

Official Title: An Exploratory Multicenter, Open-Label, Single Arm Study of the Safety and Tolerability of Pirfenidone (Esbriet®) in Combination With Nintedanib (Ofev®) in Patients With Idiopathic Pulmonary Fibrosis

NCT Number: NCT02598193

Document Date: Statistical Analysis Plan Version 1: 21-Nov-2016
Statistical Analysis Plan Version 2: 17-May-2017

STATISTICAL ANALYSIS PLAN

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET®) IN COMBINATION WITH NINTEDANIB (OFEV®) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: MA29895

STUDY DRUG: Pirfenidone (Esbriet®) and nintedanib (Ofev®)

VERSION NUMBER: Version 1.0 Final, 21Nov2016

IND NUMBER: 67,284

EUDRACT NUMBER: 2015-003280-11

SPONSOR: F. Hoffmann-La Roche Ltd

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DATE FINAL: 21 November 2016

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Not applicable, as this is the first version of the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
%FVC	Percent predicted forced vital capacity
ACS	Acute coronary syndrome
AE	Adverse event
AEGT	Standard Adverse Event Group Terms
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
DLco	Carbon monoxide diffusing capacity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FVC	Forced vital capacity
GCP	Good clinical practice
GI	Gastrointestinal
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
██████	████████████████████ ████████████████████
LPLV	Last patient, last visit
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
ms	Millisecond
PRO	Patient-reported outcome
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event

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TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TID	Three times daily
TMS	Trial Management System
UA	Unstable angina
ULN	Upper limit of normal
WHO	World Health Organization

1. **BACKGROUND**

As described in the Clinical Study Protocol (CSP) (Section 1.3), the mechanism of action of pirfenidone in Idiopathic Pulmonary Fibrosis (IPF) has not been established (Esbriet® EU SmPc and US label 2014), while nintedanib is thought to act by inhibiting multiple RTKs and nRTKs (Esbriet® US label 2014). Because multiple co-activated pathways are involved in the pathogenesis of IPF, experts have suggested that targeted therapies may work better in combination (Wuyts et al. 2014). Furthermore, experience in other pulmonary diseases (e.g., asthma, chronic obstructive pulmonary disease, and pirfenidone and nintedanib — F. Hoffmann-La Roche Ltd 18 / Protocol MA29895, Version 2 pulmonary hypertension) has demonstrated the value of moving from monotherapy to combination therapy.

The positive benefit risk assessment of both drugs have been established in respective Phase II and Phase III programs which led to approval in the EU, the US, Japan and many other countries worldwide. Both drugs demonstrated that pulmonary function could be significantly improved in IPF patients, while the safety and tolerability profile was considered acceptable.

Considering the overlap in the gastrointestinal (GI) and hepatic Adverse Events (AEs) associated with these two drugs, it is worthwhile to characterize the safety and tolerability of nintedanib when added to pirfenidone as a combination treatment using the doses recommended in the respective pirfenidone and nintedanib labels.

This prospective study will evaluate the safety and tolerability of 24 weeks of nintedanib combination treatment in patients with IPF who are on a stable dose of pirfenidone with demonstrated tolerability. The study is not designed to evaluate the efficacy of combination treatment, nor is it designed to assess the safety and tolerability of adding pirfenidone to ongoing nintedanib treatment.

2. **STUDY DESIGN**

This is a multicenter, international, open-label, single-arm safety and tolerability study of pirfenidone/nintedanib combination treatment in patients with IPF who have been on a stable dose of pirfenidone with demonstrated tolerability. In this study, a stable pirfenidone dose will be defined as 1602–2403 mg/d (801 mg twice daily [BID] or three times daily [TID]). Up to approximately 60 clinical centers in the US, Europe, and Canada are expected to enroll up to approximately 80 patients. Patients who are withdrawn from the study will not be replaced.

At the start of Screening, patients will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; also, the dose must be expected to remain within that range throughout the study. In addition, in the 28 days before the start of Screening, patients must not have experienced either a new or
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ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment for > 7 days for any reason.

2.1 **PROTOCOL SYNOPSIS**

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#). For additional details, please see the Protocol Amendment Version 3, 21 June 2016 (and its Appendices).

2.2 **OUTCOME MEASURES**

The primary objective for this study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with IPF. Consequently, the primary objectives of this study focus on safety and tolerability and not efficacy.

2.2.1 **Primary Efficacy Outcome Measures**

Not applicable.

2.2.2 **Secondary Efficacy Outcome Measures**

Not applicable.

2.2.3 **Exploratory Efficacy Outcome Measures**

[REDACTED]

- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]

2.2.4 **Patient-Reported Outcome Measures**

- [REDACTED]
[REDACTED]
[REDACTED]

2.2.5 Safety Outcome Measures

The primary safety outcome measure is:

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d.

Secondary safety outcome measures are:

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 visit,
- Total number of patient days of combination treatment with pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d,
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments,
- Frequency and timing of Adverse Events (AEs) and Serious Adverse Events (SAEs).

2.3 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 80 patients was selected based on the AE discontinuation rates after one year observed in the randomized Phase 3 pirfenidone studies and the randomized Phase 2 and 3 nintedanib studies (pirfenidone 14.6% AE discontinuation [Esbriet® US label 2014]; nintedanib 21% AE discontinuation [Ofev® US label 2014]). Given that for pirfenidone the discontinuation rate after 24 weeks was 6%-8% in studies PIPF-004 and PIPF-006 it is a reasonable assumption that the nintedanib discontinuation rate was around 10%-11%. As in this study of combination treatment, it is possible that the addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients who discontinue because of an AE, given the overlap in the GI and hepatic effects of pirfenidone and nintedanib.

Assuming 85% of the patients complete 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2% - 92.8% using a 95% confidence interval (CI). [Table 1](#) shows the 95% CIs associated with projected completion rates of 75%, 80%, 85%, 90% or 95%, assuming an 80-patient sample size.

Table 1 Confidence Limits for Sample Size Determination

Number of Patients who completed 24 weeks	Proportion of Patients who completed 24 weeks	Lower Bound of 95% CI	Upper Bound of 95% CI
76	95.0%	90.2%	99.8%
72	90.0%	84.4%	96.6%
68	85.0%	77.2%	92.8%
64	80.0%	71.2%	88.8%
60	75.0%	65.5%	84.5%

CI = confidence interval

Patients who are withdrawn from the study will not be replaced.

2.4 ANALYSIS TIMING

The following analyses will be performed for this study:

Table 2 Analysis Timing

Analysis	Timing of Analysis
First iDMC	When the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments
Second iDMC	When approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments
Third iDMC	When approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments
Final	All patients completed 24 weeks of combination treatment or permanently discontinued study treatments

Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted.

3. STUDY CONDUCT

The study conduct is described in Section 2 (Study design).

3.1 RANDOMIZATION ISSUES

This will be an open-label trial involving only one treatment arm.

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

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3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct at least three times during the study. For details on timing of the safety reviews please see Table 2 above. Efficacy data will only be provided if requested by the iDMC. For details please see Section 4.10.

4. STATISTICAL METHODS

This is a safety and tolerability study, not designed to assess efficacy, comprising only one treatment group. There are no formal statistical hypothesis tests to be performed, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons. Efficacy analyses will be limited to descriptive statistics.

Categorical data will be summarized using frequencies and percentages (including a category for missing, if appropriate).

Continuous endpoints will be summarized using descriptive statistics (mean, standard deviation, minimum, 25th and 75th quartiles, median, and maximum).

Where data will be presented over time, e.g. Baseline, Week 12, Week 24, and early discontinuation visit, an end of treatment visit (EOT) will be added. This will include Week 24 data for patients who completed 24 weeks of combination treatment and data from the early discontinuation visit for patients who prematurely discontinued from combination treatment.

Other analysis methods will be specified below, where applicable. All data recorded in the electronic Case Report Form (eCRF), as well as derived data that will be used in analyses, will be listed.

Analyses will be presented for the total population, together with geographic region, i.e. US and non-US patients. Results for US and non-US will be presented as additional columns or additional blocks within the outputs of the total population.

Percentages will be based on the total population or on the number of patients in the respective geographic region, if not otherwise specified.

4.1 ANALYSIS POPULATIONS

Only one analysis population, the Safety Population, has been defined as per CSP. No further analysis populations will be assessed.

4.1.1 Full Analysis Set

Not applicable.

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4.1.2 Per Protocol Population

Not applicable.

4.1.3 Pharmacokinetic-Evaluable Population

Not applicable.

4.1.4 Safety Population

The Safety Population will consist of all patients who received at least one dose of nintedanib or pirfenidone at the Baseline visit (Day 1).

Analyses will be produced for the Safety Population, if not otherwise specified.

4.2 TRIAL PERIODS, OBSERVATION AND ANALYSIS TIMES

In case that durations are to be calculated (e.g. treatment duration), these will be derived based on days and converted to months and years if needed, using 30.4375 and 365.25, respectively, as denominator if not otherwise specified.

4.2.1 Study Days

Study day is defined as the number of days since combination treatment start date, and is calculated as:

- For assessments after or on the day of start of combination treatment:
Study day = Assessment date – Date of start of combination treatment + 1.
- For assessments before the day of start of combination treatment:
Study day = Assessment date – Date of start of combination treatment

The day of the first dose of combination treatment will be Day 1.

4.2.2 Baseline and Screening Observations

Table 3 Definition of Baseline and Screening Observations

	Definition
Combination Treatment Start Date	Combination Treatment Start Date is the date of first administration of nintedanib or pirfenidone at or after the 'Baseline (Day 1)' visit. Combination treatment start date will be used for all safety assessments and for the calculation of study days.
Baseline data	Baseline is defined as the last valid assessment prior to start of combination treatment. This may not be the same as the 'Baseline

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	<p>(Day 1)' visit as per eCRF.</p> <p>Generally, it is assumed that measurements referring to the 'Baseline (Day 1)' visit have been performed before study drug was given. This applies for laboratory values, vital signs, ECG, pulmonary function tests and [REDACTED]</p> <p>Adverse events occurring at the combination treatment start date will not be considered baseline, but treatment-emergent.</p>
Screening data	Screening measurements are all the measurements performed before the combination treatment start date and not respecting the "baseline" criteria.

4.2.3 On-treatment Assessments

On-treatment assessments will be the assessments performed on or after the combination treatment start date until the date of the Follow-up visit, which is planned to be performed 28 - 35 days after the date the subject discontinued from combination treatment (see Section 4.2.5 for details).

4.2.4 Post-treatment Assessments

Post-treatment evaluations will be the evaluations performed later than the Follow-up visit. Post-treatment evaluations are not expected to occur. If there should be any, assessments falling into this time-window will only be listed.

For adverse events, all AEs starting later than 28 days after the last dose of study drug will be considered as post-treatment.

4.2.5 Treatment Start and Stop Dates

As this is a combination treatment study, different assessments with respect to study treatment are possible: Pirfenidone alone, nintedanib alone, and combination treatment. To account for this, the following definitions will be made:

Table 4 Definition of Treatment/Combination Treatment Start and Stop Dates

	Treatment start date	Treatment end date
Pirfenidone	Date of first administration as recorded in the study drug log for pirfenidone at or after the	Date of last administration of pirfenidone as recorded in the study drug log for pirfenidone.

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	'Baseline (Day 1)' visit.	
Nintedanib	Date of first administration of nintedanib as recorded in the study drug log for nintedanib.	Date of last administration of nintedanib as recorded in the study drug log for nintedanib.
Combination treatment	Date of first administration of nintedanib or pirfenidone at or after the 'Baseline (Day 1)' visit = Start date of combination treatment	Date subject completed or early discontinued from combination treatment period as per eCRF (eCRF form Study Drug Completion/Early discontinuation). = Date of discontinuation from combination treatment
Combination treatment as used for definition of TEAEs	Date of first administration of nintedanib or pirfenidone at or after the 'Baseline (Day 1)' visit = Start date of combination treatment	Maximum of last dose of either pirfenidone or nintedanib as per study drug logs. = Last dose date of combination treatment

4.2.6 Cut-off points

The main time point for reporting of data is at the final analysis. Clinical cut-off for final analysis is defined as the date of last patient last visit (LPLV). Data cleaning cut-off date is planned for 1 week after the clinical cut-off date. After this cut-off date no additional data will be entered into the database. Data cleaning will be completed after 8 weeks after the clinical cut-off. Database extract for analysis is planned to be performed xx weeks after the clinical cut-off.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

This is an open-label single arm phase IV study that will assess the combination treatment of pirfenidone and nintedanib. Consequently, no formal assessment of treatment group comparability can be conducted.

4.4 ANALYSIS OF STUDY CONDUCT

4.4.1 Patient Disposition

An overview on patient disposition, showing number and percentages of patients screened (as per IxRS), enrolled, treated and completed the study will be provided. For

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patients who have early discontinued study treatment or the study, frequencies of reasons for early discontinuation will be provided. Patients enrolled are all patients that have signed informed consent and are entered into the clinical database.

For further safety-related disposition analyses please see Section 4.7.1.

An overview on patients' enrolment by country and center will be provided.

4.4.2 Major Protocol Deviations

A Per-Protocol population will not be defined; however, major protocol deviations and eligibility violations will be summarized by frequency tables and all patients with protocol deviations will be listed.

Protocol deviations will be assessed by Clinical Science and will be provided in a spreadsheet. All deviations provided in that spreadsheet will be considered as major protocol deviations.

4.4.3 Demographic and Baseline Characteristics

Baseline and disease characteristics such as demographics, medical history, tobacco and substance use history will be summarized by descriptive statistics or frequency tables.

Demographics

The following demographic characteristics will be summarized:

- Age (years): as entered in the eCRF at the screening visit
- Age categories: 18 – 64 years, 65 - 84 years, ≥85 years
- Gender (male/female)
- Race: White, American Indian or Alaska Native, Asian (Indian subcontinent, Other than Indian subcontinent), Black or African American, Native Hawaiian or Other Pacific Islander, Unknown. In case that more than one race will be ticked, a concatenated variable, containing all races will be presented (e.g. Asian/White).
- Ethnicity: Hispanic (Latino), Non-Hispanic (Non-Latino)
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m²) at baseline. BMI will be calculated as weight in kg / (height in cm)² × 10000

Data on female reproductive status will be presented descriptively; methods of contraception will only be listed.

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Tobacco use history and substance use

The history of tobacco use will be summarized with the following characteristics:

- Tobacco use history (never, current, previous)
- Pack-years, smokers only

Numbers and percentages of patients for following characteristics will be presented to specify substance use:

- Current substance use (yes/no)
- Substance use (cannabinoids, amphetamines, opiates, caffeine, benzodiazepines, barbiturates, cocaine)

Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 19.0 or higher and will be summarized presenting numbers and frequencies by primary System Organ Class (SOC) and Preferred Term (PT). If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

Historical Pulmonary Function Test

The number and percentage of patients who performed the respective pulmonary function test [REDACTED] (calculated) in the past will be provided. This assessment was planned to be performed closest to 6 months before the Screening visit. These historical pulmonary function test parameters will be summarized using descriptive statistics. Both, absolute and percent predicted values will be presented. The time from assessment of the historical value to Screening will be summarized and defined as follows:

Time from assessment to Screening = (Date of Screening – Date of historical assessment) + 1.

4.5 EFFICACY ANALYSIS

The efficacy measures of this study will only be analyzed in an exploratory manner. A replacement of missing values is not planned.

4.5.1 Primary Efficacy Endpoints

Not applicable.

4.5.2 Secondary Efficacy Endpoints

Not applicable.

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- [REDACTED]
- [REDACTED]

-
- | Government | Percentage |
|---------------------|------------|
| Current government | 85% |
| Previous government | 15% |

[REDACTED]
[REDACTED]
[REDACTED]

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.5.5 Sensitivity Analyses

No sensitivity analyses are planned.

4.5.6 Subgroup Analyses

Subgroup analyses will be conducted for selected endpoints. The following subgroups will be based on:

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

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Patients' safety will be assessed further through analyses of treatment exposure, laboratory tests, vital signs, and ECGs.

4.7.1 Treatment Completion/Early Discontinuation

A summary of the number and proportion of patients who complete 24 weeks of combination treatment (with 95% CI) will be presented. A patient is considered to have completed 24 weeks of combination treatment, if the eCRF question "Did the subject complete the treatment?" is ticked "Yes" (eCRF form "Study Drug Completion/Early Discontinuation"). It is expected that these patients have completed the Week 24 visit within expected time window (see Section 4.9), but patients performing the Week 24 visit outside of these windows will also be considered for this analysis.

The number and proportion of patients who complete 24 weeks of combination treatment (with 95% confidence interval (CI)) on pirfenidone at a dose of 1602-2403 mg/d and nintedanib at a dose of 200-300 mg/d will be presented. Average daily dose information as defined in Section 4.7.2 will be used to assess whether a patient completed 24 weeks on target dose.

The number and percentage of patients who discontinued combination treatment because of an adverse event (with 95% CI) will also be presented. This summary comprises patients who have reported "Adverse Event" as main reason for treatment discontinuation.

The duration of combination treatment (weeks) and duration of participation in the study (weeks) (incl. follow-up) will be summarized descriptively. Duration of combination treatment will be defined as the time from combination treatment start date (see Section 4.2.2) to the date subject completed or early discontinued from combination treatment period as per eCRF (Study Drug Completion/Early discontinuation form). Duration of participation in the study will be defined as the time from date of Screening to date of Follow-up visit.

Kaplan-Meier (KM) plots for time to treatment discontinuation will be provided, based on the date subject completed or early discontinued from combination treatment period, as per eCRF (see Section 4.2.5). Separate lines by drug that is considered to be the primary reason for discontinuation (i.e. pirfenidone, nintedanib, both or 'not applicable') will be added to this presentation. The date of last administration of the respective study drug as per the eCRF drug logs will be used for these presentations.

Details on treatment and study discontinuations will be listed.

Logistic regression analysis will be used to assess the influence of baseline covariates on the discontinuation rate in an exploratory manner. The following parameters will be used to explain early treatment discontinuation:

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- Age (years) at baseline,
- Sex (female = 0, male = 1),
- FVC % predicted at baseline,
- DLco % predicted at baseline.
- Region (US vs non-US)

Further parameters will be analyzed on an exploratory basis.

The regression coefficients for each covariate, together with the standard error and p-value will be presented. Further, odds ratios and 95% confidence intervals will also be given. In addition, a model including all covariates will be investigated in order to assess the consistency of the results.

4.7.2 Exposure of Study Medication

Summaries of dosing, treatment duration, dose interruptions or reductions will be provided for each treatment separately, as well as for combination treatment, if applicable.

The overall **treatment duration** (weeks), including and excluding dose interruptions, will be summarized descriptively. Also the days with dose interruptions will be given in this presentation.

The overall treatment duration **including** dose interruptions will be defined as follows:

- Overall duration of combination treatment including dose interruptions = (Maximum date of last dose of pirfenidone or nintedanib received – date of initiation of combination treatment) + 1.

The date of first administration of nintedanib or pirfenidone at or after the Baseline visit (Day 1) will be considered as initiation date of combination treatment (see Section 4.2.1).

- Overall treatment duration of pirfenidone/nintedanib including dose interruptions = (Date of last dose of treatment received – date of initiation of combination treatment) + 1.

The overall treatment duration **excluding** dose interruptions will be derived from the treatment administration panels, considering only days on treatment. When calculating duration of combination treatment, only days where both, pirfenidone and nintedanib, were interrupted will be excluded.

Dose interruptions will be calculated by summing all days where dose (pirfenidone or nintedanib) was interrupted. Combination treatment will only be considered to be interrupted if both, pirfenidone and nintedanib, were interrupted.

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The total number of patient days on treatment, including and excluding dose interruptions, and the total number of patient days with dose interruptions, will be presented.

The **total dose** (mg), the **last dose administered** (mg/d) and the **average daily dose** for each of the study treatments will be presented descriptively. The average daily dose will be calculated by summing up the number of capsules taken, divided by the number of days on combination treatment including treatment interruptions, as defined above. Further, frequencies for categories of average daily doses (e.g. <1602, 1602 – 2403, >2403 mg/d for pirfenidone, and <200, 200 – 300, >300 for nintedanib, as well as combinations of both) will be presented.

Dose modifications will be investigated for any modification, as well as for dose reductions and drug interruptions separately. Numbers and proportions of patients with at least one dose modification, dose reduction or drug interruption will be presented for each treatment separately. Numbers and proportions of patients with 1, 2, 3 or more dose modifications, dose reductions or drug interruptions will be given.

Numbers of dose modifications, reductions or interruptions will be presented together with numbers and frequencies of reasons for dose modification, reduction or interruption.

Dose modifications, defined as dose reductions or drug interruptions will be derived from the drug log information on dose strength and number of capsules taken.

4.7.3 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to a preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Agencies (MedDRA®). MedDRA version 19.0 or higher and related SMQ lists (see below) will be used for coding.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. For AEs of varying severity, the most severe grade as documented on the eCRF will be used in the summaries.

According to the protocol, after informed consent has been obtained but prior to initiation of combination treatment on Day 1, only SAEs caused by a protocol-mandated intervention should be reported.

After initiation of combination treatment at or after the 'Baseline (Day 1)' visit, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the Investigator should report any SAEs that are believed to be related to prior study drug treatment.

An AE that started or worsened on the day of initiation of combination treatment through 28 days after the last dose of combination treatment, i.e. the maximum date of nintedanib or pirfenidone treatment, will be considered treatment emergent.

The analysis of AEs will focus on treatment-emergent AEs (TEAE), but all AEs will be listed. This also includes AEs that might occur after initiation of investigational pirfenidone, but prior to Baseline (Day 1). For these AEs a separate listing will be provided.

Classifications of seriousness, severity and causality are described in the protocol sections 5.2 and 5.3.

An overview of patient safety profile will present the number and proportion of patients experiencing

- all and related treatment-emergent adverse events (TEAE),
- all and related serious treatment-emergent adverse events (serious TEAE),
- all and related severe TEAE,
- all and related TEAE of special interest (AESI) (MedDRA Preferred term for STIAMP - 'Suspected transmission of an infectious agent via product' or SMQ: 'Drug related hepatic disorders – severe events only (SMQ)'),
- all and related gastrointestinal (GI) (SOC: Gastrointestinal disorders),
- hepatic side effects (MedDRA AEGT: Esbriet - Potential Hy's Law AEGT' see [Appendix 4](#)),
- any (related) clinical significant vascular event (as angina pectoris, myocardial infarction, transient ischaemic attack (TIA), stroke) (Defined as any AE included in the MedDRA SMQs Ischemic heart disease, Central nervous system vascular disorders, Haemorrhages, Embolic and thrombotic events),
 - all and related ischemic heart disease (MedDRA SMQ: Ischemic heart disease)
 - all and related cerebrovascular event (MedDRA SMQ: Central nervous system vascular disorders),
 - all and related bleeding event (MedDRA SMQ: Haemorrhages),
 - all and related thromboembolic event (MedDRA SMQ: Embolic and thrombotic events),
- all and related major adverse cardiac event (MACE), (any CV death, non-fatal myocardial infarction, nonfatal stroke, acute coronary syndrome (ACS)/ unstable angina (UA))

- all and related photosensitivity or rash (MedDRA Preferred terms Nodular rash, Photodermatitis, Photosensitivity reaction, Pruritus, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic, Retching, Solar dermatitis, Solar urticarial, Somnolence, Sunburn, Erythema, Dry skin),
- all and related gastrointestinal (GI) perforation (MedDRA SMQ: Gastrointestinal perforation, ulceration, haemaorrhage or obstruction: sub-category Gastrointestinal perforation),
- all and related TEAEs leading to death,
- all and related TEAEs leading to treatment discontinuation,
- all and related elevated liver test results leading to treatment discontinuation,
- all and related TEAE resulting in hospitalization or prolonged hospitalization

together with the number of events in each of these event categories. For related TEAEs the relationship to pirfenidone, nintedanib or both investigational drugs will be assessed.

The number and percentage of patients with CTCAE grade 3-4 laboratory liver test results will also be included in this overview.

If relationship to study drug is missing, the event will be presented in the 'All TEAEs' column. A listing presenting all AEs with missing relationship will be added.

All categories of (all and related) TEAEs as presented in the overview will be summarized by system organ class (SOC) and preferred term (PT). Frequencies and percentages of patients experiencing (at least) one event in the respective category will be presented by decreasing frequencies. If patients have more than one AE within a SOC or PT they will be counted only once for the respective SOC or PT. Total numbers of TEAEs will be provided for each SOC and overall.

Similar summary presentations will be provided for patients with TEAEs leading to dose reduction and drug interruption and TEAEs leading to hospitalization.

Special interest in this study will be on assessment of treatment discontinuation. Therefore, TEAEs leading to treatment discontinuation will be summarized for TEAEs leading to discontinuation of any drug, and for TEAEs leading to discontinuation of both treatments, to pirfenidone alone or to nintedanib alone. These presentations will be provided for all AEs by most extreme NCI CTCAE grade. Additional presentations for the following categories of (all and related) TEAEs leading to treatment discontinuation will be presented:

- Seriousness (serious, non-serious).
- GI event,

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- Photosensitivity reaction/rash.

All TEAEs indicating “Action taken with pirfenidone/nintedanib due to SAE/AE” = “Drug withdrawn” in the eCRF will be included in these summaries.

Numbers and frequencies of patients with TEAEs by most extreme CTCAE Grade will be provided for any TEAEs and for each SOC and PT. In case the most extreme intensity is missing, it will be replaced by the initial intensity. If both most extreme and initial intensity are missing, AE will be included in the summaries for grade 3 to 5 AEs (i.e. in the total column) and a column for “missing” will be added.

All adverse event data will be listed by patient number and study day of onset. Separate listings will be provided for AEs leading to treatment discontinuation, serious adverse events (SAEs), adverse events of special interest (AESIs) and deaths.

Non-treatment-emergent AEs (i.e. AEs that start prior to first administration of combination treatment and do not worsen at/after combination treatment, or AEs that start more than 28 days after last dose of combination treatment) will be listed separately.

The following additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements:

- Both Serious Adverse Events and ‘Other’ Adverse Events will be summarized by MedDRA preferred term.

An adverse event is considered ‘Serious’ whether or not it is a TEAE. An adverse event is considered in the ‘Other’ category if it is both, a TEAE and is not serious.

For each Serious AE and ‘Other’ AE, and for each term the following are provided:

- The number of subjects at risk of an event;
- The number of subjects who experienced each event term;
- The number of events experienced.

4.7.4 Deaths

Numbers and frequencies of deaths and of deaths occurring within 28 days after the last dose of combination treatment will be presented. The primary cause of death and the information on whether an autopsy was performed will be given. All information on deaths will be collected from the eCRF panel on study discontinuation.

4.7.5 Pregnancies

Pregnancy test results will be listed, presenting the visit, date and study day of pregnancy test and test result.

4.7.6 Laboratory Data

All laboratory parameters will be assessed by a central laboratory, with the exception of the results of urine pregnancy tests, which will be determined locally and will be recorded in the eCRF.

All parameters will be graded according to NCI CTCAE (CTEP 2010), version 4.03, if applicable. Laboratory parameters that cannot be graded according to NCI CTCAE version 4.03 will be assessed with respect to normal range (low, normal, high).

The following laboratory parameters will be collected:

- Hematology: complete blood count with platelet count and automated differential, i.e. hemoglobin, hematocrit, platelet count, red blood cell count, RBC morphology, white blood cell count, absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils), MCH, MCHC, MCV,
- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, direct bilirubin*, total bilirubin, calcium, cholesterol, creatine kinase, creatinine, triglycerides, gamma-glutamyl transferase, glucose, lactic dehydrogenase*, magnesium, phosphorus*, potassium, sodium, urea nitrogen, serum uric acid*, and amylase, C-reactive protein (N HS)-PS* (CRP), Creatinine clearance rate*, calculated using the Cockcroft-Gault formula
- Serum pregnancy test*,
- Urine dipstick for pregnancy testing*(local).

* = for these parameters no grading as per NCI CTCAE, version 4.03 is possible.

Hemoglobin A1c (HbA1c) was planned to be collected according to the initial version of the Clinical Study Protocol (CSP), but was removed in Amendment 3 of the CSP as not specifically relevant for this patient population. HbA1c values are continuously reported by the central laboratory, but will not be presented in any summary presentations. HbA1c values will only be listed.

Clinical laboratory values will be presented separately for CTCAE-gradable and non-CTCAE gradable parameters by laboratory panel (hematology, serum chemistry).

Serum or urine pregnancy data will only be listed.

For laboratory analyses, visits will be assigned to visit windows as described in Section 4.9. This will also be valid for possible unscheduled visits. In case that multiple evaluable assessments occur within the same visit, the most extreme value will be used for analyses.

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The following summaries will be prepared:

For each laboratory parameter, descriptive statistics of laboratory values at each scheduled visit (derived as described above), and absolute changes from baseline to post-baseline will be presented.

Shift tables presenting changes from baseline to worst CTCAE grade, in the indicated direction, will be provided for CTCAE-gradable parameters. These changes will also be expressed as shifts of 1 to 4 grades, 3 to 4 grades and 4 grades. If no CTCAE grade is available for a specific laboratory variable, shift tables will present worst changes with respect to normal range category (low, normal, high).

For CTCAE-gradable parameters, numbers and percentages of patients with laboratory values of Grade 3 and 4 will be presented over time. Further, the total number of visits with Grade 3/4 elevations, as well as the number and percentages of patients with Grade 3/4 elevations for each parameter will be provided.

Liver abnormalities (total bilirubin, alkaline phosphatase, ALAT (SGPT), ASAT (SGOT)) of Grade 3 and 4 will be presented showing numbers and percentages of patients for each parameter separately, as well as in combination with at least one of the other parameters elevated post-baseline.

All laboratory data will be listed.

4.7.7 Vital Signs

Vital signs, body weight and body temperature assessments will be assigned to visit windows as per Section 4.9. Descriptive statistics will be used to summarize vital signs data at baseline, at each scheduled post-baseline visit, and for the absolute change from baseline to each scheduled post-baseline visit. The body mass index (BMI) will only be calculated for the BMI at baseline and presented with the demographic data.

4.7.8 ECG

QTcF values will be assigned to the following intervals: < 500 ms, 500–550 ms, and > 550 ms. Numbers and proportions of patients with their maximum QTcF interval category will be summarized at Baseline, Week 24 or early discontinuation, EOT and Follow-up. Absolute changes from the Baseline to each post-baseline visit in QTcF values will be categorized to ≤ 30 ms, 31–60 ms, and > 60 ms. Numbers and proportions of patients in each category will be presented for each post-baseline visit. Planned visits will be used for presentations.

At each visit, the ECG result is to be assessed as being normal, abnormal - not clinically significant, abnormal - clinically significant, or unable to evaluate. Changes from baseline to each post-baseline visit will be presented showing numbers and proportions of patients in each combination of categories.

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Descriptive statistics for heart rate and changes from baseline for each visit will be presented.

4.7.9 Previous and Concomitant Medication

Previous and concomitant medications are non-study medications. Different from the description in the Clinical Study Protocol, which describes that the non-study medications will be coded using the World Health Organization (WHO) Drug Dictionary, the previous and concomitant medication will be coded using the Genentech (GNE) drug dictionary. This is a proprietary Roche Dictionary which is used to code concomitant medications in the Trial Management System (TMS) coding tool. The Standardized Medication Name (CMDECOD), which is the medication generic or combination generic as defined by the Drug Thesaurus (proprietary Genentech/Roche dictionary), and the Medication Class (CMCLAS), which is the primary medication class as defined by the Drug Thesaurus, will be used for the analyses.

Therapies will be classified as previous or concomitant as follows:

- Previous: If the medication end date is prior to start of combination treatment,
- Concomitant: If medication is taken anytime between the start of combination treatment (Day 1) and 28 days after last dose of combination treatment.

The number and frequency of previous and concomitant medications will be given per Medication Class and Standardized Medication Name. If patients receive more than one drug within an Medication Class or Standardized Medication Name they will be counted only once for the respective Medication Class or Standardized Medication Name.

All medications will be listed. Medication that starts after the end of study treatment will be considered as post-treatment. This medication will be identified by a flag in the data listing.

4.8 MISSING DATA

In general, missing data will not be imputed. Exceptions will be made for the data related to adverse events and concomitant medications as described below.

For adverse events, missing start or end dates will only be imputed for determination of whether the adverse event is considered to be treatment-emergent or not by using the following principles:

Incomplete or missing onset dates will be imputed to the earliest date possible (using any reliable portions of the onset date that are available and the eCFR flag on whether the event/medication occurred prior to study drug administration) following the first dose of combination treatment. Note that the onset day is considered unreliable if the month or year portions of the date are missing, and the onset month is considered unreliable if the year portion of the date is missing. If, given the

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completed portions of the adverse event onset date and the known first combination treatment start date, the event could not have started after the first dose of combination treatment, then the adverse event will be considered non-treatment-emergent and the onset date will be left as an incomplete date.

If the stop date is completely missing, then the event will be assumed to be ongoing and a stop date will not be imputed.

For imputation and handling of missing intensity or relationship to study medication, please see Section 4.7.3.

All other missing or incomplete adverse event data will be left as missing.

For concomitant medications, missing start or end dates will only be imputed for determination of whether the concomitant medication is considered to be prior, on-treatment, post-treatment. The eCRF flag 'Select if (medication) taken prior to study' will be used in addition.

4.9 VISIT WINDOWS

Visit windows will be applied to vital signs and laboratory data and the derived visits will be used in the by-visit summarizations. If multiple observations fall within the same visit window, the observation with the most extreme value will be used in the analysis, if not stated otherwise.

For presentation of vital signs, laboratory tests, exposure and pulmonary function test results, an end of treatment (EOT) visit will be defined. This will include Week 24 data for patients who completed 24 weeks of combination treatment and data from the early discontinuation visit for patients who prematurely discontinued from combination treatment.

Table 5 Visit Windows for vital signs and laboratory data

Analysis Visit [AVISITN]	Target Day	Window (Study Days)
Baseline [0]	1	Last valid assessment prior to start of combination treatment
Week 1 [1] – lab data only	7	2 to 10
Week 2 [2]	14	11 to 17 (2 to 21 vital signs)
Week 3 [3] – lab data only	21	18 to 24
Week 4 [4]	28	25 to 42 (22 to 42 vital signs)
Week 8 [8]	56	43 to 70
Week 12 [12]	84	71 to 98
Week 16 [16]	112	99 to 126
Week 20 [20]	140	127 to 154
Week 24 [24]	168	155 to 174
Early discontinuation [25]	Not applicable	As occurred
End of treatment (EOT) [26]	Not applicable	As occurred

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Follow-up [28]	Combination treatment end date + 28	As occurred
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4.10 INTERIM ANALYSES

Throughout the study, an external independent Data Monitoring Board (iDMC) will review individual SAE reports and laboratory toxicities. In addition, the iDMC is scheduled to review safety data and advise on study conduct at least three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments, and when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments, when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments.

The iDMC may recommend that the Sponsor stop the study for safety concerns set forth in the iDMC Charter. Enrollment will continue during iDMC review of the 8-week data, unless the iDMC recommends that enrollment be paused or halted. Additional ad hoc meetings or data review can be requested by the iDMC or Sponsor, if warranted. Additional information is provided in the iDMC Charter.

No formal interim analyses for efficacy are planned.

4.11 BIOMARKER ANALYSES

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5. REFERENCES

Respiratory Medicine

[REDACTED]

Thorax

[REDACTED]

Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET®) IN COMBINATION WITH NINTEDANIB (OFEV®) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: MA29895

VERSION NUMBER: 3

EUDRACT NUMBER: 2015-003280-11

IND NUMBER: 67,284

TEST PRODUCT: Pirfenidone (Esbriet®) and nintedanib (Ofev®)

PHASE: IV

INDICATION: Idiopathic Pulmonary Fibrosis

SPONSOR: F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

The primary objective for this study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with Idiopathic Pulmonary Fibrosis (IPF).

Eligible patients must be receiving chronic treatment with pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days. In patients eligible for this study, nintedanib will be added as an additional treatment for IPF (combination treatment) for 24 weeks.

STUDY OBJECTIVES

Primary Safety Objective

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d

Secondary Safety Objectives

Secondary Safety Objectives are:

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 Visit
- Total number of patient days of combination treatment with pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments
- Frequency and timing of adverse events (AE) and Serious Adverse Events (SAEs)

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- Blood samples will be collected for the purposes of assessing the pharmacodynamics effect of nintedanib on pirfenidone or IPF-related biomarkers.

DESCRIPTION OF THE STUDY

This is a multicenter, international, open-label, single-arm safety and tolerability study of pirfenidone/nintedanib combination treatment in patients with IPF who have been on a stable dose of pirfenidone with demonstrated tolerability. In this study, a stable pirfenidone dose will be defined as 1602–2403 mg/d (801 mg twice daily [BID] or three times daily [TID]). Up to approximately 60 clinical centers in the US, Europe, and Canada are expected to enroll up to approximately 80 patients. Patients who are withdrawn from the study will not be replaced. The study design is presented in the figure below.

At the start of Screening, patients will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; also, the dose must be expected to remain within that range throughout the study. In addition, in the 28 days before the start of Screening, patients must not have experienced either a new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment for > 7 days for any reason.

After providing informed consent and discussing the risks and benefits of the study with the Investigator, patients will be required to taper and/or discontinue all prohibited medications (Section 4.4.2) at least 28 days before the start of Screening; this is the Washout Period. Patients will be instructed to continue their commercial pirfenidone during the Washout Period. If a prohibited medication must be tapered, tapering must start early enough that the patient has discontinued the medication 28 days before the start of Screening. After completing Washout, patients will enter Screening, which lasts up to 21 days; during Screening, patients will be evaluated for eligibility based on the inclusion and exclusion criteria. Patients not taking a **Pirfenidone and nintedanib —F. Hoffmann-La Roche Ltd**

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prohibited medication will forgo Washout and directly enter Screening. At screening, after eligibility criteria have been met, patients may be provided pirfenidone for the study and will be instructed on proper use. In this case, patients will be instructed to stop taking their commercial pirfenidone and start taking the study provided pirfenidone.

During Screening, patients on a stable dose of pirfenidone may return for the Baseline Visit (Study Day 1) as soon eligibility has been confirmed. At this visit, they will have nintedanib added to the ongoing pirfenidone treatment. Nintedanib dosing will start at 100 mg once daily (QD) and be titrated to 150 mg BID over 15 days, as tolerated, according to the schedule provided in protocol **Error! Reference source not found..**

The Sponsor will supply pirfenidone and nintedanib for use in the study; nintedanib will be supplied in 100 mg and 150 mg capsules to facilitate temporary dose reduction if required for the management of AEs.

Combination treatment will continue through Week 24, with monitoring by office visits and telephone contacts. Blood samples will be obtained from all patients for analysis of clinical laboratory values.

Patients will be encouraged to remain on stable doses of pirfenidone (1602–2403 mg/d) and nintedanib (200–300 mg/d) throughout the combination-treatment period, unless dosing is modified to manage an AE. Patients will return to the clinic for a final Follow-up Visit 28–35 days after the completion of combination treatment.

If one or both study treatments are prematurely discontinued or interrupted for ≥ 28 consecutive days, nintedanib treatment will end as will the patient's participation in the study; whether commercial pirfenidone treatment continues will be left to the judgment of the Investigator. The patient will then return to the clinic as soon as possible (≤ 7 days after the decision to discontinue nintedanib) for an Early Discontinuation Visit.

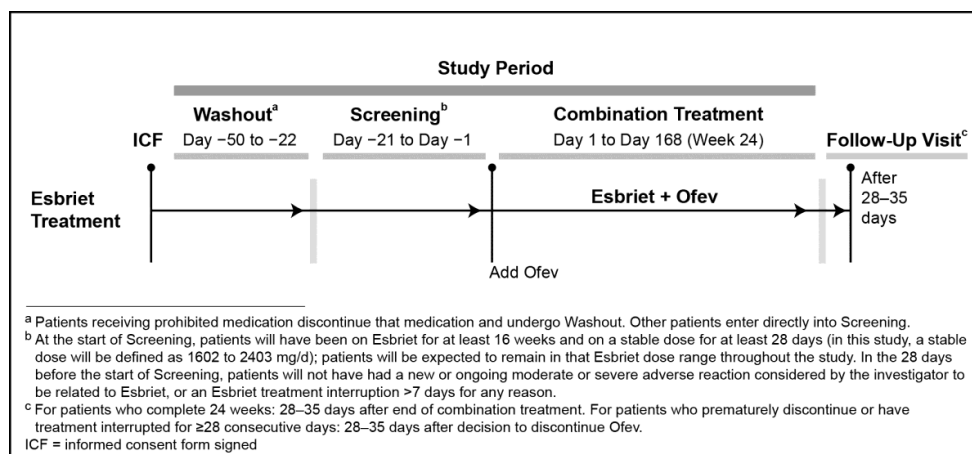
In addition, 28–35 days after the decision to discontinue nintedanib, the patient will return for a final Follow-up Visit.

A patient diary will be used to record AEs, daily dosing adherence for both pirfenidone and nintedanib, and concomitant medication use from the screening visit to the final Follow-up Visit. Also, patients will receive a wallet card that provides important information relevant to study participation.

On completion of study participation, patients may be prescribed appropriate IPF treatment at the discretion of the treating physician.

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct at least three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments, when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments and when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments. Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted.

Design of Study



NUMBER OF PATIENTS

Number of patients to be enrolled: approximately 80

TARGET POPULATION

Inclusion Criteria

Eligible patients for this study must meet the following criteria for study entry:

1. Written informed consent to participate in the study
2. Male or female, and age 40 through 80 years old at the start of Screening (inclusive).
3. At the start of Screening, on pirfenidone for at least 16 weeks and on a stable dose for at least 28 days (in this study, a stable dose will be defined as 1602–2403 mg/d); the dose must be expected to remain in that range throughout the study.
4. Documented diagnosis of IPF, per the Investigator per using the criteria of the 2011 American Thoracic Society / European Respiratory Society / Japanese Respiratory Society / Latin American Thoracic Association guidelines
5. The value from pulmonary function test results (from documented pulmonary function laboratory reports) measured at the screening visit as follows:
 - Percent predicted FVC ≥ 50%.
 - Percent predicted DLco (or carbon monoxide transfer capacity converted to DLco) ≥ 30%
6. Able to understand the importance of adherence to the study treatment regimen and the study protocol, and willing to follow all study requirements, including the concomitant medication restrictions, throughout the study.
7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at

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least one method with a failure rate of < 1% per year, during the treatment period and for at least 3 months after the final Follow-up Visit.

- A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 - Barrier methods must always be supplemented with the use of a spermicide.
8. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
- With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least for at least 4 months after the final Follow-up Visit. Men must refrain from donating sperm during this same period.
 - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least for at least 4 months after the final Follow-up Visit.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

2. Clinical evidence of any active infection which according to the judgment of the investigator may interfere with study conduct, measurement of pulmonary function, or impact the course of IPF.
3. In the 28 days before the start of Screening, any new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an pirfenidone treatment interruption > 7 days for any reason.
4. Any condition that is likely to result in death in the 12 months after the start of Screening.
5. Lung transplantation anticipated in the 12 months after the start of Screening.
6. Any planned significant surgical intervention from the start of Screening through the final Follow-up Visit. This does not include minor surgical procedures (e.g., excision of a localized basal cell carcinoma).
7. Known hypersensitivity to the active substance or any excipient of either pirfenidone or nintedanib.
8. Any condition that, in the Investigator's judgment, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone or nintedanib.
9. Mild (Child Pugh A), moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.

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10. Severe renal impairment (creatinine clearance < 30 mL/min by the Cockcroft-Gault calculation), including end-stage renal disease requiring dialysis.
11. History or risk of gastrointestinal (GI) tract perforation.
12. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) in the 6 months before the start of Screening, including but not limited to, the following:
 - Unstable angina pectoris or myocardial infarction.
 - Congestive heart failure expected to require hospitalization during the study.
 - Uncontrolled clinically significant arrhythmias.
13. Electrocardiogram (ECG) with a heart-rate-corrected QT interval (corrected using Fridericia's formula, QTcF) \geq 500 ms at Screening, or a family or personal history of long QT syndrome.
14. Bleeding risk: genetic predisposition to bleeding, a hemorrhagic event in the 12 months before the start of Screening, or abnormal laboratory coagulation parameters. Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g., vitamin K antagonists, dabigatran, heparin, hirudin), high-dose antiplatelet therapy, or other therapy that may substantially increase bleeding risk are excluded.

Note: the following are permitted: prophylactic low-dose heparin or heparin flush as needed for maintaining an indwelling intravenous device (e.g., enoxaparin 4000 IU SC per day), as well as prophylactic use of antiplatelet therapy (e.g., acetylsalicylic acid up to 325 mg/d, clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy).

15. Use of strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin) in the 28 days before the start of Screening.
16. Use of inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, erythromycin) or their inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's wort) in the 28 days before the start of Screening.
17. History of alcohol or substance abuse in the 2 years before the start of Screening.
18. Use of any tobacco product in the 12 weeks before the start of Screening, or an unwillingness to abstain from their use through the final Follow-up Visit.
19. In the judgment of the Investigator, not a suitable candidate for enrollment, or unlikely or unable to comply with the requirements of this study.
20. Use of any investigational therapy in a clinical study protocol in the 28 days before the start of Screening
21. Pregnancy or lactation.
22. Hypersensitivity to peanuts.
23. Hypersensitivity to soy.

END OF STUDY AND LENGTH OF STUDY

Length of Study

The expected study length is up to 21 months

End of Study

January 2018

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INVESTIGATIONAL MEDICINAL PRODUCTS

PIRFENIDONE

Pirfenidone is approved in a 267 mg capsule dosage form.

The recommended dose is 801 mg (i.e., three 267 mg capsules) TID, at the same times each day, taken with food (total dose, 2403 mg/d). At the beginning of the study, patients will be on a stable pirfenidone dose, as defined in the inclusion criteria.

NINTEDANIB

Nintedanib is approved in 100 mg and 150 mg capsule dosage forms.

The recommended dose is 150 mg BID, approximately 12 hours apart, at the same times each day, taken with food (total dose, 300 mg/d). Both 100 mg and 150 mg capsules will be supplied to facilitate temporary dose reduction if required to manage AEs.

STATISTICAL METHODS

PRIMARY ANALYSIS

The analysis population will be the Safety Population. It will consist of all patients who received at least one dose of nintedanib or pirfenidone at the Baseline Visit (Day 1).

AEs will be coded to a preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Because this is a safety and tolerability study that is not designed to assess efficacy, no formal statistical hypotheses for efficacy will be assessed. The efficacy analyses will be limited to descriptive statistics.

Data summaries will be provided for baseline characteristics; patient disposition; extent of exposure; the number and proportion of patients who complete 24 weeks on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d (with 95% confidence interval [CI]); the numbers and proportions of patients with a dose reduction or a dose interruption; the number and proportion of patients who discontinued combination treatment because of a AE (with 95% CI); the total number of days on combination treatment at an pirfenidone dose of 1602–2403 mg/d and a nintedanib dose of 200–300 mg/d; the total number of days from the start of combination treatment to discontinuation of one or both study treatments; the final prescribed doses of pirfenidone and nintedanib; and the reasons for premature discontinuation of combination treatment.

AEs and SAEs leading to discontinuation will be summarized by incidence, severity, seriousness, and relationship to treatment. Additional summaries will be provided for the numbers and proportions of patients with a Major Adverse Cardiac Event (MACE), a cerebrovascular event, a bleeding event, or a thromboembolic event; the numbers and proportions of patients discontinuing combination treatment for a liver test abnormality, a GI event, or a photosensitivity reaction/rash; the numbers and proportions of patients with an emergency department visit or hospitalization; and deaths.

Observed and change values for clinical laboratory and vital signs data will be summarized. Grade 3 and 4 laboratory abnormalities will be summarized by CTCAE grade, and shift tables by CTCAE grade will be provided.

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ECG data will be summarized, presenting the numbers and proportions of patients with a maximum QTcF interval < 500 ms, 500–550 ms, and > 550 ms; with a maximum change from the baseline QTcF interval of ≤ 30 ms, 31–60 ms, and > 60 ms; and with ECG changes considered by the Investigator to be clinically significant.

DETERMINATION OF SAMPLE SIZE

A sample size of approximately 80 patients was selected based on the AE discontinuation rates after one year observed in the randomized Phase 3 pirfenidone studies and the randomized Phase 2 and 3 nintedanib studies (pirfenidone 14.6%, nintedanib 21%; per the 2014 US labels). Given that for pirfenidone the discontinuation rate after 24 weeks was 6%-8% in studies PIPF-004 and PIPF-006 it is a reasonable assumption that the nintedanib discontinuation rate was around 10% - 11%. As in this study of combination treatment, it is possible that the addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients who discontinue because of an AE, given the overlap in the GI and hepatic effects of the two medications.

Assuming 85% of the patients complete 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2% to 92.8% using a 95% CI

Number of Patients who completed 24 weeks	Proportion of Patients who completed 24 weeks	Lower Bound of 95% CI	Upper Bound of 95% CI
76	95.0%	90.2%	99.8%
72	90.0%	84.4%	96.6%
68	85.0%	77.2%	92.8%
64	80.0%	71.2%	88.8%
60	75.0%	65.5%	84.5%

CI = confidence interval

Appendix 2 Schedule of Assessments

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Informed consent [d]	X	X																
Complete medical history [e]	X	X																
Directed medical history [f]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pirfenidone treatment history	X	X [g]	X [h]															
Document IPF diagnosis		X																

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d										
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140	168	Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20	24		
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Complete physical examination, including vital signs [i]		X	X		X		X		X		X		X		X	X	X	X
Body weight (kg)		X	X		X		X		X		X		X		X	X	X	X
Height (cm)		X																
12-lead ECG [j]		X	X													X	X	X
Spirometry (FVC), and DLco [k]		X	X								X					X		X
Spirometry (FEV1) [k]		X	X															
Hematology, serum chemistry [l], CRP		X	X [m]	X [m]	X [m]	X [m]	X		X		X		X		X	X	X	X

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If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Urine pregnancy test [n]							X [r]		X [r]		X [r]		X [r]		X [r]	X [r]		
Serum pregnancy test [n]		X	X													X	X	X
Biomarker sample collection [o]			X				X									X		X
Review patient diary			X		X		X		X		X		X		X	X	X	X
Review AEs [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review pirfenidone dosing adherence [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Review nintedanib dosing adherence [p]				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Review concomitant medications [p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review inclusion / exclusion criteria	X	X	X															
Obtain historical FEV1, FVC and DLco data [q]		X																
██████████			X													X		X
Dispense/collect patient diary		X															X	

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Dispense wallet card			X															
Dispense pirfenidone and explain dosing		X	X						X				X					
Dispense nintedanib and explain dosing			X						X				X					
Instruct to resume commercial pirfenidone and explain dosing																X		X
Collect unused pirfenidone and empty bottles			X						X				X			X		X

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Collect unused nintedanib and empty bottles									X				X			X		X

AE = adverse event; ASAP = as soon as possible; BL = Baseline; d = day; d/c = discontinue; DLco = carbon monoxide diffusing capacity; ECG = electrocardiogram; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; ; O = office visit; P = telephone contact; SAE = serious adverse event; W/O = Washout

- Patients taking prohibited medications enter Washout; if prohibited medication must be tapered, patient must be off that medication 28 days before start of Screening. Other patients directly enter Screening.
- For patients who complete 24 weeks of study treatment, visit should occur 28–35 days after completion of combination treatment. For patients who prematurely discontinue study treatment or have a treatment interruption of ≥ 28 consecutive days, visit should occur 28–35 days after decision to discontinue nintedanib.
- If a patient cannot return in ≤ 7 days, study center is to call patient to review medical history and to send laboratory kit and shipping supplies to patient so that blood samples can be drawn at another study center, commercial laboratory or by home nursing agency; Early Discontinuation Visit should then be scheduled as soon as possible.
- Written informed consent must be obtained before any study-mandated assessment or procedure, including tapering and/or discontinuing prohibited medication. If written informed consent was not obtained at Washout, it must be obtained at start of Screening.
- Including systems review, and review of concomitant medications, events in 28 days before start of Screening, and historical data (including prior high-resolution computed tomography scans, pulmonary function tests, and surgical lung biopsy data, if available). If complete medical

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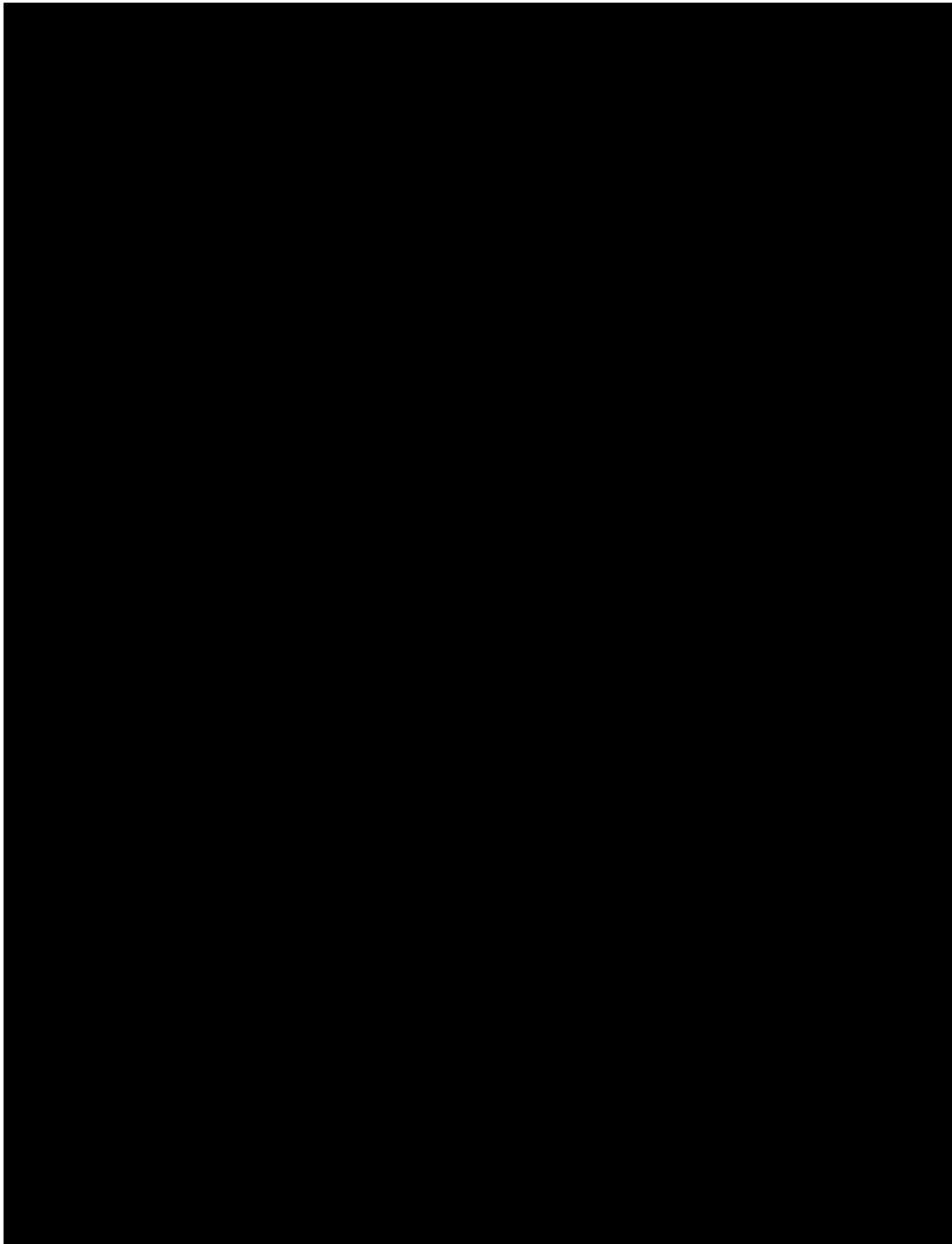
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history was obtained during Washout, during Screening the list of concomitant medications and medical history should be updated with changes since patient signed informed consent form.

- f. Includes AEs, concomitant medications, dosing adherence, hospitalizations, inquiry regarding compliance with protocol requirements for contraceptive use and avoiding tobacco products, and inquiry regarding whether patient is aware of being pregnant.
- g. At start of Screening, patient must have been on pirfenidone for ≥ 16 weeks and on stable dose (1602–2403 mg/d) for ≥ 28 days; dose must be expected to remain in that range throughout study. Treatment interruptions > 7 days are not permitted in the 28 days before start of Screening.
- h. At Baseline Visit, patient must have been at least approximately 80% adherent to pirfenidone dosing regimen since Screening Visit.
- i. Resting BP and HR, respiratory rate, body temperature.
- j. To be performed before laboratory assessments; use of short-acting bronchodilators is prohibited in preceding 6 hours, and use of long-acting bronchodilators is prohibited in preceding 24 hours.
- k. Spirometry (FVC, FEV1) is done before and approximately 30 minutes after short-acting bronchodilator administration; DLco testing is done before or at least 30 minutes after last puff of short-acting bronchodilator. Use of short-acting bronchodilators is prohibited in 6 hours before start of pre-bronchodilator spirometry test or a pre-bronchodilator DLco test. Use of long-acting bronchodilators is prohibited in 24 hours before start of tests.
- l. Including creatinine clearance rate, calculated using Cockcroft-Gault formula.
- m. If sample cannot be drawn at investigator's study center on Days 7 and Day 21, it can be drawn at another study center, commercial laboratory or by a home nursing agency. Patient is to be given laboratory kit and shipping supplies at Day 1 Visit (for Day 7 blood draw) and Day 14 Visit (for Day 21 blood draw).
- n. Women of childbearing potential.

[REDACTED]

- p. Done as part of patient diary review at office visits from Week 2 through Week 24 or Early Discontinuation Visit (for dosing adherence) or through final Follow-up Visit (for AEs and concomitant medications).
- q. If available, obtain percent predicted FVC, FEV1 and percent predicted DLco measurements from 12 months before start of Screening (from documented pulmonary function laboratory reports)
- r. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.



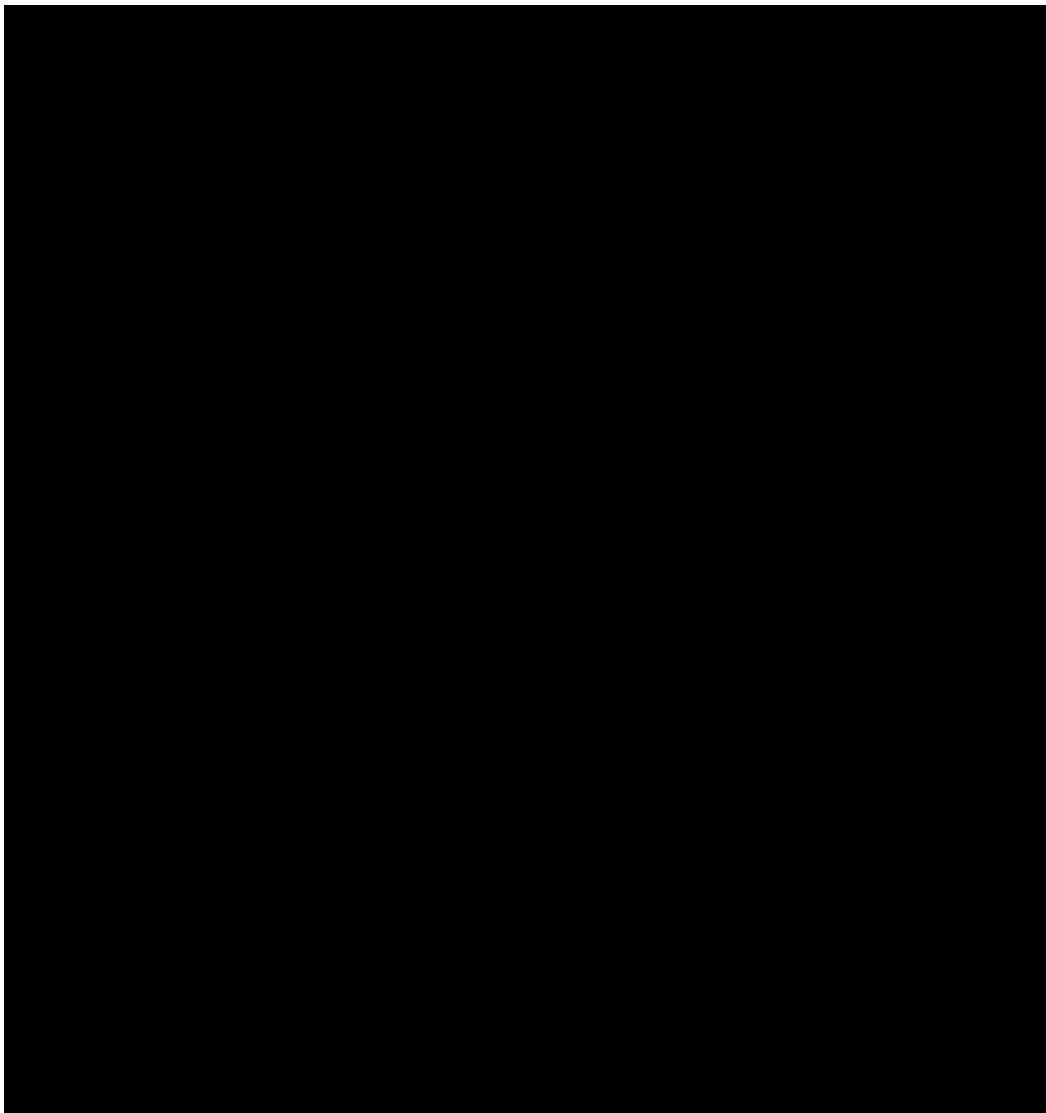
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[REDACTED]

[REDACTED]

[REDACTED]

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Appendix 4

MedDRA Browser Basket: Esbriet – Potential Hy’s Law AEGT

Project: Esbriet

Title: Esbriet - Potential Hy's Law AEGT

Description

AEGT to identify cases of potential Hy's Law: 49 Terms

Created Date 11-May-2016

By User [REDACTED]

Last Modified Date 03-Nov-2016

By User [REDACTED]

Last Reviewed Date 04-Nov-2016

By User [REDACTED]

Included MedDRA Preferred Terms

Liver injury
 Bilirubin conjugated increased
 Urine bilirubin increased
 Hepatobiliary disease
 Jaundice
 Transaminases abnormal
 Subacute hepatic failure
 Aspartate aminotransferase increased
 Cholestatic liver injury
 Bilirubin conjugated abnormal
 Mixed liver injury
 Hyperbilirubinaemia
 Drug-induced liver injury
 Hepatic enzyme abnormal
 Blood alkaline phosphatase abnormal
 Gamma-glutamyltransferase increased
 Hepatic failure
 Acute hepatic failure
 Blood alkaline phosphatase increased
 Hepatic enzyme increased
 Aspartate aminotransferase abnormal
 Biopsy liver abnormal
 Liver function test increased
 Liver function test abnormal
 Blood bilirubin increased
 Jaundice hepatocellular
 Hepatitis
 Alanine aminotransferase abnormal
 Hepatitis fulminant
 Hepatitis cholestatic
 Hepatitis acute
 Acute yellow liver atrophy
 Cholestasis
 Blood bilirubin unconjugated increased
 Prothrombin time ratio increased
 Chronic hepatitis
 Prothrombin time abnormal
 Hepatic infiltration eosinophilic
 Hepatic function abnormal
 Prothrombin time prolonged
 Hepatotoxicity
 Hepatitis toxic

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Transaminases increased
Blood bilirubin abnormal
Prothrombin time ratio abnormal
Liver disorder
Alanine aminotransferase increased
Hepatic necrosis
Gamma-glutamyltransferase abnormal
Hepatocellular injury

Excluded MedDRA Terms

Nested Baskets

End of Esbriet - Potential Hy's Law AEGT definition

MedDRA Version 19.1
Language English

STATISTICAL ANALYSIS PLAN

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET®) IN COMBINATION WITH NINTEDANIB (OFEV®) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: MA29895
STUDY DRUG: Pirfenidone (Esbriet®) and nintedanib (Ofev®)
VERSION NUMBER: Version 2.0 Final
IND NUMBER: 67,284
EUDRACT NUMBER: 2015-003280-11
SPONSOR: F. Hoffmann-La Roche Ltd
PLAN PREPARED BY: [REDACTED]
[REDACTED] (F. Hoffmann-La Roche Ltd)
DATE FINAL: 17 May 2017

SIGNATURE PAGE

Roche Biostatistician

[REDACTED]

[REDACTED]

Signature

17-May-2017

Date

Study Biostatistician

[REDACTED]

[REDACTED]

Signature

17-May-2017

Date

Senior International
Medical Director

[REDACTED]

[REDACTED]

Signature

17-May-2017

Date

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This SAP update was necessary to reflect ongoing discussions with respect to statistical analysis. Please see the following summary for details.

SAP section	Change	Rationale for Change
4.2.2 Baseline and Screening Observations	Combination Treatment Start Date is the date of first administration of nintedanib and pirfenidone on or after the Baseline visit.	Drug log contains pirfenidone entries during screening period
4.4.3 Demographic and Baseline Characteristics	Description of analyses of previous pirfenidone treatment added.	Not included in previous version.
4.7.1 Treatment Completion/Early Discontinuation	KM-plots presenting separate lines by treatment which is primary reason for treatment discontinuation are deleted.	Cannot be derived.
4.7.2 Exposure to Study Medication	Clarify dose modifications and treatment interruptions	Decision to only rely on the information as provided by the investigator on the drug-log CRF page.
4.7.2 Exposure to Study Medication	Treatments administered from combination treatment start date up to the 'Date subject completed or early discontinued from combination treatment period' as per eCRF 'Study drug completion/Early Discontinuation' will be considered for exposure analyses.	Drug log contains pirfenidone entries during screening period or after end of combination treatment.
4.7.3 Adverse Events	Updated definition of 'treatment-emergent: "An AE that started or worsened on the day of initiation of combination treatment through 28 days after the date subject completed or early discontinued from combination treatment period as per eCRF (eCRF form Study Drug Completion/Early discontinuation), will be considered treatment emergent."	Need to account for cases of pirfenidone IMP intake after the date of completion of combination treatment (up to Follow-up visit)
4.7.3 Adverse Events	Updated definition for major adverse cardiac event (MACE): Specific terms from SMQs Arrhythmia related investigations, signs and symptoms, Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias), Cardiac arrhythmias, Cardiac failure: Cardiac arrest, Cardiac death, Cardio-respiratory arrest, Sudden cardiac death, Sudden death, Ventricular asystole, Agonal rhythm, Sinus arrest, Pulseless electrical	Need to specify terms.

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	activity, Torsade de pointes, Ventricular fibrillation, Ventricular flutter, Ventricular tachycardia, Cardiac fibrillation, Cardiac flutter	
	Retching and Somnolence were deleted from the basket for photosensitivity reaction or rash	Terms also belong to other AE baskets
	'All and related elevated liver test results leading to treatment discontinuation' was deleted from the safety summary output.	The link between liver test results and respective AEs not established.
	'Number of events' was removed from the safety overview table.	Numbers of events are presented with the 'by SOC and PT' outputs
	Categories of TEAEs that are presented separately by SOC and PT specified in detail.	Description was not specific.
	Categories of TEAEs leading to treatment discontinuation specified in detail.	Description was not specific
	Analysis of timing of TEAEs added.	Not included in previous version.
4.7.6 Laboratory data	Paragraph added describing grading of laboratory values as per NCI CTCAE, when criteria for grading conflict with normal ranges as per central laboratory. Safety assessment of creatinine values changed from NCI-CTC grading to non-NCI-CTC grading.	Not included in previous version.
4.7.6 Laboratory data	Paragraph added on handling of values below the limit of quantification	Not included in previous version.
4.7.9 Previous and Concomitant medication	Note added that previously administered Pirfenidone will be presented separately.	Presented with previous/concomitant medications, previously.
4.8 Missing Data	Description added for imputation of missing start dates for previously administered Pirfenidone.	Presented with previous/concomitant medications, previously.
Appendix 5 Calculation of GAP Index Categories	Description of derivation of GAP Index added.	Not included in previous version.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
%FVC	Percent predicted forced vital capacity
ACS	Acute coronary syndrome
AE	Adverse event
AEGT	Standard Adverse Event Group Terms
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCE	Biostatistical Computing Environment
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
DLco	Carbon monoxide diffusing capacity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FVC	Forced vital capacity
GCP	Good clinical practice
GI	Gastrointestinal
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
██████	████████████████████ ████████████████████
LPLV	Last patient, last visit
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
ms	Millisecond
PDMS	Protocol Deviation Management System
PRO	Patient-reported outcome
QD	Once daily

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QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TID	Three times daily
TMS	Trial Management System
UA	Unstable angina
ULN	Upper limit of normal
WHO	World Health Organization

1. **BACKGROUND**

As described in the Clinical Study Protocol (CSP) (Section 1.3), the mechanism of action of pirfenidone in Idiopathic Pulmonary Fibrosis (IPF) has not been established (Esbriet® EU SmPc and US label 2014), while nintedanib is thought to act by inhibiting multiple RTKs and nRTKs (Esbriet® US label 2014). Because multiple co-activated pathways are involved in the pathogenesis of IPF, experts have suggested that targeted therapies may work better in combination (Wuyts et al. 2014). Furthermore, experience in other pulmonary diseases (e.g., asthma, chronic obstructive pulmonary disease, and pirfenidone and nintedanib — F. Hoffmann-La Roche Ltd 18 / Protocol MA29895, Version 2 pulmonary hypertension) has demonstrated the value of moving from monotherapy to combination therapy.

The positive benefit risk assessment of both drugs have been established in respective Phase II and Phase III programs which led to approval in the EU, the US, Japan and many other countries worldwide. Both drugs demonstrated that pulmonary function could be significantly improved in IPF patients, while the safety and tolerability profile was considered acceptable.

Considering the overlap in the gastrointestinal (GI) and hepatic Adverse Events (AEs) associated with these two drugs, it is worthwhile to characterize the safety and tolerability of nintedanib when added to pirfenidone as a combination treatment using the doses recommended in the respective pirfenidone and nintedanib labels.

This prospective study will evaluate the safety and tolerability of 24 weeks of nintedanib combination treatment in patients with IPF who are on a stable dose of pirfenidone with demonstrated tolerability. The study is not designed to evaluate the efficacy of combination treatment, nor is it designed to assess the safety and tolerability of adding pirfenidone to ongoing nintedanib treatment.

2. **STUDY DESIGN**

This is a multicenter, international, open-label, single-arm safety and tolerability study of pirfenidone/nintedanib combination treatment in patients with IPF who have been on a stable dose of pirfenidone with demonstrated tolerability. In this study, a stable pirfenidone dose will be defined as 1602–2403 mg/d (801 mg twice daily [BID] or three times daily [TID]). Up to approximately 60 clinical centers in the US, Europe, and Canada are expected to enroll up to approximately 80 patients. Patients who are withdrawn from the study will not be replaced.

At the start of Screening, patients will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; also, the dose must be expected to remain within that range throughout the study. In addition, in the 28 days before the start of Screening, patients must not have experienced either a new or
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ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment for > 7 days for any reason.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#). For additional details, please see the Protocol Amendment Version 3, 21 June 2016 (and its Appendices).

2.2 OUTCOME MEASURES

The primary objective for this study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with IPF. Consequently, the primary objectives of this study focus on safety and tolerability and not efficacy.

2.2.1 Primary Efficacy Outcome Measures

Not applicable.

2.2.2 Secondary Efficacy Outcome Measures

Not applicable.

2.2.3 Exploratory Efficacy Outcome Measures

[REDACTED]

• [REDACTED]

• [REDACTED]

[REDACTED]

• [REDACTED]

• [REDACTED]

• [REDACTED]

2.2.4 Patient-Reported Outcome Measures

• [REDACTED]

2.2.5 Safety Outcome Measures

The primary safety outcome measure is:

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d.

Secondary safety outcome measures are:

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 visit,
- Total number of patient days of combination treatment with pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d,
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments,
- Frequency and timing of Adverse Events (AEs) and Serious Adverse Events (SAEs).

2.3 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 80 patients was selected based on the AE discontinuation rates after one year observed in the randomized Phase 3 pirfenidone studies and the randomized Phase 2 and 3 nintedanib studies (pirfenidone 14.6% AE discontinuation [Esbriet® US label 2014]; nintedanib 21% AE discontinuation [Ofev® US label 2014]). Given that for pirfenidone the discontinuation rate after 24 weeks was 6%-8% in studies PIPF-004 and PIPF-006 it is a reasonable assumption that the nintedanib discontinuation rate was around 10%-11%. As in this study of combination treatment, it is possible that the addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients who discontinue because of an AE, given the overlap in the GI and hepatic effects of pirfenidone and nintedanib.

Assuming 85% of the patients complete 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2% - 92.8% using a 95% confidence interval (CI). [Table 1](#) shows the 95% CIs associated with projected completion rates of 75%, 80%, 85%, 90% or 95%, assuming an 80-patient sample size.

Table 1 Confidence Limits for Sample Size Determination

Number of Patients who completed 24 weeks	Proportion of Patients who completed 24 weeks	Lower Bound of 95% CI	Upper Bound of 95% CI
76	95.0%	90.2%	99.8%
72	90.0%	84.4%	96.6%
68	85.0%	77.2%	92.8%
64	80.0%	71.2%	88.8%
60	75.0%	65.5%	84.5%

CI = confidence interval

Patients who are withdrawn from the study will not be replaced.

2.4 ANALYSIS TIMING

The following analyses will be performed for this study:

Table 2 Analysis Timing

Analysis	Timing of Analysis
First iDMC	When the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments
Second iDMC	When approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments
Third iDMC	When approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments
Final	All patients completed 24 weeks of combination treatment or permanently discontinued study treatments, and have performed the Follow-up visit.

3. STUDY CONDUCT

The study conduct is described in Section 2 (Study design).

3.1 RANDOMIZATION ISSUES

This will be an open-label trial involving only one treatment arm.

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct at least three times during the study. For details on timing of the safety

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reviews please see Table 2 above. Efficacy data will only be provided if requested by the iDMC. For details please see Section 4.10.

4. STATISTICAL METHODS

This is a safety and tolerability study, not designed to assess efficacy, comprising only one treatment group. There are no formal statistical hypothesis tests to be performed, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons. Efficacy analyses will be limited to descriptive statistics.

Categorical data will be summarized using frequencies and percentages (including a category for missing, if appropriate).

Continuous endpoints will be summarized using descriptive statistics (mean, standard deviation, minimum, 25th and 75th quartiles, median, and maximum).

Where data will be presented over time, e.g. Baseline, Week 12, Week 24, and early discontinuation visit, an end of treatment visit (EOT) will be added. This will include Week 24 data for patients who completed 24 weeks of combination treatment and data from the early discontinuation visit for patients who prematurely discontinued from combination treatment.

Other analysis methods will be specified below, where applicable. All data recorded in the electronic Case Report Form (eCRF), as well as derived data that will be used in analyses, will be listed.

Analyses will be presented for the total population, together with geographic region, i.e. US and non-US patients. Results for US and non-US will be presented as additional columns or additional blocks within the outputs of the total population.

Percentages will be based on the total population or on the number of patients in the respective geographic region, if not otherwise specified.

4.1 ANALYSIS POPULATIONS

Only one analysis population, the Safety Population, has been defined as per CSP. No further analysis populations will be assessed.

4.1.1 Full Analysis Set

Not applicable.

4.1.2 Per Protocol Population

Not applicable.

4.1.3 Pharmacokinetic-Evaluable Population

Not applicable.

4.1.4 Safety Population

The Safety Population will consist of all patients who received at least one dose of nintedanib or pirfenidone on or after the Baseline visit.

Analyses will be produced for the Safety Population, if not otherwise specified.

4.2 TRIAL PERIODS, OBSERVATION AND ANALYSIS TIMES

In case that durations are to be calculated (e.g. treatment duration), these will be derived based on days and converted to months and years if needed, using 30.4375 and 365.25, respectively, as denominator if not otherwise specified.

4.2.1 Study Days

Study day is defined as the number of days since combination treatment start date, and is calculated as:

- For assessments on or after the day of start of combination treatment:
Study day = Assessment date – Date of start of combination treatment + 1.
- For assessments before the day of start of combination treatment:
Study day = Assessment date – Date of start of combination treatment

The day of the first dose of combination treatment is defined as Day 1.

4.2.2 Baseline and Screening Observations

Table 3 Definition of Baseline and Screening Observations

	Definition
Combination Treatment Start Date	Combination Treatment Start Date is the date of first administration of nintedanib and pirfenidone on or after the Baseline visit. Combination treatment start date will be used for all safety assessments and for the calculation of study days.
Baseline data	Baseline is defined as the last valid assessment prior to start of combination treatment. This may not be the same as the Baseline visit as per eCRF. Generally, it is assumed that measurements referring to the Baseline visit have been performed before study drug was given. This applies

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	for laboratory values, vital signs, ECG, pulmonary function tests and [REDACTED] Adverse events occurring on the combination treatment start date will not be considered baseline, but treatment-emergent.
Screening data	Screening measurements are all the measurements performed before the combination treatment start date and not respecting the “baseline” criteria.

4.2.3 On-treatment Assessments

On-treatment assessments will be the assessments performed on or after the combination treatment start date until the date of the Follow-up visit, which is planned to be performed 28 - 35 days after the date the subject discontinued from/completed combination treatment (see Section 4.2.5 for details).

However, treatment emergent adverse events are defined as adverse events with an onset date on or after the day of initiation of combination treatment up to 28 days after the date subject completed or early discontinued from combination treatment period as per eCRF (eCRF form Study Drug Completion/Early discontinuation).

4.2.4 Post-treatment Assessments

Post-treatment evaluations will be the evaluations performed later than the Follow-up visit. Post-treatment evaluations are not expected to occur. If there should be any, the data of assessments falling into this time-window will only be listed.

In addition adverse events, reporting more than 28 days after early discontinuation/completion of combination treatment will be considered as post-treatment.

4.2.5 Treatment Start and Stop Dates

As this is a combination treatment study, different assessments with respect to study treatment are possible: Pirfenidone alone, nintedanib alone, and combination treatment. To account for this, the following definitions will be made:

Table 4 Definition of Treatment/Combination Treatment Start and Stop Dates

	Treatment start date	Treatment end date
Combination treatment	Date of first administration of nintedanib and pirfenidone on or after the Baseline visit = Start date of combination treatment	Date subject completed or early discontinued from combination treatment period as per eCRF (eCRF form Study Drug Completion/Early discontinuation). = Date of completion or discontinuation from combination treatment
Pirfenidone	Start date of combination treatment	Date of last administration of pirfenidone as recorded in the study drug log for pirfenidone, until the date of completion or discontinuation from combination treatment.
Nintedanib	Start date of combination treatment	Date of last administration of nintedanib as recorded in the study drug log for nintedanib, until the date of completion or discontinuation from combination treatment.

4.2.6 Cut-off points

Clinical cut-off for final analysis is defined as the date of last patient last visit (LPLV). A description of data cleaning activities and a date for database lock will be provided by Data Management in a separate document.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

This is an open-label single arm phase IV study that will assess the combination treatment of pirfenidone and nintedanib. Consequently, no formal assessment of treatment group comparability can be conducted.

4.4 ANALYSIS OF STUDY CONDUCT

4.4.1 Patient Disposition

An overview on patient disposition, showing number and percentages of patients screened (as per IxRS), enrolled, treated and completed the study will be provided. For patients who have early discontinued study treatment or the study, frequencies of reasons for early discontinuation will be provided. Patients enrolled are all patients that have signed informed consent and are entered into the clinical database.

For further safety-related disposition analyses please see Section [4.7.1](#).

An overview on patients' enrolment by country and center will be provided.

4.4.2 Major Protocol Deviations

A Per-Protocol population will not be defined; however, major protocol deviations and eligibility violations will be summarized by frequency tables and all patients with protocol deviations will be listed.

Protocol deviations will be collected in PDMS, reviewed by the medical monitors, and will be provided in a SAS dataset via the Biometrics Computing Environment (BCE). All deviations provided in that spreadsheet will be considered as major protocol deviations.

4.4.3 Demographic and Baseline Characteristics

Baseline and disease characteristics such as demographics, medical history, tobacco and substance use history will be summarized by descriptive statistics or frequency tables.

Demographics

The following demographic characteristics will be summarized:

- Age (years): as entered in the eCRF at the screening visit
- Age categories: 18 – 64 years, 65 - 84 years, ≥85 years
- Gender (male/female)
- Race: White, American Indian or Alaska Native, Asian (Indian subcontinent, Other than Indian subcontinent), Black or African American, Native Hawaiian or Other Pacific Islander, Unknown. In case that more than one race will be ticked, a concatenated variable, containing all races will be presented (e.g. Asian/White).
- Ethnicity: Hispanic (Latino), Non-Hispanic (Non-Latino)
- Weight (kg) at baseline
- Height (cm) at baseline

- BMI (kg/m²) at baseline. BMI will be calculated as weight in kg / (height in cm)² × 10000

Data on female reproductive status will be presented descriptively; methods of contraception will only be listed.

Tobacco use history and substance use

The history of tobacco use will be summarized with the following characteristics:

- Tobacco use history (never, current, previous)
- Pack-years, smokers only

Numbers and percentages of patients for following characteristics will be presented to specify substance use:

- Current substance use (yes/no)
- Substance use (cannabinoids, amphetamines, opiates, caffeine, benzodiazepines, barbiturates, cocaine)

Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 19.0 or higher and will be summarized presenting numbers and frequencies by primary System Organ Class (SOC) and Preferred Term (PT). If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

Historical Pulmonary Function Test

The number and percentage of patients who performed the respective pulmonary function test (FVC, DLco, FEV₁, and FEV₁/FVC ratio (calculated)) in the past will be provided. This assessment was planned to be performed closest to 6 months before the Screening visit. These historical pulmonary function test parameters will be summarized using descriptive statistics. Both, absolute and percent predicted values will be presented. The time from assessment of the historical value to Screening will be summarized and defined as follows:

Time from assessment to Screening = (Date of Screening – Date of historical assessment) + 1.

Previous Pirfenidone Treatment

The number and percentage of patients with previous pirfenidone treatment and the duration of previous pirfenidone treatment will be summarized descriptively.

4.5 EFFICACY ANALYSIS

The efficacy measures of this study will only be analyzed in an exploratory manner. A replacement of missing values is not planned.

4.5.1 Primary Efficacy Endpoints

Not applicable.

4.5.2 Secondary Efficacy Endpoints

Not applicable.

4.5.3 Exploratory Efficacy Endpoints

[REDACTED]

■ [REDACTED]

■ [REDACTED]

[REDACTED]

■ [REDACTED]

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4.5.4 Analyses of Patient-Reported Outcomes

The [REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

4.5.5 Sensitivity Analyses

No sensitivity analyses are planned.

4.5.6 Subgroup Analyses

Subgroup analyses will be conducted for selected endpoints. The following subgroups will be based on:

[REDACTED]

- | [REDACTED]
- | [REDACTED]

[REDACTED]

- | [REDACTED]
- | [REDACTED]
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[REDACTED]

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

No pharmacokinetic or pharmacodynamic analyses are planned for this study.

4.7 SAFETY ANALYSES

The primary objective for this study is to investigate safety and tolerability of adding nintedanib to treatment with pirfenidone. Consequently, safety endpoints related to patient disposition, early discontinuations and adverse events are of main interest.

Analyses will be descriptive. No confirmatory analyses are defined and no comparative statistics will be generated.

Patients' safety will be assessed further through analyses of treatment exposure, laboratory tests, vital signs, and ECGs.

4.7.1 Treatment Completion/Early Discontinuation

A summary of the number and proportion of patients who complete 24 weeks of combination treatment (with 95% CI) will be presented. A patient is considered to have completed 24 weeks of combination treatment, if the eCRF question "Did the subject complete the treatment?" is ticked "Yes" (eCRF form "Study Drug Completion/Early Discontinuation"). It is expected that these patients have completed the Week 24 visit within expected time window (see Section 4.9).

The number and proportion of patients who complete 24 weeks of combination treatment (with 95% confidence interval (CI)) on pirfenidone at a dose of 1602-2403 mg/d and nintedanib at a dose of 200-300 mg/d will be presented. Average daily dose information as defined in Section 4.7.2 will be used to assess whether a patient completed 24 weeks on target dose.

The number and percentage of patients who discontinued combination treatment because of an adverse event (with 95% CI) will also be presented. This summary comprises patients who have reported "Adverse Event" as the main reason for treatment discontinuation.

The duration of combination treatment will be summarized descriptively. Duration of combination treatment will be defined as the time (days) from combination treatment start date (see Section 4.2.2) to the date subject completed or early discontinued from combination treatment period as per eCRF (Study Drug Completion/Early discontinuation form).

Kaplan-Meier (KM) plots for time to treatment discontinuation will be provided, based on the date subject completed or early discontinued from combination treatment period, as per eCRF (see Section 4.2.5).

Details on treatment and study discontinuations will be listed.

Logistic regression analysis will be used to assess the influence of baseline covariates on the discontinuation rate in an exploratory manner. The following parameters will be used to explain early treatment discontinuation:

- Age (years) at baseline,
- Sex (female = 0, male = 1),
- FVC % predicted at baseline,
- DLco % predicted at baseline.
- Region (US vs non-US)

Further parameters will be analyzed on an exploratory basis.

The regression coefficients for each covariate, together with the standard error and p-value will be presented. Further, odds ratios and 95% confidence intervals will also be given. In addition, a model including all covariates will be investigated in order to assess the consistency of the results.

4.7.2 Exposure of Study Medication

Summaries of dosing, treatment duration, dose interruptions or reductions will be provided for each treatment separately, as well as for combination treatment, if applicable.

Generally, treatments administered from combination treatment start date up to the 'Date subject completed or early discontinued from combination treatment period' as per eCRF 'Study drug completion/Early Discontinuation' will be considered for exposure analyses. All drug records before or after these dates reported in the drug-log will be disregarded. The below definitions are to be interpreted within this time window.

The overall **treatment duration** (weeks), including and excluding dose interruptions, will be summarized descriptively. Also the days with dose interruptions will be given in this presentation.

The overall treatment duration **including** dose interruptions will be defined as follows:

- Overall duration of combination treatment including dose interruptions = [(Date of discontinuation/completion of combination treatment – date of initiation of combination treatment) + 1]/7.

The date of first administration of nintedanib and pirfenidone on or after the Baseline visit will be considered as initiation date of combination treatment (see Section 4.2.1).

- Overall treatment duration of pirfenidone or nintedanib alone including dose interruptions = [(Date of last non-zero dose of treatment received until

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discontinuation/completion of combination treatment – date of initiation of combination treatment) + 1]/7.

The overall treatment duration **excluding** dose interruptions will be derived from the treatment administration panels, considering only days on treatment. When calculating duration of combination treatment, only days where both, pirfenidone and nintedanib, were interrupted will be excluded.

Dose interruptions will be calculated by summing all days where dose (pirfenidone or nintedanib) was interrupted. Combination treatment will only be considered to be interrupted if both, pirfenidone and nintedanib, were interrupted.

The total number of patient days on treatment, including and excluding dose interruptions, and the total number of patient days with dose interruptions, will be presented.

The **total dose** (mg), the **last dose administered** (mg/d) and the **average daily dose** for each of the study treatments will be presented descriptively. The average daily dose will be calculated by summing up the number of capsules taken during the combination treatment period, divided by the number of days on combination treatment including treatment interruptions, as defined above. Further, frequencies for categories of average daily doses (e.g. <1602, 1602 – 2403, >2403 mg/d for pirfenidone, and <200, 200 – 300, >300 for nintedanib, as well as combinations of both) will be presented.

Dose modifications and dose interruptions will be analyzed for any dose modification or dose interruption, as well as for dose modifications and drug interruptions separately. Numbers and proportions of patients with at least one dose modification or dose interruption will be presented for each treatment separately. Numbers and proportions of patients with 1, 2, 3 or more dose modifications or drug interruptions will be given.

Numbers and frequencies of reasons for dose modification or dose interruption will be presented.

Analyses will be based on the information on dose modifications or dose interruptions as provided by the investigator on the eCRF study drug administration page for data collected between the time of start of combination treatment and discontinuation/completion of combination treatment.

4.7.3 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to a preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Agencies (MedDRA®). MedDRA version 19.0 or higher and related SMQ lists (see below) will be used for coding.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. For AEs of varying severity, the most severe grade as documented on the eCRF will be used in the summaries.

According to the protocol, after informed consent has been obtained but prior to initiation of combination treatment on Day 1, only SAEs caused by a protocol-mandated intervention should be reported.

After initiation of combination treatment at or after the Baseline visit, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the Investigator should report any SAEs that are believed to be related to prior study drug treatment.

An AE that started or worsened on the day of initiation of combination treatment through 28 days after the date a subject completed or early discontinued from combination treatment period' as per eCRF 'Study drug completion/Early Discontinuation' will be considered treatment emergent.

The analysis of AEs will focus on treatment-emergent AEs (TEAE), but all AEs will be listed. For AEs that might occur after initiation of investigational pirfenidone up to start of combination treatment or more than 28 days after the end of combination treatment a separate listing will be provided.

Classifications of seriousness, severity and causality are described in the protocol sections 5.2 and 5.3.

An overview of patient safety profile will present the number and proportion of patients experiencing

- all and related treatment-emergent adverse events (TEAE),
- all and related serious treatment-emergent adverse events (serious TEAE),
- all and related severe TEAE,
- all and related TEAE of special interest (AESI) (MedDRA Preferred term for STIAMP - 'Suspected transmission of an infectious agent via product' or SMQ: 'Drug related hepatic disorders – severe events only (SMQ)'),
- all and related gastrointestinal (GI) disorders (SOC: Gastrointestinal disorders),

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- hepatic side effects (MedDRA AEGT: Esbriet - Potential Hy's Law AEGT' see [Appendix 4](#)),
 - all and related clinical significant vascular event (as angina pectoris, myocardial infarction, transient ischaemic attack (TIA), stroke) (Defined as any AE included in the MedDRA SMQs Ischemic heart disease, Central nervous system vascular disorders, Haemorrhages, Embolic and thrombotic events),
 - all and related ischemic heart disease (MedDRA SMQ: Ischemic heart disease)
 - all and related cerebrovascular event (MedDRA SMQ: Central nervous system vascular disorders),
 - all and related bleeding event (MedDRA SMQ: Haemorrhages),
 - all and related thromboembolic event (MedDRA SMQ: Embolic and thrombotic events),
 - all and related major adverse cardiac event (MACE), (Specific terms from SMQs Arrhythmia related investigations, Signs and symptoms, Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias), Cardiac arrhythmias, Cardiac failure:
Cardiac arrest, Cardiac death, Cardio-respiratory arrest, Sudden cardiac death, Sudden death, Ventricular asystole, Agonal rhythm, Sinus arrest, Pulseless electrical activity, Torsade de pointes, Ventricular fibrillation, Ventricular flutter, Ventricular tachycardia, Cardiac fibrillation, Cardiac flutter.)
 - all and related photosensitivity or rash (MedDRA Preferred terms Nodular rash, Photodermatosis, Photosensitivity reaction, Pruritus, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic, Solar dermatitis, Solar urticarial, Sunburn, Erythema, Dry skin),
 - all and related gastrointestinal (GI) perforation (MedDRA SMQ: Gastrointestinal perforation, ulceration, haemorrhage or obstruction: sub-category Gastrointestinal perforation),
 - all and related TEAEs leading to death,
 - all and related TEAEs leading to treatment discontinuation,
 - all and related TEAE resulting in hospitalization or prolonged hospitalization.
- . For related TEAEs the relationship to pirfenidone, nintedanib or both investigational drugs will be assessed.

The number and percentage of patients with CTCAE grade 3-4 laboratory liver test results will also be included in this overview.

If relationship to study drug is missing, the event will be presented in the 'All TEAEs' column. A listing presenting all AEs with missing relationship will be added.

The following categories of TEAEs as presented in the overview will be summarized by system organ class (SOC) and preferred term (PT):

- all and related treatment-emergent adverse events (TEAE),
- all serious treatment-emergent adverse events (serious TEAE),
- all non-serious treatment-emergent adverse events (non-serious TEAE),
- all severe (Grade 3 – 5) treatment-emergent adverse events (severe TEAE),
- all TEAEs resulting in hospitalization or prolonged hospitalization

Similar summary presentations will be provided for patients with TEAEs leading to dose modification.

Frequencies and percentages of patients experiencing (at least) one event in the respective category will be presented by decreasing frequencies. If patients have more than one AE within a SOC or PT they will be counted only once for the respective SOC or PT. Total numbers of TEAEs will be provided for each SOC and overall.

Special interest in this study will be on assessment of treatment discontinuation. Therefore, TEAEs leading to treatment discontinuation will be summarized for TEAEs leading to discontinuation of any drug, and for TEAEs leading to discontinuation of both treatments, to pirfenidone alone or to nintedanib alone. Additional presentations for the following categories of TEAEs leading to treatment discontinuation will be presented:

- Serious TEAEs).
- GI event,
- Photosensitivity reaction or rash
- TEAEs by intensity.

All TEAEs indicating "Action taken with pirfenidone/nintedanib due to SAE/AE" = "Drug withdrawn" in the eCRF will be included in these summaries.

Numbers and frequencies of patients with TEAEs by most extreme CTCAE Grade will be provided for any TEAEs and for each SOC and PT. In case the most extreme intensity is missing, it will be replaced by the initial intensity. If both most extreme and initial intensity are missing, AE will be included in the summaries for grade 3 to 5 AEs (i.e. in the total column) and a column for "missing" will be added.

The timing of TEAEs will be assessed by presenting numbers of patients with TEAEs occurring in the first 28 days (Days 0 – 28), from Day 29 to Day 84 (Weeks >4 - 12), and for the total study period by SOC and PT.

Further, Kaplan-Meier curves for time to onset of first adverse event of the most relevant related TEAEs will be provided. These will include the following PTs or baskets (as defined above): Nausea, Diarrhoea, GI disorder basket, Weight decreased, Fatigue, Decreased appetite, photosensitivity or rash basket.

All adverse event data will be listed by patient number and study day of onset. Separate listings will be provided for TEAEs leading to treatment discontinuation, serious TEAEs (STEAEs), adverse events of special interest (AESIs), TEAEs leading to dose modification, TEAEs leading to hospitalization, severe (Grade 3 – 5) TEAEs and deaths.

Non-treatment-emergent AEs (i.e. AEs that start prior to first administration of combination treatment and do not worsen at/after combination treatment, or AEs that start more than 28 days after last dose of combination treatment) will be listed separately.

The following additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements:

- Both Serious Adverse Events and 'Other' Adverse Events will be summarized by MedDRA preferred term.

An adverse event is considered 'Serious' whether or not it is a TEAE. An adverse event is considered in the 'Other' category if it is both, a TEAE and is not serious.

For each Serious AE and 'Other' AE, and for each term the following are provided:

- The number of subjects at risk of an event;
- The number of subjects who experienced each event term;
- The number of events experienced.

4.7.4 Deaths

Numbers and frequencies of deaths and of deaths occurring within 28 days after the last dose of combination treatment will be presented. The primary cause of death and the information on whether an autopsy was performed will be given. All information on deaths will be collected from the eCRF panel on study discontinuation.

4.7.5 Pregnancies

Pregnancy test results will be listed, presenting the visit, date and study day of pregnancy test and test result.

4.7.6 Laboratory Data

All laboratory parameters will be assessed by a central laboratory, with the exception of the results of urine pregnancy tests, which will be determined locally and will be recorded in the eCRF.

All parameters will be graded according to NCI CTCAE (CTEP 2010), version 4.03, if applicable. Laboratory parameters that cannot be graded according to NCI CTCAE version 4.03 will be assessed with respect to normal range (low, normal, high).

For laboratory parameters and specific age ranges, the upper limit of normal provided by the central laboratory might be higher than the criterion for Grade 1 in NCI CTCAE. In such cases, the definitions provided in the NCI CTCAE, version 4.03 will be followed. This means that a shift of a laboratory value above the ULN that corresponds to a grade 2 abnormality or higher will be reported as such. Grade 1 abnormalities will not be reported for such situations.

Laboratory values that are reported to be below the limit of quantification (e.g. '<2') will be considered as to be 'LOW' for presentation in shift tables, if the value (e.g. '2') equals the lower limit of normal. The value as such (e.g. '2') will be used for descriptive statistics.

The following laboratory parameters will be collected:

- Hematology: complete blood count with platelet count and automated differential, i.e. hemoglobin, hematocrit, platelet count, red blood cell count, RBC morphology, white blood cell count, absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils), MCH, MCHC, MCV,
- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, direct bilirubin*, total bilirubin, calcium, cholesterol, creatine kinase, creatinine*, triglycerides, gamma-glutamyl transferase, glucose, lactic dehydrogenase*, magnesium, phosphorus*, potassium, sodium, urea nitrogen, serum uric acid*, and amylase, C-reactive protein (N HS)-PS* (CRP), Creatinine clearance rate*, calculated using the Cockcroft-Gault formula
- Serum pregnancy test*,
- Urine dipstick for pregnancy testing*(local).

* = for these parameters no grading as per NCI CTCAE, version 4.03 is applicable.

Hemoglobin A1c (HbA1c) was planned to be collected according to the initial version of the Clinical Study Protocol (CSP), but was removed in Amendment 3 of the CSP as not specifically relevant for this patient population. HbA1c values are continuously reported by the central laboratory, but will not be presented in any summary presentations. HbA1c values will only be listed.

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Clinical laboratory values will be presented separately for CTCAE-gradable and non-CTCAE gradable parameters by laboratory panel (hematology, serum chemistry).

Serum or urine pregnancy data will only be listed.

For laboratory analyses, visits will be assigned to visit windows as described in Section 4.9. This will also be valid for possible unscheduled visits. In case that multiple evaluable assessments occur within the same visit, the most extreme value will be used for analyses.

The following summaries will be prepared:

For each laboratory parameter, descriptive statistics of laboratory values at each scheduled visit (derived as described above), and absolute changes from baseline to post-baseline will be presented.

Shift tables presenting changes from baseline to worst CTCAE grade, in the indicated direction, will be provided for CTCAE-gradable parameters. These changes will also be expressed as shifts of 1 to 4 grades, 3 to 4 grades and 4 grades. If no CTCAE grade is available for a specific laboratory variable, shift tables will present worst changes with respect to normal range category (low, normal, high).

For CTCAE-gradable parameters, numbers and percentages of patients with laboratory values of Grade 3 and 4 will be presented over time. Further, the total number of visits with Grade 3/4 elevations, as well as the number and percentages of patients with Grade 3/4 elevations for each parameter will be provided.

Liver abnormalities (total bilirubin, alkaline phosphatase, ALAT (SGPT), ASAT (SGOT)) of Grade 3 and 4 will be presented showing numbers and percentages of patients for each parameter separately, as well as in combination with at least one of the other parameters elevated post-baseline. Line graphs will also be provided.

All laboratory data will be listed.

4.7.7 Vital Signs

Vital signs, body weight and body temperature assessments will be assigned to visit windows as per Section 4.9. Descriptive statistics will be used to summarize vital signs data at baseline, at each scheduled post-baseline visit, and for the absolute change from baseline to each scheduled post-baseline visit. Line graphs for systolic and diastolic blood pressure will be provided. The body mass index (BMI) will only be calculated for the BMI at baseline and presented with the demographic data.

4.7.8 ECG

QTcF values will be assigned to the following intervals: < 500 ms, 500–550 ms, and > 550 ms. Numbers and proportions of patients with their maximum QTcF interval category will be summarized at Baseline, Week 24 or early discontinuation, EOT and Follow-up. Absolute changes from the Baseline to each post-baseline visit in QTcF values will be categorized to ≤ 30 ms, 31–60 ms, and > 60 ms. Numbers and proportions of patients in each category will be presented for each post-baseline visit. Planned visits will be used for presentations.

At each visit, the ECG result is to be assessed as being normal, abnormal - not clinically significant, abnormal - clinically significant, or unable to evaluate. Changes from baseline to each post-baseline visit will be presented showing numbers and proportions of patients in each combination of categories.

Descriptive statistics for heart rate and changes from baseline for each visit will be presented.

4.7.9 Previous and Concomitant Medication

Previous and concomitant medications are non-study medications. Different from the description in the Clinical Study Protocol, which describes that the non-study medications will be coded using the World Health Organization (WHO) Drug Dictionary, the previous and concomitant medication will be coded using the Genentech (GNE) drug dictionary. This is a proprietary Roche Dictionary which is used to code concomitant medications in the Trial Management System (TMS) coding tool. The Standardized Medication Name (CMDECOD), which is the medication generic or combination generic as defined by the Drug Thesaurus (proprietary Genentech/Roche dictionary), and the Medication Class (CMCLAS), which is the primary medication class as defined by the Drug Thesaurus, will be used for the analyses.

Therapies will be classified as previous or concomitant as follows:

- Previous: If the medication end date is prior to start of combination treatment,
- Concomitant: If medication is taken anytime between the start of combination treatment and the Follow-up visit.

The number and frequency of previous and concomitant medications will be given per Medication Class and Standardized Medication Name. If patients receive more than one drug within an Medication Class or Standardized Medication Name they will be counted only once for the respective Medication Class or Standardized Medication Name.

Previously administered pirfenidone will be presented separately (see Section 4.4.3). For imputation of missing or incomplete pirfenidone start or end dates please see Section 4.8.

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All medications will be listed. Medication that starts after the Follow-up visit will be considered as post-treatment. This medication will be identified by a flag in the data listing.

4.8 MISSING DATA

In general, missing data will not be imputed. Exceptions will be made for the data related to adverse events and concomitant medications as described below.

For adverse events, missing start or end dates will only be imputed for determination of whether the adverse event is considered to be treatment-emergent or not by using the following principles:

Incomplete or missing onset dates will be imputed to the earliest date possible (using any reliable portions of the onset date that are available and the eCFR flag on whether the event/medication occurred prior to study drug administration) following the first dose of combination treatment. Note that the onset day is considered unreliable if the month or year portions of the date are missing, and the onset month is considered unreliable if the year portion of the date is missing. If, given the completed portions of the adverse event onset date and the known first combination treatment start date, the event could not have started after the first dose of combination treatment, then the adverse event will be considered non-treatment-emergent and the onset date will be left as an incomplete date.

If the stop date is completely missing, then the event will be assumed to be ongoing and a stop date will not be imputed.

For imputation and handling of missing intensity or relationship to study medication, please see Section [4.7.3](#).

All other missing or incomplete adverse event data will be left as missing.

For concomitant medications, missing start or end dates will only be imputed for determination of whether the concomitant medication is considered to be prior, on-treatment, post-treatment. The eCRF flag 'Select if (medication) taken prior to study' will be used in addition.

For previous pirfenidone treatment, recorded in the concomitant medication eCRF, missing month and day for the start year will be imputed with July 1st of the respective year. If the day is unknown, the 15th of the respective month will be imputed. Imputations will only be used for calculation of duration of previous pirfenidone treatment. An imputation will only be applied if not artificially leading to a previous treatment period of more than 16 weeks.

4.9 VISIT WINDOWS

Visit windows will be applied to vital signs and laboratory data and the derived visits will be used in the by-visit summarizations. If multiple observations fall within the same visit window, the observation with the most extreme value will be used in the analysis, if not stated otherwise.

For presentation of vital signs, laboratory tests, exposure and pulmonary function test results, an end of treatment (EOT) visit will be defined. This will include Week 24 data for patients who completed 24 weeks of combination treatment and data from the early discontinuation visit for patients who prematurely discontinued from combination treatment.

Table 5 Visit Windows for vital signs and laboratory data

Analysis Visit [AVISITN]	Target Day	Window (Study Days)
Baseline [0]	1	Last valid assessment prior to start of combination treatment
Week 1 [1] – lab data only	7	2 to 10
Week 2 [2]	14	11 to 17 (2 to 21 vital signs)
Week 3 [3] – lab data only	21	18 to 24
Week 4 [4]	28	25 to 42 (22 to 42 vital signs)
Week 8 [8]	56	43 to 70
Week 12 [12]	84	71 to 98
Week 16 [16]	112	99 to 126
Week 20 [20]	140	127 to 154
Week 24 [24]	168	155 to 174
Early discontinuation [25]	Not applicable	As occurred
End of treatment (EOT) [26]	Not applicable	As occurred
Follow-up [28]	Combination treatment end date + 28	As occurred

4.10 INTERIM ANALYSES

Throughout the study, an external independent Data Monitoring Board (iDMC) will review individual SAE reports and laboratory toxicities. In addition, the iDMC is scheduled to review safety data and advise on study conduct at least three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments, and when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments, when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments.

The iDMC may recommend that the Sponsor stop the study for safety concerns set forth in the iDMC Charter. Enrollment will continue during iDMC review of the 8-week data, unless the iDMC recommends that enrollment be paused or halted. Additional ad hoc

meetings or data review can be requested by the iDMC or Sponsor, if warranted.
Additional information is provided in the iDMC Charter.

No formal interim analyses for efficacy are planned.

4.11 BIOMARKER ANALYSES

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5. REFERENCES

Respiratory Medicine

[REDACTED]

Thorax

[REDACTED]

European Respiratory Review

Kolb M, Collard HR. Staging of idiopathic pulmonary fibrosis: past, present and future.
Eur Resp Rev 2014, 23: 220-224.

Appendix 1

Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET®) IN COMBINATION WITH NINTEDANIB (OFEV®) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: MA29895

VERSION NUMBER: 3

EUDRACT NUMBER: 2015-003280-11

IND NUMBER: 67,284

TEST PRODUCT: Pirfenidone (Esbriet®) and nintedanib (Ofev®)

PHASE: IV

INDICATION: Idiopathic Pulmonary Fibrosis

SPONSOR: F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

The primary objective for this study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with Idiopathic Pulmonary Fibrosis (IPF).

Eligible patients must be receiving chronic treatment with pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days. In patients eligible for this study, nintedanib will be added as an additional treatment for IPF (combination treatment) for 24 weeks.

STUDY OBJECTIVES

Primary Safety Objective

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d

Secondary Safety Objectives

Secondary Safety Objectives are:

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 Visit
- Total number of patient days of combination treatment with pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments
- Frequency and timing of adverse events (AE) and Serious Adverse Events (SAEs)

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[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Blood samples will be collected for the purposes of assessing the pharmacodynamics effect of nintedanib on pirfenidone or IPF-related biomarkers.

DESCRIPTION OF THE STUDY

At the start of Screening, patients will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; also, the dose must be expected to remain within that range throughout the study. In addition, in the 28 days before the start of Screening, patients must not have experienced either a new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment for > 7 days for any reason.

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prohibited medication will forgo Washout and directly enter Screening. At screening, after eligibility criteria have been met, patients may be provided pirfenidone for the study and will be instructed on proper use. In this case, patients will be instructed to stop taking their commercial pirfenidone and start taking the study provided pirfenidone.

During Screening, patients on a stable dose of pirfenidone may return for the Baseline Visit (Study Day 1) as soon eligibility has been confirmed. At this visit, they will have nintedanib added to the ongoing pirfenidone treatment. Nintedanib dosing will start at 100 mg once daily (QD) and be titrated to 150 mg BID over 15 days, as tolerated, according to the schedule provided in protocol **Error! Reference source not found..**

The Sponsor will supply pirfenidone and nintedanib for use in the study; nintedanib will be supplied in 100 mg and 150 mg capsules to facilitate temporary dose reduction if required for the management of AEs.

Combination treatment will continue through Week 24, with monitoring by office visits and telephone contacts. Blood samples will be obtained from all patients for analysis of clinical laboratory values.

Patients will be encouraged to remain on stable doses of pirfenidone (1602–2403 mg/d) and nintedanib (200–300 mg/d) throughout the combination-treatment period, unless dosing is modified to manage an AE. Patients will return to the clinic for a final Follow-up Visit 28–35 days after the completion of combination treatment.

If one or both study treatments are prematurely discontinued or interrupted for ≥ 28 consecutive days, nintedanib treatment will end as will the patient's participation in the study; whether commercial pirfenidone treatment continues will be left to the judgment of the Investigator. The patient will then return to the clinic as soon as possible (≤ 7 days after the decision to discontinue nintedanib) for an Early Discontinuation Visit.

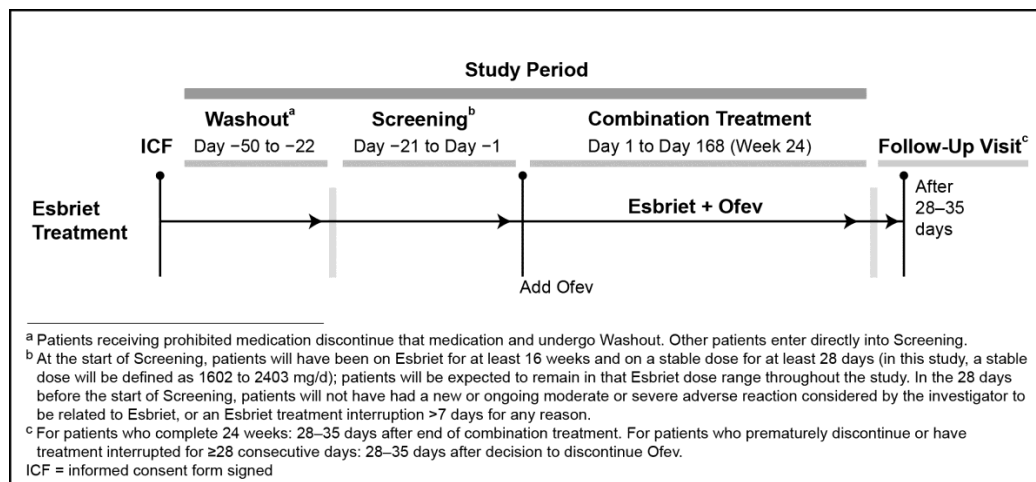
In addition, 28–35 days after the decision to discontinue nintedanib, the patient will return for a final Follow-up Visit.

A patient diary will be used to record AEs, daily dosing adherence for both pirfenidone and nintedanib, and concomitant medication use from the screening visit to the final Follow-up Visit. Also, patients will receive a wallet card that provides important information relevant to study participation.

On completion of study participation, patients may be prescribed appropriate IPF treatment at the discretion of the treating physician.

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct at least three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments, when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments and when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments. Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted.

Design of Study



NUMBER OF PATIENTS

Number of patients to be enrolled: approximately 80

TARGET POPULATION

Inclusion Criteria

Eligible patients for this study must meet the following criteria for study entry:

1. Written informed consent to participate in the study
2. Male or female, and age 40 through 80 years old at the start of Screening (inclusive).
3. At the start of Screening, on pirfenidone for at least 16 weeks and on a stable dose for at least 28 days (in this study, a stable dose will be defined as 1602-2403 mg/d); the dose must be expected to remain in that range throughout the study.
4. Documented diagnosis of IPF, per the Investigator per using the criteria of the 2011 American Thoracic Society / European Respiratory Society / Japanese Respiratory Society / Latin American Thoracic Association guidelines
5. The value from pulmonary function test results (from documented pulmonary function laboratory reports) measured at the screening visit as follows:
 - Percent predicted FVC ≥ 50%.
 - Percent predicted DLco (or carbon monoxide transfer capacity converted to DLco) ≥ 30%
6. Able to understand the importance of adherence to the study treatment regimen and the study protocol, and willing to follow all study requirements, including the concomitant medication restrictions, throughout the study.
7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at

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least one method with a failure rate of < 1% per year, during the treatment period and for at least 3 months after the final Follow-up Visit.

- A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 - Barrier methods must always be supplemented with the use of a spermicide.
8. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
- With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least for at least 4 months after the final Follow-up Visit. Men must refrain from donating sperm during this same period.
 - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least for at least 4 months after the final Follow-up Visit.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

2. Clinical evidence of any active infection which according to the judgment of the investigator may interfere with study conduct, measurement of pulmonary function, or impact the course of IPF.
3. In the 28 days before the start of Screening, any new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an pirfenidone treatment interruption > 7 days for any reason.
4. Any condition that is likely to result in death in the 12 months after the start of Screening.
5. Lung transplantation anticipated in the 12 months after the start of Screening.
6. Any planned significant surgical intervention from the start of Screening through the final Follow-up Visit. This does not include minor surgical procedures (e.g., excision of a localized basal cell carcinoma).
7. Known hypersensitivity to the active substance or any excipient of either pirfenidone or nintedanib.
8. Any condition that, in the Investigator's judgment, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone or nintedanib.
9. Mild (Child Pugh A), moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.

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10. Severe renal impairment (creatinine clearance < 30 mL/min by the Cockcroft-Gault calculation), including end-stage renal disease requiring dialysis.
11. History or risk of gastrointestinal (GI) tract perforation.
12. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) in the 6 months before the start of Screening, including but not limited to, the following:
 - Unstable angina pectoris or myocardial infarction.
 - Congestive heart failure expected to require hospitalization during the study.
 - Uncontrolled clinically significant arrhythmias.
13. Electrocardiogram (ECG) with a heart-rate-corrected QT interval (corrected using Fridericia's formula, QTcF) \geq 500 ms at Screening, or a family or personal history of long QT syndrome.
14. Bleeding risk: genetic predisposition to bleeding, a hemorrhagic event in the 12 months before the start of Screening, or abnormal laboratory coagulation parameters. Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g., vitamin K antagonists, dabigatran, heparin, hirudin), high-dose antiplatelet therapy, or other therapy that may substantially increase bleeding risk are excluded.

Note: the following are permitted: prophylactic low-dose heparin or heparin flush as needed for maintaining an indwelling intravenous device (e.g., enoxaparin 4000 IU SC per day), as well as prophylactic use of antiplatelet therapy (e.g., acetylsalicylic acid up to 325 mg/d, clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy).

15. Use of strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin) in the 28 days before the start of Screening.
16. Use of inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, erythromycin) or their inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's wort) in the 28 days before the start of Screening.
17. History of alcohol or substance abuse in the 2 years before the start of Screening.
18. Use of any tobacco product in the 12 weeks before the start of Screening, or an unwillingness to abstain from their use through the final Follow-up Visit.
19. In the judgment of the Investigator, not a suitable candidate for enrollment, or unlikely or unable to comply with the requirements of this study.
20. Use of any investigational therapy in a clinical study protocol in the 28 days before the start of Screening.
21. Pregnancy or lactation.
22. Hypersensitivity to peanuts.
23. Hypersensitivity to soy.

END OF STUDY AND LENGTH OF STUDY

Length of Study

The expected study length is up to 21 months

End of Study

January 2018

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INVESTIGATIONAL MEDICINAL PRODUCTS

PIRFENIDONE

Pirfenidone is approved in a 267 mg capsule dosage form.

The recommended dose is 801 mg (i.e., three 267 mg capsules) TID, at the same times each day, taken with food (total dose, 2403 mg/d). At the beginning of the study, patients will be on a stable pirfenidone dose, as defined in the inclusion criteria.

NINTEDANIB

Nintedanib is approved in 100 mg and 150 mg capsule dosage forms.

The recommended dose is 150 mg BID, approximately 12 hours apart, at the same times each day, taken with food (total dose, 300 mg/d). Both 100 mg and 150 mg capsules will be supplied to facilitate temporary dose reduction if required to manage AEs.

STATISTICAL METHODS

PRIMARY ANALYSIS

The analysis population will be the Safety Population. It will consist of all patients who received at least one dose of nintedanib or pirfenidone at the Baseline Visit (Day 1).

AEs will be coded to a preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Because this is a safety and tolerability study that is not designed to assess efficacy, no formal statistical hypotheses for efficacy will be assessed. The efficacy analyses will be limited to descriptive statistics.

Data summaries will be provided for baseline characteristics; patient disposition; extent of exposure; the number and proportion of patients who complete 24 weeks on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d (with 95% confidence interval [CI]); the numbers and proportions of patients with a dose reduction or a dose interruption; the number and proportion of patients who discontinued combination treatment because of a AE (with 95% CI); the total number of days on combination treatment at an pirfenidone dose of 1602–2403 mg/d and a nintedanib dose of 200–300 mg/d; the total number of days from the start of combination treatment to discontinuation of one or both study treatments; the final prescribed doses of pirfenidone and nintedanib; and the reasons for premature discontinuation of combination treatment.

AEs and SAEs leading to discontinuation will be summarized by incidence, severity, seriousness, and relationship to treatment. Additional summaries will be provided for the numbers and proportions of patients with a Major Adverse Cardiac Event (MACE), a cerebrovascular event, a bleeding event, or a thromboembolic event; the numbers and proportions of patients discontinuing combination treatment for a liver test abnormality, a GI event, or a photosensitivity reaction/rash; the numbers and proportions of patients with an emergency department visit or hospitalization; and deaths.

Observed and change values for clinical laboratory and vital signs data will be summarized. Grade 3 and 4 laboratory abnormalities will be summarized by CTCAE grade, and shift tables by CTCAE grade will be provided.

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ECG data will be summarized, presenting the numbers and proportions of patients with a maximum QTcF interval < 500 ms, 500–550 ms, and > 550 ms; with a maximum change from the baseline QTcF interval of ≤ 30 ms, 31–60 ms, and > 60 ms; and with ECG changes considered by the Investigator to be clinically significant.

DETERMINATION OF SAMPLE SIZE

A sample size of approximately 80 patients was selected based on the AE discontinuation rates after one year observed in the randomized Phase 3 pirfenidone studies and the randomized Phase 2 and 3 nintedanib studies (pirfenidone 14.6%, nintedanib 21%; per the 2014 US labels). Given that for pirfenidone the discontinuation rate after 24 weeks was 6%-8% in studies PIPF-004 and PIPF-006 it is a reasonable assumption that the nintedanib discontinuation rate was around 10% - 11%. As in this study of combination treatment, it is possible that the addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients who discontinue because of an AE, given the overlap in the GI and hepatic effects of the two medications.

Assuming 85% of the patients complete 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2% to 92.8% using a 95% CI

Number of Patients who completed 24 weeks	Proportion of Patients who completed 24 weeks	Lower Bound of 95% CI	Upper Bound of 95% CI
76	95.0%	90.2%	99.8%
72	90.0%	84.4%	96.6%
68	85.0%	77.2%	92.8%
64	80.0%	71.2%	88.8%
60	75.0%	65.5%	84.5%

CI = confidence interval

Appendix 2 Schedule of Assessments

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20	24		
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Informed consent [d]	X	X																
Complete medical history [e]	X	X																
Directed medical history [f]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pirfenidone treatment history	X	X [g]	X [h]															
Document IPF diagnosis		X																

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Complete physical examination, including vital signs [i]		X	X		X		X		X		X		X		X	X	X	X
Body weight (kg)		X	X		X		X		X		X		X		X	X	X	X
Height (cm)		X																
12-lead ECG [j]		X	X													X	X	X
Spirometry (FVC), and DLco [k]		X	X								X					X		X
Spirometry (FEV1) [k]		X	X															
Hematology, serum chemistry [l], CRP		X	X [m]	X [m]	X [m]	X [m]	X		X		X		X		X	X	X	X

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Urine pregnancy test [n]							X [r]		X [r]		X [r]		X [r]		X [r]	X [r]		
Serum pregnancy test [n]		X	X													X	X	X
Biomarker sample collection [o]			X				X									X		X
Review patient diary			X		X		X		X		X		X		X	X	X	X
Review AEs [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review pirfenidone dosing adherence [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Review nintedanib dosing adherence [p]				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Review concomitant medications [p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review inclusion / exclusion criteria	X	X	X															
Obtain historical FEV1, FVC and DLco data [q]		X																
██████████			X													X		X
Dispense/collect patient diary		X															X	

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Dispense wallet card			X															
Dispense pirfenidone and explain dosing		X	X						X				X					
Dispense nintedanib and explain dosing			X						X				X					
Instruct to resume commercial pirfenidone and explain dosing																X		X
Collect unused pirfenidone and empty bottles			X						X				X			X		X

If	Study Period																Follow-up	Early d/c
	W/O [a]	Screen-ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Collect unused nintedanib and empty bottles									X				X			X		X

AE = adverse event; ASAP = as soon as possible; BL = Baseline; d = day; d/c = discontinue; DLco = carbon monoxide diffusing capacity; ECG = electrocardiogram; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; [REDACTED] O = office visit; P = telephone contact; SAE = serious adverse event; W/O = Washout

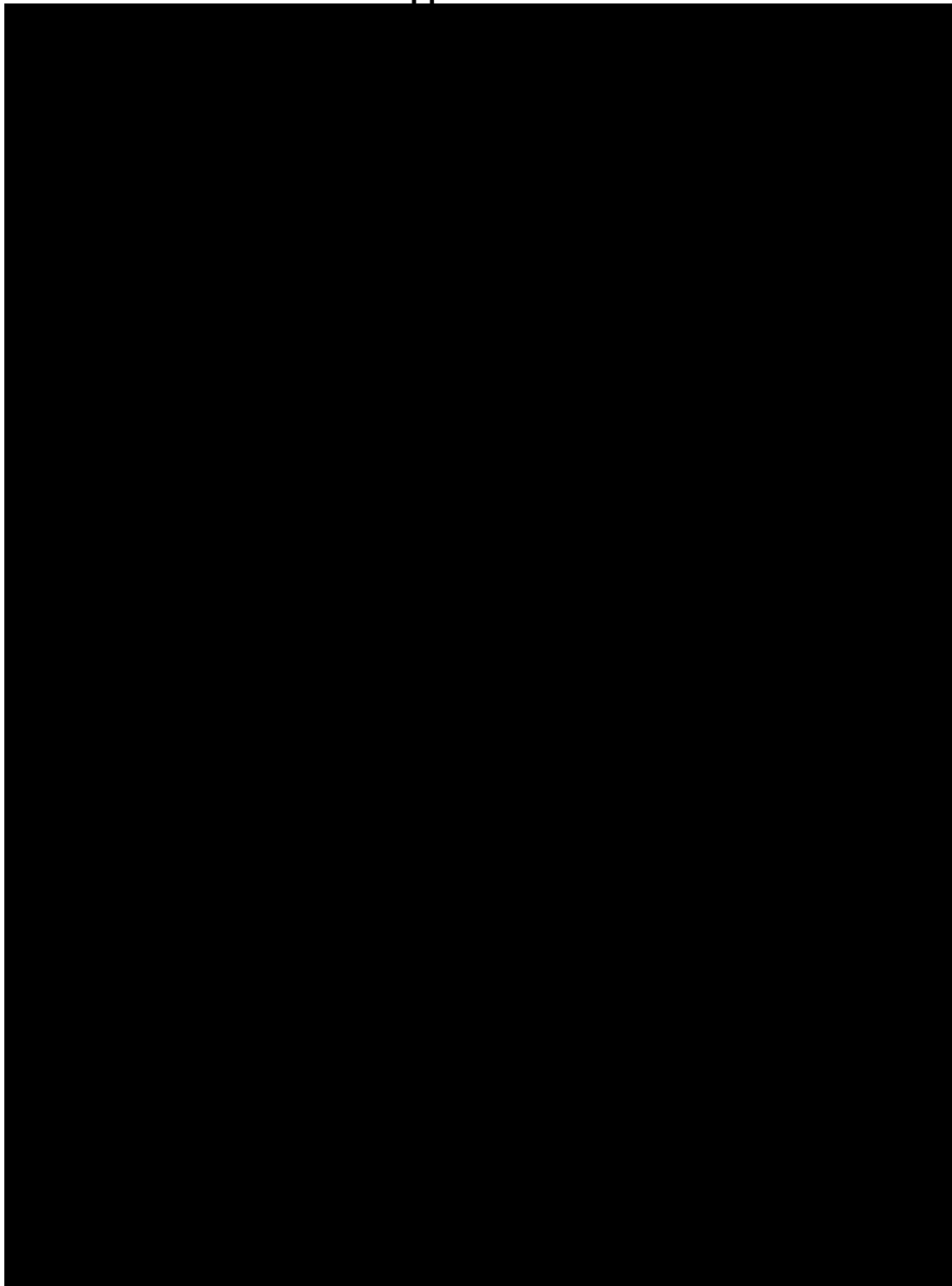
- Patients taking prohibited medications enter Washout; if prohibited medication must be tapered, patient must be off that medication 28 days before start of Screening. Other patients directly enter Screening.
- For patients who complete 24 weeks of study treatment, visit should occur 28–35 days after completion of combination treatment. For patients who prematurely discontinue study treatment or have a treatment interruption of ≥ 28 consecutive days, visit should occur 28–35 days after decision to discontinue nintedanib.
- If a patient cannot return in ≤ 7 days, study center is to call patient to review medical history and to send laboratory kit and shipping supplies to patient so that blood samples can be drawn at another study center, commercial laboratory or by home nursing agency; Early Discontinuation Visit should then be scheduled as soon as possible.
- Written informed consent must be obtained before any study-mandated assessment or procedure, including tapering and/or discontinuing prohibited medication. If written informed consent was not obtained at Washout, it must be obtained at start of Screening.
- Including systems review, and review of concomitant medications, events in 28 days before start of Screening, and historical data (including prior high-resolution computed tomography scans, pulmonary function tests, and surgical lung biopsy data, if available). If complete medical

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history was obtained during Washout, during Screening the list of concomitant medications and medical history should be updated with changes since patient signed informed consent form.

- f. Includes AEs, concomitant medications, dosing adherence, hospitalizations, inquiry regarding compliance with protocol requirements for contraceptive use and avoiding tobacco products, and inquiry regarding whether patient is aware of being pregnant.
- g. At start of Screening, patient must have been on pirfenidone for ≥ 16 weeks and on stable dose (1602–2403 mg/d) for ≥ 28 days; dose must be expected to remain in that range throughout study. Treatment interruptions > 7 days are not permitted in the 28 days before start of Screening.
- h. At Baseline Visit, patient must have been at least approximately 80% adherent to pirfenidone dosing regimen since Screening Visit.
- i. Resting BP and HR, respiratory rate, body temperature.
- j. To be performed before laboratory assessments; use of short-acting bronchodilators is prohibited in preceding 6 hours, and use of long-acting bronchodilators is prohibited in preceding 24 hours.
- k. Spirometry (FVC, FEV1) is done before and approximately 30 minutes after short-acting bronchodilator administration; DLco testing is done before or at least 30 minutes after last puff of short-acting bronchodilator. Use of short-acting bronchodilators is prohibited in 6 hours before start of pre-bronchodilator spirometry test or a pre-bronchodilator DLco test. Use of long-acting bronchodilators is prohibited in 24 hours before start of tests.
- l. Including creatinine clearance rate, calculated using Cockcroft-Gault formula.
- m. If sample cannot be drawn at investigator's study center on Days 7 and Day 21, it can be drawn at another study center, commercial laboratory or by a home nursing agency. Patient is to be given laboratory kit and shipping supplies at Day 1 Visit (for Day 7 blood draw) and Day 14 Visit (for Day 21 blood draw).
- n. Women of childbearing potential.
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- p. Done as part of patient diary review at office visits from Week 2 through Week 24 or Early Discontinuation Visit (for dosing adherence) or through final Follow-up Visit (for AEs and concomitant medications).
- q. If available, obtain percent predicted FVC, FEV1 and percent predicted DLco measurements from 12 months before start of Screening (from documented pulmonary function laboratory reports)
- r. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.

Appendix 3



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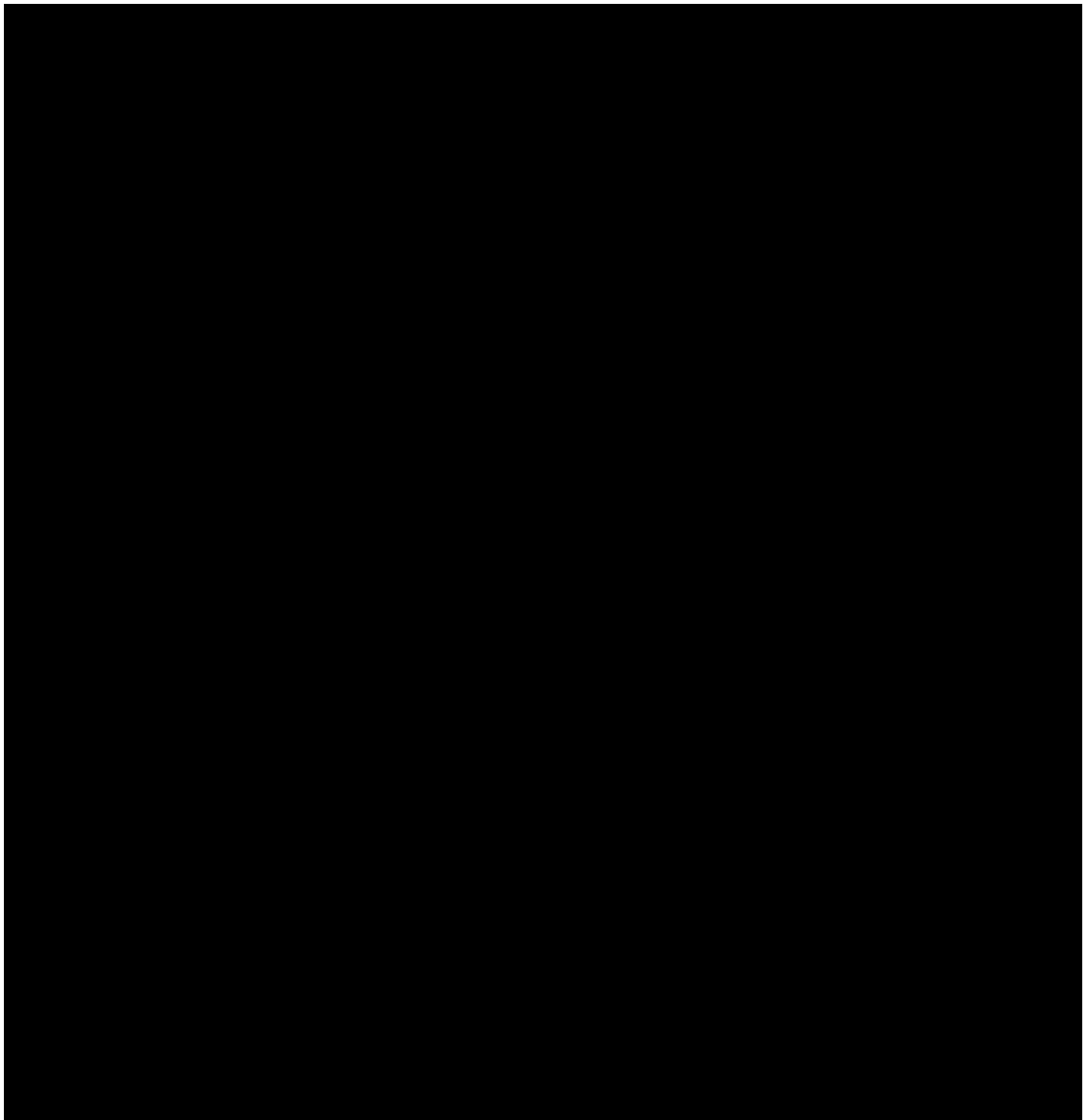
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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55

Appendix 4

MedDRA Browser Basket: Esbriet – Potential Hy's Law AEGT

Project: Esbriet

Title: Esbriet - Potential Hy's Law AEGT

Description

AEGT to identify cases of potential Hy's Law: 49 Terms

Created Date 11-May-2016

By User [REDACTED]

Last Modified Date 03-Nov-2016

By User [REDACTED]

Last Reviewed Date 04-Nov-2016

By User [REDACTED]

Included MedDRA Preferred Terms

Liver injury
Bilirubin conjugated increased
Urine bilirubin increased
Hepatobiliary disease
Jaundice
Transaminases abnormal
Subacute hepatic failure
Aspartate aminotransferase increased
Cholestatic liver injury
Bilirubin conjugated abnormal
Mixed liver injury
Hyperbilirubinaemia
Drug-induced liver injury
Hepatic enzyme abnormal
Blood alkaline phosphatase abnormal
Gamma-glutamyltransferase increased
Hepatic failure
Acute hepatic failure
Blood alkaline phosphatase increased
Hepatic enzyme increased
Aspartate aminotransferase abnormal
Biopsy liver abnormal
Liver function test increased
Liver function test abnormal
Blood bilirubin increased
Jaundice hepatocellular
Hepatitis
Alanine aminotransferase abnormal
Hepatitis fulminant
Hepatitis cholestatic
Hepatitis acute
Acute yellow liver atrophy
Cholestasis
Blood bilirubin unconjugated increased
Prothrombin time ratio increased
Chronic hepatitis
Prothrombin time abnormal
Hepatic infiltration eosinophilic
Hepatic function abnormal
Prothrombin time prolonged
Hepatotoxicity
Hepatitis toxic

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Transaminases increased
Blood bilirubin abnormal
Prothrombin time ratio abnormal
Liver disorder
Alanine aminotransferase increased
Hepatic necrosis
Gamma-glutamyltransferase abnormal
Hepatocellular injury

Excluded MedDRA Terms

Nested Baskets

End of Esbriet - Potential Hy's Law AEGT definition

MedDRA Version 19.1
Language English

Appendix 5 Calculation of GAP Index Categories

Calculation of GAP Score

The GAP score and staging system is based on four baseline characteristics, gender, age, %FVC at baseline and %DLco at baseline. If any of the four baseline characteristics is missing then the GAP score is missing.

Table 9 GAP Index and Staging System

	Variable name from ADSL	Predictor	Points
Gender (G)	SEX	Female	0
		Male	1
Age (A)	AGERAND	Age <=60	0
		60<Age=<65	1
		Age >65	2
Physiology (P)	FVCBL	FVC >75	0
		50<=FVC<=75	1
		FVC<50	2
	DLCOBL	DLCO>55	0
		36<=DLCO<=55	1
		DLCO<36	2
		Cannot Perform	3

This definition follows the descriptions used in the Pirfenidone 2014 Resubmission Efficacy Update (RISE).

- GAP Index Stage I: Total Points: 0 to 3
- GAP Index Stage II: Total Points: 4 to 5
- GAP Index Stage III: Total Points: 6 to 8

In order to prevent possible issues with unexpected data formats, the following changes to the above definitions will be performed in this study:

	Variable name from ADIESL	Predictor	Points
Age (A)	AGERAND	Age < 61	0
		61<=Age=<65	1
		Age >65	2