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Authors

Lederer, David J
Bradford, Williamson Z
Fagan, Elizabeth A
et al.

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Sensitivity Analyses of the Change in FVC in a Phase 3 Trial of Pirfenidone for Idiopathic Pulmonary Fibrosis

David J. Lederer, MD, FCCP; Williamson Z. Bradford, MD, PhD; Elizabeth A. Fagan, MD; Ian Glaspole, MBBS, PhD; Marilyn K. Glassberg, MD, FCCP; Kenneth F. Glasscock, BA; David Kardatzke, PhD; Talmadge E. King Jr, MD, FCCP; Lisa H. Lancaster, MD, FCCP; Steven D. Nathan, MD, FCCP; Carlos A. Pereira, MD; Steven A. Sahn, MD; Jeffrey J. Swigris, DO; and Paul W. Noble, MD

BACKGROUND: FVC outcomes in clinical trials on idiopathic pulmonary fibrosis (IPF) can be substantially influenced by the analytic methodology and the handling of missing data. We conducted a series of sensitivity analyses to assess the robustness of the statistical finding and the stability of the estimate of the magnitude of treatment effect on the primary end point of FVC change in a phase 3 trial evaluating pirfenidone in adults with IPF.

METHODS: Source data included all 555 study participants randomized to treatment with pirfenidone or placebo in the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study. Sensitivity analyses were conducted to assess whether alternative statistical tests and methods for handling missing data influenced the observed magnitude of treatment effect on the primary end point of change from baseline to week 52 in FVC.

RESULTS: The distribution of FVC change at week 52 was systematically different between the two treatment groups and favored pirfenidone in each analysis. The method used to impute missing data due to death had a marked effect on the magnitude of change in FVC in both treatment groups; however, the magnitude of treatment benefit was generally consistent on a relative basis, with an approximate 50% reduction in FVC decline observed in the pirfenidone group in each analysis.

CONCLUSIONS: Our results confirm the robustness of the statistical finding on the primary end point of change in FVC in the ASCEND trial and corroborate the estimated magnitude of the pirfenidone treatment effect in patients with IPF.

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ABBREVIATIONS: ANCOVA = analysis of covariance; ASCEND = Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; INPULSIS = Investigating the Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis; IPF = idiopathic pulmonary fibrosis

AFFILIATIONS: From the Columbia University Medical Center (Dr Lederer), New York, NY; InterMune, Inc (Drs Bradford, Fagan, and Kardatzke and Mr Glasscock), Brisbane, CA; the Alfred Hospital (Dr Glaspole), Melbourne, VIC, Australia; the University of Miami Miller School of Medicine (Dr Glassberg), Miami, FL; the University of California, San Francisco (Dr King), San Francisco, CA; the Vanderbilt University Medical Center (Dr Lancaster), Nashville, TN; Inova Fairfax Hospital (Dr Nathan), Falls Church, VA; the Paulista School of Medicine (Dr Pereira), Federal University of São Paulo, São Paulo, Brazil; the Medical University of South Carolina (Dr Sahn), Charleston, SC; National Jewish Health (Dr Swigris), Denver, CO; and the Cedars-Sinai Medical Center (Dr Noble), Los Angeles, CA.

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CORRESPONDENCE TO: David J. Lederer, MD, FCCP, Columbia University Medical Center, 622 W 168th St, PH14-101, New York, NY 10032; e-mail: davidlederer@columbia.edu

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The selection of robust and clinically meaningful primary efficacy end points for therapeutic clinical trials in patients with idiopathic pulmonary fibrosis (IPF) has been the subject of considerable debate.[1-7] FVC, a widely used measure of disease status and a strong independent predictor of mortality in patients with IPF,[8-14] has emerged as the most common primary end point in IPF clinical trials. However, it is widely recognized that the analytic strategy and the method used to handle missing data can have a substantial influence on the magnitude of change in FVC and the estimate of effect size in therapeutic clinical trials in adults with IPF.[15,16]

The Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study was a multinational, randomized, double-blind, placebo-controlled, phase 3 trial evaluating pirfenidone in adults with IPF.[17] The primary efficacy end point in the study was the change from baseline to week 52 in FVC % predicted, analyzed using a nonparametric rank analysis of covariance (ANCOVA) model that tested for between-group differences in the distribution of ranked change in FVC at week 52.

The rank ANCOVA model was selected as the test statistic for the primary efficacy analysis for three primary reasons. First, unlike some tests, the rank ANCOVA model requires no assumptions regarding data structure and distribution. Second, as a landmark analysis, it minimizes assumptions about the course preceding the measurement (ie, no assumption of linearity) and provides an estimated effect size at a clinically relevant time point. Finally, it provides a satisfactory solution to the problem of missing data due to death—a clinically important outcome—without overweighting. Since deaths are assigned the lowest ranks according to the time of death since randomization, the model incorporates time to death and accounts for the effect of deaths on the primary outcome without the need to rely on the assignment of an arbitrary value for missing data.[18,19]

Importantly, although the rank ANCOVA model tests for between-group differences in the distribution of change from baseline, it provides no clinically interpretable information regarding the magnitude of the treatment effect. Therefore, the magnitude of treatment effect in the ASCEND study was estimated by comparing the distribution of patients in the pirfenidone and placebo groups across two clinically meaningful thresholds of change at week 52: an absolute decline of $\geq 10\%$ in FVC % predicted or death and no decline in FVC % predicted ($\geq 0\%$ change from baseline).

In the rank ANCOVA analysis of change from baseline to week 52 in FVC % predicted, there was a statistically significant between-group difference that favored treatment with pirfenidone ($P < .001$). Categorical analysis of outcomes at week 52 demonstrated that the proportion of patients with a $\geq 10\%$ decline in FVC or death was decreased by 47.8% and the proportion of patients with no decline was increased by 132.5% in the pirfenidone group compared with placebo.[17] The mean change from baseline to week 52 in FVC was -235 mL in the pirfenidone group and -428 mL in the placebo group (relative difference, 45.1%; $P < .001$). To examine the robustness of the statistical finding and the stability of the estimate of the magnitude of treatment effect in the ASCEND study, we conducted a series of sensitivity analyses of the primary end point of change in FVC using alternative analytic methods and approaches to managing missing data.

Materials and Methods

Patients

All study participants who were randomized to treatment with pirfenidone 2,403 mg/d (n = 278) or placebo (n = 277) in the ASCEND study were included in the analyses. Eligibility criteria for the ASCEND study have been previously described.[1] Briefly, eligible patients were between the ages of 40 and 80 years with a centrally confirmed diagnosis of IPF at least 6 months prior to randomization. Physiologic eligibility criteria included a baseline percent predicted FVC $\geq 50\%$ and $\leq 90\%$, percent predicted diffusing capacity of lung for carbon monoxide $\geq 30\%$ and $\leq 90\%$, and 6-min walk test distance ≥ 150 m.

Statistical Analyses

The protocol-defined test statistic for the primary efficacy analysis in the ASCEND trial was a rank ANCOVA model with the standardized rank change in FVC % predicted as the outcome variable and the standardized rank baseline value as a covariate. Missing values due to death were assigned the worst ranks according to the time of death since randomization. Missing values due to reasons other than death were imputed as the average value from the three patients (regardless of treatment assignment) with the smallest sum of squared differences at each study visit with nonmissing values.[20]

A series of sensitivity analyses was conducted to assess the effect of alternative statistical tests and strategies for handling missing data on the robustness of the statistical finding and the observed magnitude of treatment effect on the primary end point of FVC change at week 52. Alternative statistical tests included the following: mixed effects linear model with repeated measures analysis of the annual rate of change in FVC; random coefficients model of the annual rate of change in FVC (slope analysis); mean change in FVC volume, analyzed using an ANCOVA model; Cochran-Mantel-Haenszel row mean score test based on two categories of change in FVC % predicted ($\geq 10\%$ absolute decline or death and $< 10\%$ absolute decline); and Cochran-Mantel-Haenszel row mean score test based on three categories of change in FVC % predicted ($\geq 10\%$ absolute decline or death, $> 0\%$ and $< 10\%$ absolute decline, and no decline).

Alternative methods for handling missing data due to death included the following: last observation carried forward, replacement with the average value from the three patients in either treatment group with the

smallest sum of squared differences at each study visit with nonmissing values, assignment to the worst category (for categorical analyses), replacement with the worst observed value at week 52 in the placebo group, replacement with the worst observed value at week 52 among patients in the placebo group who discontinued treatment prior to week 52, replacement with the worst possible value (FVC = 0), replacement with an intermediate value (FVC = 1,500 mL), and no imputation (ie, observed data only).

For missing data due to reasons other than death, alternative imputation methods included the following: last observation carried forward, replacement with the average value from the three patients in either treatment group with the smallest sum of squared differences at each study visit with nonmissing data, multiple imputation using data from patients in the same treatment group who discontinued treatment prematurely but had a week 52 observation, multiple imputation using data from patients in the placebo group who had a week 52 observation, and no imputation.

The ASCEND study was conducted in accordance with the modified Declaration of Helsinki. All patients provided written informed consent, and the study protocol was approved by the institutional review board or the ethics committee at each participating study center (e-Appendix 1).

Results

A total of 555 patients were included in the analysis. The proportion of patients with missing FVC data at the week 52 study visit is summarized in Table 1. A total of 482 patients (86.6%) completed an FVC assessment at the week 52 study visit (243 [87.4%] in the pirfenidone group and 239 [86.3%] in the placebo group). Fewer patients in the pirfenidone group compared with placebo had a missing value due to death (11 [4.0%] vs 20 [7.2%]), and slightly more patients in the pirfenidone group compared with placebo had a missing value due to a reason other than death (24 [8.6%] vs 18 [6.5%]).

The statistical results of the various sensitivity analyses are summarized in Table 2. The distribution of change in FVC was systematically different between the pirfenidone and placebo groups and favored pirfenidone in each analysis. The *P* value for the comparison between pirfenidone and placebo was $<.001$ for each test statistic, supporting the robustness of the statistical finding in the primary efficacy analysis in the ASCEND study.

TABLE 1] FVC Assessment at Week 52

Patients	Pirfenidone (n = 278)	Placebo (n = 277)	Total (N = 555)
Observed	243 (87.4)	239 (86.3)	482 (86.8)
Imputed due to death	11 (4.0)	20 (7.2)	31 (5.6)
Imputed due to reasons other than death	24 (8.6)[a]	18 (6.5)[b]	42 (7.6)

Data are presented as No. (%). Patients were required to complete two wk 52 visits (wk 52A and wk 52B); the wk 52 value was reported as the average value of the wk 52A and wk 52B assessments.
[a]Includes withdrawal by subject (n = 7), adverse event (n = 6), lung transplantation (n = 6), lost to follow-up (n = 2), did not complete an FVC assessment (n = 1), physician decision (n = 1), and other (n = 1).
[b]Includes withdrawal by subject (n = 7), adverse event (n = 5), did not complete an FVC assessment (n = 2), lost to follow-up (n = 1), lung transplantation (n = 1), sponsor decision (n = 1), and other (n = 1).

The effects of various analytic strategies and imputation methods on the observed magnitude of treatment effect are presented in Table 3. Replacement of missing values due to death with the worst possible value (FVC = 0) resulted in larger mean declines in FVC in both treatment groups (−235 mL in the pirfenidone group and −428 mL in the placebo group) compared with the analysis in which missing data due to death were imputed using the sum of squared differences methodology (−162 mL and −274 mL in the pirfenidone and placebo groups, respectively) or the analysis in which only observed data were used (−145 mL and −256 mL, respectively).

Although the method used to impute missing data due to death had a marked effect on the observed magnitude of change in FVC in both treatment groups, the magnitude of the treatment effect (as measured by the relative difference between treatment groups) was generally consistent across the various analyses. The relative reduction in the mean decline in FVC at week 52 in the pirfenidone group was 45.1% when missing values due to death were replaced with the worst possible value, 41.1% when missing values due to death were imputed using the sum of squared differences methodology, and 43.3% when using observed data only. In other analyses, relative reductions in FVC decline in the pirfenidone group compared with placebo were consistently in the range of 40% to 57%, further supporting the stability of the estimate of the magnitude of treatment effect in the primary analysis (Table 3).

Discussion

We found a consistent and statistically persuasive treatment effect of pirfenidone on the change in FVC in patients with IPF in multiple sensitivity analyses using a variety of statistical tests and data imputation methods. In each analysis, the distribution of FVC change from baseline to week 52 in the ASCEND trial was systematically different between the treatment groups and favored treatment with pirfenidone. The

TABLE 2] Effect of Alternative Analytic Methods and Data Imputation Strategies on the Statistical Finding on the Primary End Point of Change From Baseline to Week 52 in FVC in the ASCEND Study

Analysis	Imputation Methodology		*P* Value[a]
	Missing for Reasons Other Than Death	Missing Due to Death	
Rank ANCOVA	SSD[b]	Worst rank[b]	<.001[b]
	SSD	SSD	<.001
	LOCF	Worst rank	<.001
	LOCF	LOCF	<.001
	MI[c]	Worst observed value[d]	<.001
	No imputation	No imputation	<.001
MMRM, mL	No imputation	No imputation	<.001
RCM (slope analysis), mL	Slope	Slope	<.001
Mean change, mL (ANCOVA)	SSD	FVC = 0	<.001
	SSD	FVC = 1,500 mL	<.001
	SSD	SSD	<.001
CMH row mean score test (2 categories)[e]	SSD	Worst category	<.001
CMH row mean score test (3 categories)[f]	SSD	Worst category	<.001

ANCOVA = analysis of covariance; ASCEND = Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; MI = multiple imputation; MMRM = mixed effect model with repeated measures; RCM = random coefficients model; SSD = sum of squared differences.
[a]Pirfenidone 2,403 mg/d vs placebo.
[b]Prespecified primary efficacy analysis.
[c]Multiple imputation using data from patients in the same treatment group who discontinued treatment prematurely but had a wk 52 observation.
[d]Worst observed value among patients on placebo who discontinued treatment prematurely but had a wk 52 observation.
[e]Categorical thresholds: ≥ 10% absolute decline and < 10% absolute decline.
[f]Categorical thresholds: ≥ 10% absolute decline, > 0 to < 10% absolute decline, no decline.

strength of the statistical finding was consistent across all analyses and was not affected by the manner in which missing data were handled. Additionally, although the method used to impute missing data due to death influenced the observed magnitude of mean change in FVC in both treatment groups, the overall magnitude of the treatment effect (as measured by relative differences between treatment groups) remained consistent: Treatment with pirfenidone was associated with a roughly 50% reduction in FVC decline, regardless of the analytic strategy or the method used to impute missing data.

In previous studies, various analytic methods and data imputation strategies have been used to evaluate longitudinal change in FVC.[20-24] Importantly, the manner in which each method addresses issues like variability in the rates of disease progression and the confounding effect of missing data—including data that are missing due to death—has potential implications for statistical inference and estimation of the magnitude of treatment effect. In the present analysis, we used a broad variety of analytic strategies to evaluate the robustness of the statistical finding and the stability of the estimate of the magnitude of treatment effect on the change from baseline to week 52 in FVC in the ASCEND study.

Our findings have two potentially important implications for the design and execution of clinical trials in IPF and the interpretation of study results. First, the influence of the data imputation methodology on the observed magnitude of change in FVC in both treatment groups in our study underscores the importance of ensuring that similar analytic methods are used when comparing FVC results across clinical trials. By way of illustration, it has been observed that the reported magnitude of decline in FVC at 1 year in the placebo group in the ASCEND trial (−428 mL) was substantially larger than the observed annual rate of decline in the placebo group in the Investigating the Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis (INPULSIS) trials (−223.5 mL),[23] leading to speculation that this difference might be due to phenotypic differences in the study populations.[7] Our analyses demonstrate that the apparent difference in the magnitude of decline in FVC in the ASCEND and INPULSIS trials is almost entirely attributable to differences in analytic methodology, including the handling of missing data due to deaths. Specifically, the reported magnitude of decline in the ASCEND trial was

TABLE 3] Effect of Alternative Analytic Methods and Data Imputation Strategies on the Estimated Magnitude of Treatment Effect on Change in FVC at Week 52 in the ASCEND Study

Analysis	Imputation Methodology		Pirfenidone (n = 278)	Placebo (n = 277)	Relative Reduction, %
	Missing Other Than Death	Missing Due to Death			
Categorical analysis (proportion of patients with ≥ 10% decline or death)	SSD	Worst category	16.5%	31.8%	47.9
	SSD	SSD	12.6%	29.2%	56.9
	LOCF	Worst category	16.2%	31.0%	47.9
	LOCF	LOCF	12.2%	28.5%	57.1
	No imputation	No imputation	11.1%	25.9%	57.2
MMRM, mL	No imputation	No imputation	−149.6	−268.5	44.3
RCM (slope), mL	Slope	Slope	−163.6	−279.6	41.5
Mean change, mL	SSD	FVC = 0	−235.1	−427.9	45.1
	SSD	FVC = 1,500 mL	−175.5	−319.6	45.0
	SSD	SSD	−161.6	−274.4	41.1
	LOCF	FVC = 0	−231.6	−423.2	45.3
	MI[a]	Worst observed[b]	−154.3	−266.8	42.2
	No imputation	No imputation	−144.9	−255.5	43.3

See Table 2 legend for expansion of abbreviations.
[a]Multiple imputation using data from patients in the same treatment group who discontinued treatment prematurely but had a wk 52 observation.
[b]Worst observed value among patients on placebo who discontinued treatment prematurely but had a wk 52 observation.

based on an analysis of mean change in FVC in which missing data due to death were assigned the worst possible value (FVC = 0); the annual rate of decline in the INPULSIS trials was based on a slope analysis in which missing values due to death were not assigned a worst possible value. When the ASCEND data were analyzed using the methodology used in the INPULSIS trials, the placebo rates of FVC decline were quite similar (−279.6 mL and −223.5 mL, respectively, in ASCEND and INPULSIS). Notably, the difference in the rates of decline between the placebo groups in the ASCEND and INPULSIS trials was roughly equivalent to the difference between the placebo groups in INPULSIS-1 and INPULSIS-2. Second, our results highlight the fundamental importance of study conduct in achieving robust and clinically interpretable results. Indeed, the robustness of the findings in the ASCEND study is attributable in part to the fact that there were minimal missing data; fully 94% of patients in both treatment groups completed the study, thereby limiting the influence of imputed data on study outcomes.

Conclusions

In conclusion, our results confirm the robustness of the statistical finding on the primary end point of change from baseline to week 52 in percent predicted FVC in the ASCEND study and corroborate the estimated magnitude of the pirfenidone treatment effect on FVC change in patients with IPF. Additionally, our findings demonstrate the effect of various analytic methods and data imputation strategies on the magnitude of change in FVC, thereby providing benchmarks to facilitate comparisons with other clinical trials.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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