Idiopathic Pulmonary Fibrosis: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials

Ganesh Raghu[1]*, Harold R. Collard[2]*, Kevin J. Anstrom[3], Kevin R. Flaherty[4], Thomas R. Fleming[5], Talmadge E. King, Jr.[2], Fernando J. Martinez[4], and Kevin K. Brown[6]

[1]Department of Medicine, and [5]Department of Biostatistics, University of Washington, Seattle, Washington; [2]Department of Medicine, University of California San Francisco, San Francisco, California; [3]Duke Clinical Research Institute, Duke University, Durham, North Carolina; [4]Department of Medicine, University of Michigan, Ann Arbor, Michigan; and [6]Department of Medicine, National Jewish Health, Denver, Colorado

Definitive evidence of clinical efficacy in a Phase 3 trial is best shown by a beneficial impact on a clinically meaningful endpoint—that is, an endpoint that directly measures how a patient feels (symptoms), functions (the ability to perform activities in daily life), or survives. In idiopathic pulmonary fibrosis (IPF), we believe the endpoints that best meet these criteria are all-cause mortality and all-cause nonelective hospitalization. There are no validated measures of symptoms or broader constructs such as health status or funtional status in IPF. A surrogate endpoint is defined as an indirect measure that is intended to substitute for a clinically meaningful endpoint. Surrogate endpoints can be appropriate outcome measures if validated. However, validation requires substantial evidence that the effect of an intervention on a clinically meaningful endpoint is reliably predicted by the effect of an intervention on the surrogate endpoint. For patients with IPF, there are currently no validated surrogate endpoints.

Keywords: idiopathic pulmonary fibrosis; clinical trials; endpoints; survival; surrogate endpoints

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disease of unknown etiology that affects an estimated 100,000 Americans and accounts for over 15,000 deaths a year (1). The median survival from the time of diagnosis is 2 to 3 years (2–5). Drug agents evaluated in clinical trials of patients with IPF have failed to demonstrate improvement in clinically meaningful outcomes (e.g., symptoms, functional status, and survival) (6). Furthermore, recently conducted Phase 3 clinical trials of novel therapies in IPF have lacked a standardized approach to key study design issues, most prominently the choice of a primary endpoint (7) (Table 1).

The purpose of this document is to provide an overview of the strengths and limitations of the major endpoints used in Phase 3 clinical trials of patients with IPF and to provide perspective and guidance for their use as primary endpoints in future Phase 3 clinical trials globally. In addition, we identify critical gaps in knowledge regarding endpoints in IPF and suggest future directions for endpoint development. This document is intended as a scientific review, not as a guidance to regulatory agencies in the United States or elsewhere. Regulatory agencies responsible for drug approval act within a framework of region-specific rules that influence the level of evidence regarding risk and benefit that is required before an approval is granted. Some of the results of the studies included in this perspective have been reported in the form of a press release or an abstract (8–10).

METHODS

Planning and Participants

Ongoing discussions among three clinical investigators in the field of IPF (G.R., H.R.C., and K.K.B.) led to a formal request to the Pulmonary Fibrosis Foundation, a nonprofit patient advocacy group, to sponsor a working group (termed by the sponsor a "summit") to meet and discuss appropriate endpoints for future Phase 3 trials in IPF. Additional participants were invited based on their experience and expertise in clinical trials of patients with IPF. Representatives from the Division of Lung Diseases within the National Heart, Lung, Blood Institute (NHLBI) of the National Institutes of Health and the Division of Pulmonary, Allergy, and Rheumatology of the Food and Drug Administration (FDA) were invited to attend and participate in the meeting. The NHLBI and FDA participants listened to the discussion, asked questions, and provided perspective, but did not participate in the authorship of the perspective. The meeting was held on July 11th and 12th, 2011, in Bethesda, Maryland.

Meeting Structure and Document Development

Potential endpoints for Phase 3 trials in patients with IPF were identified prior to the meeting by three clinical investigators (G.R., H.R.C., and K.K.B.). For each endpoint, the definition, clinical relevance, strengths, and limitations were discussed. A consensus summary regarding the use of each endpoint as a primary endpoint in a Phase 3 trial was developed. The results of the discussion and consensus summary are reported in this document.

CLINICALLY MEANINGFUL ENDPOINTS

As defined by the National Institute of Heath Biomarkers Definitions Working Group, the term "clinically meaningful endpoints" refers to endpoints that directly measure how a patient feels (e.g., symptoms), functions (i.e., a patient's ability to perform activities in daily life), or survives (i.e., mortality) (11, 12). In other words, they are directly relevant to the goals and priorities of patients. The ideal clinically meaningful endpoint should also be well defined, reliable, measurable, interpretable, and sensitive to the effects of the intervention. Clinically meaningful endpoints are unarguably appropriate primary outcome measures in Phase 3 clinical trials.

MORTALITY

Mortality-related measures can be defined in various ways—all-cause mortality, respiratory-related mortality, or IPF-related mortality—

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Correspondence and requests for reprints should be addressed to Ganesh Raghu, M.D., Division of Pulmonary and Critical Care Medicine, Campus Box 356175, University of Washington, Seattle, WA 98195. E-mail: graghu@u.washington.edu

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TABLE 1. PRIMARY ENDPOINTS IN PHASE 3 CLINICAL TRIALS IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

Study	Drug agent	Primary endpoint
Published studies		
Raghu *et al.*, 2004	IFN-γ	Death or disease progression (composite)
Demedts *et al.*, 2005	Acetylcysteine	Change in VC and D_{LCO}
King *et al.*, 2009	IFN-γ	All-cause mortality
King *et al.*, 2011	Bosentan	Death or disease progression (composite)
Taniguchi *et al.*, 2010*	Pirfenidone	Change in VC
Noble *et al.*, 2011	Pirfenidone	Change in FVC
Unpublished studies		
ACE-IPF†	Warfarin	Death, hospitalization or disease progression (composite)
PANTHER-IPF‡	N-acetylcysteine (NAC) with or without prednisone/azathioprine	Change in FVC
ARTEMIS-IPF§	Ambrisentan	Death, respiratory hospitalization, or disease progression (composite)
ARTEMIS-PH§	Ambrisentan	Change in 6MWD

Definition of abbreviation: 6MWD = 6-minute-walk test distance.

* Primary endpoint was changed from "change in lowest O_2 saturation during 6-minute steady-state exercise test" during the course of the trial.

† Trial was stopped early for lack of efficacy. Data not yet published (9).

‡ One arm of trial was stopped early for lack of efficacy. Data not yet published (8).

§ Trial was stopped early for lack of efficacy. Data not yet published (10)

and can be analyzed as a time-to-event endpoint or an endpoint at a fixed time (e.g., 1 year). *The most clinically relevant of these is all-cause mortality. It is also well defined, reliable, and easy to measure.* All-cause mortality avoids losing clinically relevant information and inducing informative missingness that occurs when deaths related to the study intervention are misclassified as "unrelated" and are censored. The all-cause mortality endpoint also captures potential off-target effects that could impact risk of mortality (e.g., death due to drug-related toxicity such as liver failure or arrhythmia). Ultimately, if a drug benefits IPF-related mortality but not all-cause mortality, it is of questionable clinical utility.

Clinical trials with mortality-related endpoints often need to have large sample sizes and have long duration, leading to the need for more resources to complete than non–survival-based studies. This has led to concern that mortality-based studies are impractical in IPF. However, a properly powered Phase 3 clinical trial using all-cause mortality as the primary endpoint has been successfully conducted in IPF, establishing that it is possible (13). A second Phase 3 trial recently reported an increase in mortality (a key secondary endpoint) in one treatment arm compared with placebo, leading to discontinuation of the treatment arm (8).

Summary

Mortality is the most robust primary endpoint for Phase 3 clinical trials in IPF, *and a previous Phase 3 clinical trial has proven that an adequately powered all-cause mortality study can be successfully performed.* ***All-cause mortality is the cleanest and most easily interpreted mortality-related endpoint****. Consideration of cause-specific mortality endpoints (e.g., IPF-related or respiratory-related mortality) should balance potential increased sensitivity to treatment effect against the risk of adjudication errors and decreased sensitivity to off-target effects.*

HOSPITALIZATION

Hospitalization is a clinically meaningful event that is relevant to the goals and priorities of patients with IPF. Like survival, hospitalization can be defined in various ways—all-cause hospitalization, respiratory hospitalization, and IPF-related hospitalization. As discussed for all-cause mortality, all-cause hospitalization is the easiest to define and avoids important problems associated with assigning causation. An exception may be hospitalization for elective non–IPF-related causes (e.g., knee replacement surgery for previously recognized osteoarthritis). These hospitalizations can be easily identified and are less likely to be influenced by the effects of treatment. Limitations of hospitalization endpoints include a variety of non–disease-related factors that can influence whether hospitalization occurs, such as access to health care, social support, and regional practice patterns, as well as the challenge of clinical data retrieval when a subject is hospitalized at a facility outside of the study.

Summary

Hospitalization, in particular all-cause nonelective hospitalization, is an appropriate primary endpoint for Phase 3 clinical trials in IPF. While factors external to disease progression or exacerbation may influence decisions regarding hospitalization, it remains a clinically meaningful endpoint.

ACUTE EXACERBATION OF IPF

Acute exacerbation of IPF is most commonly defined using standard criteria, which include clinically relevant worsening of dyspnea (14). It is a direct measure of symptoms, in addition to being associated with high mortality and impaired functional status in survivors (14). In many cases, documentation of acute exacerbations in a clinical trial involves centralized adjudication. While adjudication of endpoints is useful for standardizing measurement, the complexity of the adjudication process can create substantial practical and logistical challenges that can lead to measurement error and lack of sensitivity due to missing data. If adjudication is necessary, the simplest criteria and procedure possible should be chosen and then implemented in a timely manner during the course of the clinical trial.

Summary

Acute exacerbation of IPF, while a clinically meaningful endpoint, can be challenging to adjudicate and is at risk of measurement error in the context of a clinical trial.

PATIENT-REPORTED OUTCOMES

Patient-reported outcomes (PROs) are defined to be "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (15). PROs for disease symptoms (e.g., dyspnea, cough) and for broader constructs (e.g., health status) have not been used as primary endpoints in any Phase 3 clinical trial in patients with IPF, largely because of the lack of properly established PROs in this population. The ideal PRO is developed through an iterative process of interviewing patients with the disease of interest, with rigorous evidence of its validity, including that it is well-defined and reliable. In the context of PRO development, validity is both content related (the PRO measures the concept of interest) and construct related (the relationship between PRO items are as expected) (15). PROs developed for other diseases have been used as secondary endpoints in Phase 3 clinical trials of IPF (16, 17).

Summary

There are no PROs that are properly established in patients with IPF. While PROs can be clinically meaningful endpoints, it is currently unknown if existing PROs accurately measure symptoms

and broader constructs such as health status in patients with IPF, and whether they are sensitive enough to detect treatment effects.

FUNCTIONAL STATUS

Endpoints that directly measure how well a patient conducts their daily activities (i.e., functional status) are clinically meaningful. In patients with IPF, the most widely used measure of physical activity is the distance walked during a 6-minute-walk test (6MWD). However, 6-minute-walk test variables such as 6MWD are an abbreviated measure of exercise capacity rather than being a direct measure the daily activity of the patient. Recent evidence also suggests that the change in 6MWD is correlated with mortality in patients with IPF (*see* section below on surrogate endpoints) (18). Change in 6MWD has been used as a primary endpoint in several late-stage clinical trials of IPF (16, 17), but there have been both statistical and study design issues including problems with reproducibility, handling of missing data, and standardization of methodology across multiple sites.

Summary

There are currently no direct measures of functional status in patients with IPF*. Six-minute-walk test variables such as the 6MWD do not fully capture how a patient conducts their daily activities and may have technical limitations.*

SURROGATE ENDPOINTS

A surrogate endpoint is defined as an indirect measure that is intended to substitute for a clinically meaningful endpoint. Many indirect measures are biomarkers, defined as objectively measured indicators of a normal biological process, pathologic process, or pharmacologic response to a therapeutic agent (11). Surrogate endpoints are of interest to clinical trialists who wish to reduce the sample size, shorten the duration, or lower the costs of an interventional study.

There are several potential surrogate endpoints that have been measured in IPF clinical trials, including pulmonary physiology (e.g., forced vital capacity [FVC] and diffusion capacity for carbon monoxide [D_{LCO}]), 6MWD, imaging features on high-resolution computed tomography (HRCT) scanning, and circulating biomarkers (18, 19). *However, the correlation of potential surrogate endpoints with clinically meaningful endpoints does not establish the potential surrogate to be a valid replacement endpoint.* Validation of a surrogate endpoint requires substantial evidence that the effect of the intervention on the clinically meaningful endpoint is reliably predicted by the effect of the intervention on the surrogate endpoint (11). This generally requires a comprehensive understanding of the causal pathways of the disease, knowledge of the intervention's intended and unintended mechanisms of action, and data from multiple Phase 3 trials to provide precise estimates of treatment effect on the potential surrogate and the clinically meaningful endpoints. Importantly, validation of a potential surrogate endpoint, as described above, is different from validation, or validity, as used in PRO development (*see* PRO section above). The ideal surrogate endpoint also should be responsive across multiple pathophysiological targets; that is, it should be valid regardless of the specific therapeutic mechanism of action under study. Without validation, there are several ways in which potential surrogate endpoints can provide inaccurate information regarding the effect of an intervention (Figure 1) (20).

To date, there are no validated surrogate endpoints in IPF. This does not mean that some of the replacement endpoints that have been measured (e.g., FVC) do not have the potential to be valid surrogates. It is simply not known if they are valid—they have not been validated. It is important that ongoing and future clinical trials include the measurement of multiple potential surrogate endpoints, including serial biological samples. This will allow for an evidence-based assessment of the validity of these potential surrogate endpoints, by contrasting the effects of an intervention on these replacement endpoints with its effects on clinically meaningful endpoints in a mixture of clinical trials.

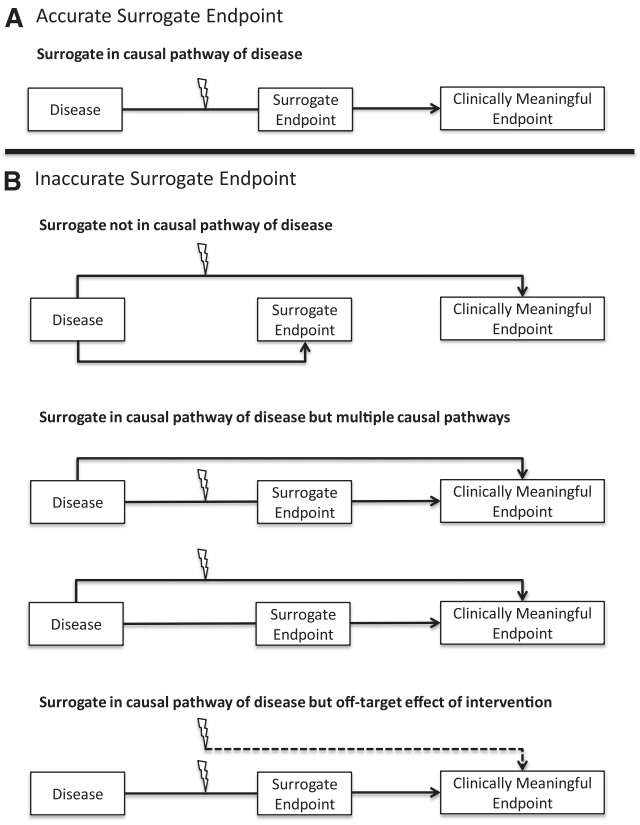

Figure 1. (*A*) A candidate surrogate endpoint is in the pathway through which the disease causally induces risk of the clinically meaningful endpoint, and the intervention's (lightning bolt) effect is on that pathway. (*B*) An intervention's effect on candidate surrogate endpoints can provide inaccurate predictions of its effect on clinically meaningful endpoints for several reasons. First, the candidate surrogate may not be directly involved in a causal pathway of the disease. Second, the surrogate may be in a causal pathway of the disease, but there may be other causal pathways of the disease that it does not capture (i.e., there are multiple causal pathways of disease). Third, the surrogate is in the causal pathway of the disease, but there are off-target effects of the intervention. Based on a presentation of data in Reference 20.

The most commonly used physiological measurement in clinical trials is FVC. FVC has been widely used as a primary endpoint for Phase 3 clinical trials in IPF (21–23). Changes in a patient's FVC over time (whether analyzed continuously or categorically as above or below a threshold value) have been correlated with survival time in multiple large cohorts of patients with IPF (19, 24–26), and it is widely accepted in natural history settings that a decline of 10% in an individual's FVC is a sign of disease progression, making this a useful prognostic factor (6). As discussed earlier, changes in 6MWD also have been documented to be correlated with survival time (18). However, such correlations are inadequate to establish FVC or 6MWD changes as validated surrogate endpoints. Specifically, the major limitation to FVC and 6MWD (and other potential surrogate endpoints) as endpoints in Phase 3 trials in IPF is the lack of evidence establishing that treatment-induced changes in these potential surrogate endpoints reliably

predict treatment-induced changes in clinically meaningful endpoints. Other potential surrogate endpoints such as the $D_{L_{CO}}$ and composite scoring systems have the same limitation.

There are also statistical challenges in how best to formulate changes in FVC, 6MWD, or other such measurements. Change over time has generally been reported as a mean value per treatment group rather than as a percentage of subjects in each treatment group who cross a predetermined, clinically meaningful threshold (i.e., responder analysis). Data from retrospective cohort studies have suggested the use of thresholds between 5% and 10% for FVC and around 30 m for 6MWD; however, these thresholds require validation as surrogate endpoints in prospective clinical trials (18, 19, 27, 28). It is unknown whether differences in the mean change for two treatment groups or a responder analysis is more likely to predict differences in clinically meaningful outcomes such as survival.

An additional problem is the handling of missing data (29). Many patients with IPF in clinical trials will be unable to complete follow-up FVC and 6MWD measurements, either because they become too sick, are lost to follow-up, or have died. Other potential surrogate endpoints such as the $D_{L_{CO}}$ and the composite scoring systems have similar limitations (2, 30, 31).

Summary

Measures of pulmonary physiology, such as FVC and 6MWD, are not validated as surrogates for clinically meaningful outcomes such as survival in patients with IPF. ***At this time, change in FVC, 6MWD, and other physiological variables are not robust primary endpoints for use in Phase 3 clinical trials in IPF.***

COMPOSITE ENDPOINTS

Composite endpoints consist of two or more individual endpoints combined together, and generally require that only one of the individual components be substantially affected for the composite endpoint to be met. Typically composite endpoints include a mortality component and one or more nonmortality components. Progression-free survival, most commonly defined as a composite of decline in FVC or death, has been used as a primary endpoint in recent IPF studies (10, 32, 33).

Composite endpoints have several potential advantages, including reducing the required sample size of a trial (through increasing the number of events), and better estimating net clinical benefit across multiple important outcomes likely affected by the intervention (e.g., patient symptoms as well as survival time). The disadvantages of composite endpoints are primarily related to loss of specificity and interpretability. It is hard to know the impact of an intervention on survival, for example, if the endpoint measured is a composite of survival, hospitalization, and change in FVC. Indeed, it is possible that discordant effects of a drug agent on components of the composite (e.g., the drug agent worsens survival but slows the rate of decline in FVC) could hide important efficacy information. Finally, the clinical relevance of composite endpoints is primarily determined by its weakest component, particularly when that component contributes the most events. In the example given above, the inclusion of an unvalidated surrogate endpoint (FVC) makes the clinical relevance of the entire composite endpoint unclear. The ideal composite endpoint contains only measures that are clinically meaningful endpoints or validated surrogates.

Summary

Composite endpoints should be constructed from clinically meaningful endpoints or validated surrogates that are likely to be influenced by the studied intervention. *A combination of all-cause mortality and all-cause nonelective hospitalization could be considered as a primary endpoint for Phase 3 clinical trials in IPF.*

LUNG TRANSPLANTATION

Lung transplantation is an increasingly common outcome for patients with IPF, and one that presents unique challenges when considered as an outcome measure. Lung transplantation might be a clinically meaningful endpoint, although one that is not necessarily related to the natural history of IPF. Disease-independent factors such as donor availability, age, comorbidity, social support, insurance status, and heterogeneity in clinical practice across centers (e.g., differences in allocation regimens) all contribute substantial additional risk for achieving this endpoint. Because of these additional factors, it is debatable how best to handle lung transplantation in clinical trials. While it commonly is censored, doing so could lead to informative missingness.

CONCLUSIONS

The choice of a primary endpoint for Phase 3 clinical trials for IPF is an important and complex decision that includes scientific, practical, financial, and regulatory considerations. *We believe the most scientifically appropriate primary endpoints for Phase 3 clinical trials are clinically meaningful endpoints that directly inform how a patient feels, functions, or survives. In IPF, the endpoints that most clearly meet these criteria are all-cause mortality and all-cause nonelective hospitalization.* A composite endpoint of all cause-mortality or all-cause nonelective hospitalization is also scientifically robust. This does not mean that all Phase 3 clinical trials should use all cause-mortality or all cause-mortality plus all-cause nonelective hospitalization as the primary endpoint; in some cases, endpoints measuring symptom severity or health status may be more desirable. However, to date there are no validated PROs to measure symptoms or broader constructs such as health status in patients with IPF, and there are no validated measures of functional status. Unfortunately, there are similarly no validated surrogate endpoints for clinically meaningful endpoints in IPF at this time.

AREAS FOR FUTURE RESEARCH

It should be emphasized that we have made important progress in understanding the strengths and limitations of potential endpoints in Phase 3 trials in IPF. Moving forward, it is important to develop established PROs and functional measures to allow for accurate measurement of how patients with IPF feel and function. These are essential components of efficacy that are clearly important to patients and providers, and established PROs would add a critical dimension to efficacy assessment in Phase 3 clinical trials. It also is important to develop validated surrogate endpoints for IPF. Validated surrogates would give the IPF scientific community an additional and more efficient way to move forward. To achieve this, ongoing and future clinical trials should include measurement of multiple potential surrogate endpoints, including serial biological samples. Finally, a consensus on trial design methodology (e.g., inclusion criteria, approach to handling of missing data, handling of lung transplantation) would allow for easier comparison and meta-analysis of Phase 3 clinical trial results. These topics and others will require input and collaboration from all concerned stakeholders, including clinicians, investigators, sponsors, regulators, statisticians, and patients. It is our sincere hope that by providing a framework for discussion, this document helps all concerned to move forward together in pursuit of effective treatments for IPF.

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