervals for ther standard care therapy assigned patients. Time to event plots will be generated also. The rates of thearpy crossover are to be estimated at 6 and 12 months for the standard care therapy assigned patients.

XI. Exploratory analyses

Six minute walk test

Endpoint Description: Change in six minute walk test and pre/post walk Borg assessment from randomization to 12 months

Response Variable Definition: The six minute walk test data will be collected at baseline and 12 months. The change from baseline will be calculated for the 12 month values by subtracting the baseline result.

Additional Covariates: Age, sex, baseline DLCO, baseline FVC, use of NAC at enrollment, use of standard of care medications at enrollment, and choice of antimicrobial agent prior to randomization.

Handling of Dropouts and Missing Data: All patients will have some information regarding mortality and last visit of follow-up. Lung transplantation will be additional

censoring variable in this analyses. The censoring mechanism is assumed to be non-informative. Supportive analyses will be performed to assess the impact of a potential informative censoring.

Diagnostic tests: The additional continuous covariates to be used in the primary analysis model will be assessed for major departures from linearity by inspection scatter plots with LOESS curves. If a departure is observed then a suitable transformation will be explored. The validity of this model in terms of meeting modeling assumptions will be assessed via standard modeling diagnostics and goodness-of-fit measures.

Statistical Tests: The linear regression model will be used to estimate outcome differences between the two treatment arms: "Standard care + oral antimicrobial therapy" and "Standard care". The outcome is the measured result at 12 months with model terms for treatment arm, baseline measurement, and covariates. Descriptive statistics will be calculated at baseline and 12 months by treatment group.

Interpretation of Results: For linear models a difference below 0.00 will indicate a reduction in score for "Standard care + oral antimicrobial therapy" arm. A difference above 0.00 will indicate increase in score for "Standard care + oral antimicrobial therapy" arm.

XII. Interim Analyses

There will be one planned interim review for efficacy. The efficacy review will focus on the composite endpoint of respiratory hospitalization or all-cause death and should occur once 300 enrolled subjects have been followed for 12 months. The information time will be computed by dividing the observed number of primary endpoint events by the projected number of primary endpoint events. To conserve the overall type I error rate of 0.05 the O'Brien-Fleming Spending Function will be used to allow for stopping if large treatment effects are observed while allowing the final significance level to be conserved at the nominal level (Lan and DeMets 1983).

XIII. Subgroup of Interest

The following subgroups of interest will be based on information available prior to randomization:

- Use of standard of care medications at enrollment
- Antimicrobial therapy determined prior to randomization
- Use of NAC at enrollment

The subgroups of interest will be assess sepereately for the primary endpoint within the framework of cox proportional hazards regression model. The subgroup variable and subgroup by treatment arm intereaction will be added to the model. If the interaction is significant then the hazard ratios and 95% confidence intervals will be

estimated for the difference in treatment arms for the separate levels of the subgroup variable.

The antimicrobial therapy determined prior to randomization is made up to 2 groups: 1) Co-trimoxazole and 2) Doxycycline. The baseline and primary/secondary analyses will be repeated for these 2 groups seperately.

XIV. References

Berglund, Patricia and Heeringa, Steven. Multiple Imputation of Missing Data Using SAS®. SAS Institute, July 2014, pp83-89.

Lan, KK Gordan, Demets, David L, Discrete sequential boundaries for clinical trials, Biometrika Volume 70, Issue 3Pp. 659-663

XV. Tables/Listing/Graph Mock-ups

The tables, listings, and figures shown below are the template versions and may be modified as needed. It is planned that there will be separate sets of tables based on the subgroups of interest listed above.

CLEANUP-IPF Study
Final Analysis Table 1.1
Enrollment and Patient Follow-up
Patient Enrollment by Site

Investigational Site	Enrolled
(101) <<Site name>>	N/N (xx.x%)
(102) <<Site name>>	N/N (xx.x%)
(103) <<Site name>>	N/N (xx.x%)
(104) <<Site name>>	N/N (xx.x%)
…	…
(140) <<Site name>>	N/N (xx.x%)
Total	N/N (xx.x%)

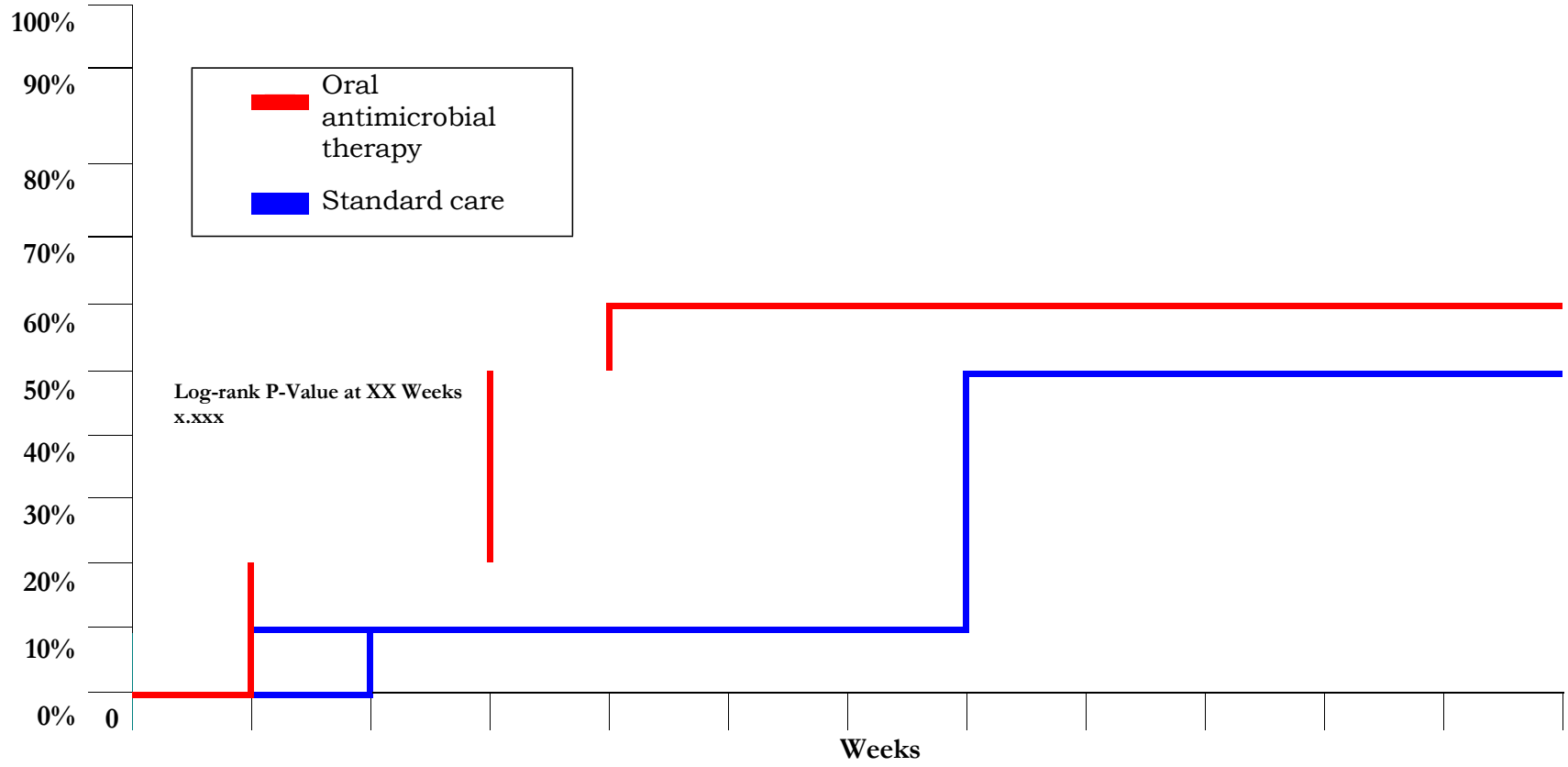
CLEANUP-IPF Study
Final Analysis Table 1.2
Enrollment and Patient Follow-up
Completed and Withdrawn Patients

Event	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Started Study	N	N	N	
Completed	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	
Study Termination due to Death	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	
Withdrawal				
6 Months				x.xxx
# of Events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
12 Months				x.xxx
# of Events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
18 Months				x.xxx
# of Events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
24 Months				x.xxx
# of Events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
Reasons for Withdrawal				
Reason #1	N	N	N	
Reason #2	N	N	N	
…	…	…	…	
Reason #X	N	N	N	
Therapy Distribution				
6 Months	N/N (xx.x%)			
12 Months	N/N (xx.x%)			
Thearpy adherence (7 Days Prior)				
6 Months	N/N (xx.x%)			
12 Months	N/N (xx.x%)			
Therapy crossover				

CLEANUP-IPF Study
Final Analysis Table 1.2
Enrollment and Patient Follow-up
Completed and Withdrawn Patients

Event	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
6 Months				
# of Events/# of Patients		N/N		
Kaplan-Meier Event Rate (95% CI)		xx.x (xx.x, xx.x)		
12 Months				
# of Events/# of Patients		N/N		
Kaplan-Meier Event Rate (95% CI)		xx.x (xx.x, xx.x)		
18 Months				
# of Events/# of Patients		N/N		
Kaplan-Meier Event Rate (95% CI)		xx.x (xx.x, xx.x)		
24 Months				
# of Events/# of Patients		N/N		
Kaplan-Meier Event Rate (95% CI)		xx.x (xx.x, xx.x)		

CLEANUP-IPF Study
Final Analysis Graph 1.2.1
Enrollment and Patient Follow-up
Completed and Withdrawn Patients
Withdrawal Rate, Kaplan-Meier Estimates



CLEANUP-IPF Study
Final Analysis Table 2.1
Baseline
Demographic and Risk Factor Summary

Parameter Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Age (Years)				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
Min, Max	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	
Female	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Weight (kg)				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
Height (cm)				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
BMI				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
Ethnicity (Hispanic or Latino)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Race				
American Indian or Alaska Native	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Asian	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Black or African American	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Native Hawaiian or other Pacific Islander	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
White	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Other	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Minorities [1]	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
BP (systolic)(mmHg)				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
BP (diastolic)(mmHg)				x.xxx

CLEANUP-IPF Study
Final Analysis Table 2.1
Baseline
Demographic and Risk Factor Summary

Parameter Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
Heart rate (bpm)				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
SpO2 (%)				x.xxx
N	xx	xx	xx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (Q1, Q3)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	xx.x (xx.x., xx.x)	
Marital Status				
Single	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Married	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Divorced	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Domestic Partner	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Widowed	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx

1. Any patient whose ethnicity is Hispanic or Latino, or whose race is non-white

CLEANUP-IPF Study
Final Analysis Table 2.2
Baseline
Medical History

Parameter	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Coronary artery disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Acute MI	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Valvular heart disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Congestive Heart failure	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Atrial fibrillation	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Intermittent claudication	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Peripheral vascular disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Cerebrovascular disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Dementia	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Chronic pulmonary disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Connective tissue disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Ulcer disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Mild liver disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Diabetes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Hemiplegia	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Moderate or severe renal disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Diabetes with end organ damage	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Any tumor	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Leukemia	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Lymphoma	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Moderate or severe liver disease	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Metastatic solid tumor	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
AIDS	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Lung cancer	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Other cancer	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Gastroesophageal reflux (GER)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx

CLEANUP-IPF Study
Final Analysis Table 2.3
Baseline
Prior Medications

Parameter	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Proton Pump Inhibitors (PPI)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
H2 Blockers (H2 Receptor Antagonists)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Chronic prednisone (>1month)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Azathioprine	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
N-acetylcystteine (NAC)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Cotrimoxazole	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Albuterol/ atrovent/ other metered-dose inhaler (MDI)	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Pirfenidone	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx
Nintedanib	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)	x.xxx

CLEANUP-IPF Study
Final Analysis Table 2.4
Baseline
6 Minute Walk Test

Parameter Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
Resting SpO2 (%)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Borg Scale Pre-Walk Rating (0-10 Range)				
N	xx	xx	xx	x.xxx
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Borg Scale Post-Walk Rating (0-10 Range)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Six Minute Walk Distance (m)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 2.5
Baseline
Spirometry and Lung Diffusion Testing

Parameter Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
FEV1 (Liters)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
FEV1% Predicted				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
FEV1/FVC Percentage				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
FVC (liters)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
FVC % Predicted				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} (mL/min/mmHg)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} Corrected (mL/min/mmHg)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} % Predicted				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 2.6
Baseline
Quality of Life

Parameter Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
UCSD Shortness of Breath Questionnaire Total Score (0*-120 Range)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
EuroQoL Score(0-1* Range)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
EuroQoL Thermometer Response (0-100* Range)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
ICECAP-O: Summary Score (0-1* Range)				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
SF-12 Score				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Fatigue Severity Scale score				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Leicester Cough Questionnaire score				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

*Indicates better health score

CLEANUP-IPF Study
Final Analysis Table 3.1
Primary Efficacy
Summary of Events

Event	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Primary Endpoint	N (xx.x%)	N (xx.x%)	N (xx.x%)	x.xxx
1st Respiratory hospitalization	N (xx.x%)	N (xx.x%)	N (xx.x%)	
Death	N (xx.x%)	N (xx.x%)	N (xx.x%)	
At 6 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 12 Monthss				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 18 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 24 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
Mortality				
# of events	N/N	N/N	N/N	
Cause of Death				
Reason #1				
Reason #	N	N	N	
…	…	…	…	
Reason #X	N	N	N	
At 6 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 12 Monthss				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 18 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	

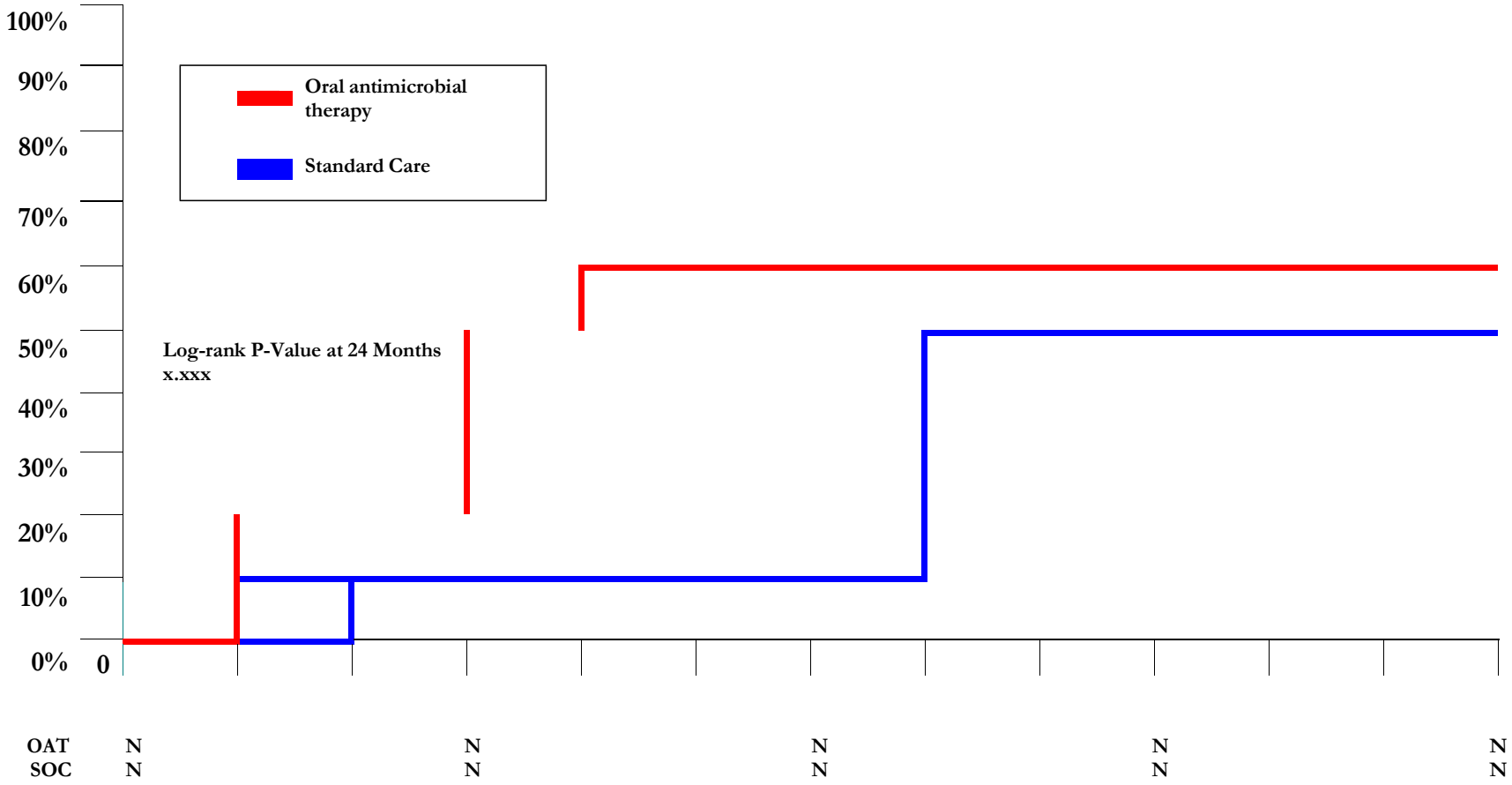
CLEANUP-IPF Study
Final Analysis Table 3.1
Primary Efficacy
Summary of Events

Event	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 24 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
Non-elective hospitalization				
Patients with one of more	N (xx.x%)	N (xx.x%)	N (xx.x%)	
Number per patient				
0	N (xx.x%)	N (xx.x%)	N (xx.x%)	
1	N (xx.x%)	N (xx.x%)	N (xx.x%)	
2	N (xx.x%)	N (xx.x%)	N (xx.x%)	
3	N (xx.x%)	N (xx.x%)	N (xx.x%)	
At 6 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 12 Monthss				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 18 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 24 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
Respiratory hospitalization				
Patients with one of more	N (xx.x%)	N (xx.x%)	N (xx.x%)	
Number per patient				
0	N (xx.x%)	N (xx.x%)	N (xx.x%)	
1	N (xx.x%)	N (xx.x%)	N (xx.x%)	
2	N (xx.x%)	N (xx.x%)	N (xx.x%)	
3	N (xx.x%)	N (xx.x%)	N (xx.x%)	

CLEANUP-IPF Study
Final Analysis Table 3.1
Primary Efficacy
Summary of Events

Event	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
At 6 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 12 Monthss				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 18 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
At 24 Months				x.xxx
# of events/# of Patients	N/N	N/N	N/N	
Kaplan-Meier Event Rate (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	
Respiratory infections				
Patients with one of more	N (xx.x%)	N (xx.x%)	N (xx.x%)	
Number per patient				
0	N (xx.x%)	N (xx.x%)	N (xx.x%)	
1	N (xx.x%)	N (xx.x%)	N (xx.x%)	
2	N (xx.x%)	N (xx.x%)	N (xx.x%)	
3	N (xx.x%)	N (xx.x%)	N (xx.x%)	

CLEANUP-IPF Study
Final Analysis Table 3.1.1
Primary Efficacy
Time to first 1st Respiratory hospitalization or Death
Kaplan-Meier Plot



CLEANUP-IPF Study
Final Analysis Table 3.1.2
Primary Efficacy
Time to Death
Kaplan-Meier Plot

CLEANUP-IPF Study
Final Analysis Table 3.1.3
Primary Efficacy
Time to first 1st Respiratory hospitalization
Kaplan-Meier Plot

CLEANUP-IPF Study
Final Analysis Table 3.1.4
Primary Efficacy
Time to first 1st Non-elective hospitalization
Kaplan-Meier Plot

CLEANUP-IPF Study
Final Analysis Table 3.2
Primary Efficacy
Model Analysis

Comparison	Estimate with 95% Confidence Interval	Test Statistic	Nominal P-Value
Time to 1st Respiratory hospitalization or Death			
Hazard ratio of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Time to first 1st Respiratory hospitalization			
Hazard ratio of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Time to first 1st Non-elective hospitalization			
Hazard ratio of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Total Respiratory hospitalizations			
Rate of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	
Rate of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	
Ratio of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Total Non-elective hospitalizations			
Rate of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Rate of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Ratio of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Total Respiratory infections			
Rate of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Rate of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Ratio of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx

CLEANUP-IPF Study
Final Analysis Table 4.1.1
Secondary Efficacy
FVC and DLCO
Descriptive Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
FVC (liters)				
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
FVC % Predicted				
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 4.1.1
Secondary Efficacy
FVC and DLCO
Descriptive Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
DL_{CO} (mL/min/mmHg)				x.xxx
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} Corrected (mL/min/mmHg)				x.xxx
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} % Predicted				x.xxx
Baseline				x.xxx

CLEANUP-IPF Study
Final Analysis Table 4.1.1
Secondary Efficacy
FVC and DLCO
Descriptive Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 4.1.2
Primary Efficacy
FVC and DLCO
Change from Baseline Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
FVC (liters)				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
FVC % Predicted				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} (mL/min/mmHg)				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	

CLEANUP-IPF Study
Final Analysis Table 4.1.2
Primary Efficacy
FVC and DLCO
Change from Baseline Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} Corrected (mL/min/mmHg)				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
DL_{CO} % Predicted				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 4.1.3
Secondary Efficacy
FVC and DLCO
Model Analysis

Comparison	Estimate with 95% Confidence Interval	Test Statistic	Nominal P-Value
FVC (liters)			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
FVC % Predicted			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
DL_{CO} (mL/min/mmHg)			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
DL_{CO} Corrected (mL/min/mmHg)			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx

DL_{CO}% Predicted			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx

CLEANUP-IPF Study
Final Analysis Table 4.2.1
Secondary Efficacy
Quality of Life Measures
Descriptive Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
UCSD Shortness of Breath Questionnaire Total Score (0*-120 Range)				
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
12 Months				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
24 Months				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
EuroQoL Score(0-1* Range)				
EuroQoL Thermometer Response (0-100* Range)				
ICECAP-O: Summary Score (0-1* Range)				
SF-12 Score				
Fatigue Severity Scale score				
Leicester Cough Questionnaire score				

CLEANUP-IPF Study
Final Analysis Table 4.2.2
Secondary Efficacy
Quality of Life Measures
Change from Baseline Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
UCSD Shortness of Breath Questionnaire Total Score (0*-120 Range)				
12 Months				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
24 Months				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
EuroQoL Score(0-1* Range)				
EuroQoL Thermometer Response (0-100* Range)				
ICECAP-O: Summary Score (0-1* Range)				
SF-12 Score				
Fatigue Severity Scale score				
Leicester Cough Questionnaire score				

CLEANUP-IPF Study
Final Analysis Table 4.2.3
Secondary Efficacy
Quality of Life Measures
Model Analysis

Comparison	Estimate with 95% Confidence Interval	Test Statistic	Nominal P-Value
UCSD Shortness of Breath Questionnaire Total Score			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
EuroQoL Thermometer Response			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
ICECAP-O: Summary Score			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
SF-12 Score			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx

Fatigue Severity Scale score			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Leicester Cough Questionnaire score			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx

CLEANUP-IPF Study
Final Analysis Table 5.1
Safety
Serious Adverse Events

Body System Event Name	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}	P-Value
Any Body System and Event	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
1st Body System Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
1st Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
2nd Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
…	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
Xth Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
2nd Body System Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
1st Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
2nd Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
…	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
Xth Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
Xth Body System Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
1st Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
2nd Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
…	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx
Xth Event Name	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	N_{PAT} (xx.x%) N_{SAE}	x.xxx

Summarization format N_{PAT} (xx.x%) N_{SAE}, where N_{PAT} is the number of patient with at least one SAE, xx.x% = N_{PAT} divided by the total number of randomized patients times 100, and N_{SAE} is the number of SAEs observed

CLEANUP-IPF Study
Final Analysis Table 5.2
Safety
Concomitant Medications Shift Table

Parameter	Baseline Usage	Post-Baseline Usage	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}
PPI					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N
		(xx.x%) Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N
		(xx.x%) Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N
		(xx.x%) Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
H2 Blocker					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Chronic prednisone					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Azathioprine					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
NAC					

CLEANUP-IPF Study
Final Analysis Table 5.2
Safety
Concomitant Medications Shift Table

Parameter	Baseline Usage	Post-Baseline Usage	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Cotrimoxazole					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
MDI					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
Pirfenidone					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

CLEANUP-IPF Study
Final Analysis Table 5.2
Safety
Concomitant Medications Shift Table

Parameter	Baseline Usage	Post-Baseline Usage	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N= N_{EVAL}
Nintedanib					
	No	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Yes	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
	Overall	No	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)
		Yes	N/N (xx.x%)	N/N (xx.x%)	N/N (xx.x%)

CLEANUP-IPF Study
Final Analysis Table 6.1.1
Exploratory Endpoint
Six Minute Walk Test
Descriptive Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
Resting SpO2 (%)				
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Borg Scale Pre-Walk Rating (0-10 Range)				
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 6.1.1
Exploratory Endpoint
Six Minute Walk Test
Descriptive Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
Borg Scale Post-Walk Rating (0-10 Range)				x.xxx
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Six Minute Walk Distance (m)				x.xxx
Baseline				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 6.1.2
Exploratory Endpoint
Six Minute Walk Test
Change from Baseline Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
Resting SpO2 (%)				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Borg Scale Pre-Walk Rating (0-10 Range)				
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Borg Scale Post-Walk Rating (0-10 Range)				x.xxx
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 6.1.2
Exploratory Endpoint
Six Minute Walk Test
Change from Baseline Summary

Parameter Visit Statistic	Oral antimicrobial therapy N= NEVAL	Standard Care N= N_{EVAL}	All Patients N=N_{EVAL}	P-Value
Six Minute Walk Distance (m)				x.xxx
Week 12				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
Week 24				x.xxx
N	xx	xx	xx	
Mean (SD)	x.xx (xx.x)	x.xx (xx.x)	x.xx (xx.x)	
Median (Q1, Q3)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	

CLEANUP-IPF Study
Final Analysis Table 6.1.3
Exploratory Endpoint
Six Minute Walk Test
Model Analysis

Comparison	Estimate with 95% Confidence Interval	Test Statistic	Nominal P-Value
Borg Scale Pre-Walk Rating (0-10 Range)			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Borg Scale Post-Walk Rating (0-10 Range)			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx
Six Minute Walk Distance (m)			
Slope of Oral antimicrobial therapy	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Slope of Standard Care	xx.xx (xx.xx, xx.xx)	xxx.xx	x.xxx
Difference of Oral antimicrobial therapy vs. Standard Care	xx.xx (xx.xx, xx.xx)	xx.xx	x.xxx

Addendum to the CleanUP-IPF Analysis Plan (signed 28NOV2016)

Fernando J. Martinez, Principal Investigator
Imre Noth, Principal Investigator
Kevin Anstrom, Principal Investigator
Jerry Kirchner, Project Leader
Eric Yow, Statistician

29MAY2020

On 19DEC2019 the DCC received a memorandum from the Executive Secretary of CleanUP-IPF DSMB regarding the recommendations for investigators of the CleanUP-IPF study following DSMB meeting 18DEC2019 meeting conference call. The recommendations were to terminate the trial and proceed with an orderly study close-out. Study PIs and DCC developed and implemented a plan to complete patient visits and follow-up in March 2020 and database lock by May 2020.

Beginning in mid-March across the United States stay at home orders were issued due to the COVID19 pandemic. The stay at home orders limited site PIs and coordinators access to medical records and other key patient data. The impact of limited access was the following:

- Entry of some visit data
- Responses to database queries
- Collecting and submitting patients records for endpoint adjudication
- Collecting and submitting patients records for medical monitor review of serious adverse events and MedDRA coding

The impact of COVID19 on the data lock and reporting the primary results for publication are the following:

- Unable to complete all adjudication of primary endpoint components: death and hospitalization
- Entry of serious adverse events and associated term in database to allow MedDRA system organ class coding

Given the need to report timely results in the public domain and the unknown end of COVID19 pandemic, the deviation of the primary statistical analysis reporting would be as follows:

- According to the Statistical Analysis Plan (SAP), the primary analysis of the primary endpoint was to be based on CEC adjudicated endpoints. Now, the plan is to use adjudicated results if available. If the CEC adjudicated result is not available then the site reported result would be used for the endpoint.
- For serious adverse events, the summary of MedDRA system organ class coding was planned for the primary statistical analysis and reporting of results. The serious adverse event analysis would be altered as follows:
    - For events with serious adverse event term entry in the database and MedDRA system organ class coding, we will use MedDRA coding.
    - For events without serious adverse event term entry in the database and without MedDRA system organ class coding, the medical monitor would

review the available documentation and if reasonable information is available to classify to MedDRA system organ class, then the medical monitor result will be used.

- For events without serious adverse event term entry in the database, and no MedDRA system organ class coding, and no documentation to support a classification by the medical monitor, then the result will not be coded.

The primary analysis is based on the final locked dataset and events collected. A sensitivity analysis of the primary results will be constructed to explore possible differences in snapshots or timeframes of the data. The results would be censored at date of the DSMB meeting on 17DEC2019 and again at 01MAR2020 (associated with the COVID 19 pandemic) to understand any differences in the data collection affected the results.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

December 19, 2019

Fernando Martinez, MD
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Weill Cornell Medical College
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New York, NY 10065

Kevin Anstrom, PhD
PI, CleanUP-IPF Trial
Duke University School of Medicine
200 Morris Street
6320 200 Morris
Durham, NC 27701

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 NHL.BI carefully reviewed the DSMB reconu nendations. On December 19, 20 19, Dr. Lora Reineck notified you of the intent of the Instirute to concur with the DSMB reconunendation for early tennination.

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

Thank you for your leadership on this important study.

Sincerely,

James P. Kiley, Ph.D.
Director, Division of Lung Diseases
National Heart, Lung, and Blood In'ilitute, NIH

cc:
Dr. Frank Sciurba
Dr. Stephen Wisniewski
Dr. Tony Punturieri
Ms. Lisa Viviano
Mr. Andre Walker
Dr. Ton1 Croxton
Dr. Lora Reineck
Dr. Amy Patterson
Dr. Nakela Cook