Clinical Study Report – CSR (Synopse ICH E3)

Study Title:	**Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF)**	
Study Acronym	DZL-RELIEF	
Study Sponsor-ID	KKS-206	
EudraCT No.	2014-000861-32	
CSR Version	V02F	
CSR Date	04-SEP-2020	
	Date	**Signature**
Sponsor Carmen Schade-Brittinger		
Principal Investigator Prof. Dr. Jürgen Behr		
Co-Principal Investigator Prof. Dr. Andreas Günther		
Statistician Dr. Johannes Johow		
Author Dr. Eckhard Bergmann		

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Clinical Study Report (Synopse ICH E3)

1 Name and address of Sponsor/Company

Justus-Liebig University Giessen, Ludwigstraße 23, 35390 Gießen

2 Name of Finished Product

Esbriet®

3 Name of Active Substance

Pirfenidone

4 Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N.A.

5 Title of Study

Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF) – latest Study protocol no.: **V04F, 23.11.2017**.

Date of approval of competent authority (CA)	01.12.2015 PP V02F (11.11.2015) + Patinfo V02F	
CA Vorlagen Nummer (BfArM)	**61-3910-4040846**	
Data of approvals of subsequent changes according to § 10 Para. 1 GCP-V, if applicable:		
Amendment No. 1	approved on	15.06.2016 (BOB) PP V02F+ Amendment No.1
Amendment No. 2 + Patinfo V03F + Patinfo Extension V01F + Appendix to Patinfo V01F	approved on	30.01.2017 (BOB) PP V03F (16.12.2016)+ Amendment No.2
Approval of additional QP- Release Site Roche Pharma AG, Grenzach	approved on	31.03.2017
Approval Amendment No. 3 + PP V04F + Patinfo V04F + Patinfo Extension V02F	approved on	02.01.2018 (BOB) PP V04F + Amendment No.3
Recruiting stop Therapy stop Database closure Close out	informed	End of recruitment since 24.04.2018 BOB End of Therapy since 19.06.2018 BOB Database closure RELIEF main study 04.02.2019 Database closure RELIEF Extension 01.08.2019 Last close out visit to the study centers was on 21.10.2019
Notification of end of study (§13 (8) GCP-V)	on:	25.10.2019

Date of approval of ethics committee	27.11.2015 PP V02F (11.11.2015) + Patinfo V02F	
Sign of ethics committee Munich	**473-15 fed**	
Data of approvals of subsequent changes according to § 10 Para. 1 GCP-V, if applicable:		
Amendment No. 1	approved on	07.07.2016 (EK) PP V02F+ Amendment No.1
Amendment No. 2 + Patinfo V03F + Patinfo Extension V01F + Appendix to Patinfo V01F	approved on	09.02.2017 (EK) PP V03F (16.12.2016) + Amendment No.2
Approval of additional QP- Release Site Roche Pharma AG, Grenzach	approved on	31.03.2017
Approval Amendment No. 3 + PP V04F + Patinfo V04F + Patinfo Extension V02F	approved on	01.02.2018 (EK) PP V04F + Amendment No.3
Recruiting stop Therapy stop Database closure Close out	informed	End of recruitment since 24.04.2018 EK End of Therapy since 19.06.2018 EK Database closure RELIEF main study 04.02.2019 Database closure RELIEF Extension 01.08.2019 Last close out visit to the study centers was on 21.10.2019
Notification of end of study (§13 (8) GCP-V)	on:	25.10.2019

Approval: + Patinfo V02F
+ interim analysis (2 patients added for statistical reasons)
+ pregnancy tests at home (BfArM)

Amendment No. 1:
4.1. Inclusion criteria:
….3 previous FVC measurements….(new) and at maximum 24 months before screening…..
-Plus various further clarifications, e.g. Concomitant Therapy Exclusions (new): Concomitant therapy with potential interaction to study drug according to SmPC

Amendment No. 2: + Patinfo V03F + Patinfo Extension V01F + Appendix to Patinfo V01F
- New DSMC member
- 5 new additional clinical sites
- 4.1 Inclusion criteria(CVDLF): new: mixed connective tissue disease MCTD), increased range: DLCO ≥10%, but < 90% at the Screening Visit
- Description of 2-day down titration
- description of label for open label extension phase,
- Flow chart with extension study + visit schedule

Approval of additional QP- Release Site Roche Pharma AG, Grenzach :

- oCatalent Bathgate (cooperation as QP-Release Site was terminated)
- oRoche Pharma AG Grenzach will do QP- Release/ + import of study medication

Amendment No. 3: + PP V04F + Patinfo V04F + Patinfo Extension V02F

Additional clinical site: Klinik Waldhof-Elgershausen (Prof. Guenther),

7.2. Undesirable effects according to SmPC: adapted (June 2017)

O Changes in Exclusion criteria 19

8 Visit schedule main study

8.3.5 Visit schedule Treatment after end of main study/ open-label extension

New chapters:

8.1.8 Additional liver function tests based on Blaue Hand Letter BfArM

8.3.2.3 Treatment discontinuation due to angioedema

8.3.2.4 Treatment discontinuation due to anaphylaxis,

8.3.2.5 Treatment discontinuation due to aminotransferase,

Safety: 10.4 Expectedness

14.4 Patient insurance:

New name +Address

Visit schedule main study,

Visit schedule extension study

Recruiting Stop/Therapy Stop: The End of recruitment based on the result of futility analysis. The End of therapy based on the recommendation of the ethics committee

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Agaplesion Pneumologische Klinik Waldhof Elgershausen **Germany-35753 Greifenstein**	**Prof. Dr. Andreas Günther**

7 Study center(s)

Center-ID	Participating center	Number of recruited patients
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04	**Universitätsklinikum Heidelberg** **Thoraxklinik-Heidelberg gGmbH** **Amalienstr. 5** **Germany-69126 Heidelberg**	**21**
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23	**Agaplesion Pneumologische Klinik Waldhof Elgershausen** **Germany-35753 Greifenstein**	**0**

8 Publication (reference)

Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF-Study); J. Behr, A. Prasse, M. Kreuter, P. Neuser, K. F. Rabe, F. Bonella, R. Bonnet, C. Grohe, M. Held, H. Wilkens, P. Hammerl, D. Koschel, S. Blaas, H. Wirtz, J. H. Ficker, W. Neumeister, N. Schönfeld, M. Claussen, N. Kneidinger, M. Frankenberger, S. Hummler, N. Kahn, S. Tello, J. Freise, T. Welte, J. Johow, A. Günther; Submitted to *The Lancet Respiratory Medicine submitted*

Exploring efficacy and safety of oral Pirfenidone for progressive, non-IPF lung fibrosis (RELIEF) - a randomized, double-blind, placebo-controlled, parallel group, multi-center, phase II trial. Behr J, Neuser P, Prasse A, Kreuter M, Rabe K, Schade-Brittinger C, Wagner J, Günther A. BMC Pulm Med. 2017 Sep 6;17(1):122.

9 Studied period (years): date of first enrolment, date of last completed, date of database closure

Date of first enrolment: 05.04.2016
Date of last completed: 04.10.2018

Database closure and notification of end of study: 04.02.2019 (database closure Main study); 01.08.2019 (database closure Extension); 25.10.2019 (notification of end of study).

10 Phase of development

Phase II

11 Objectives

Primary objective

The primary objective was to investigate the treatment effect on the absolute change in percent predicted FVC from baseline to week 48 in the pirfenidone and placebo group.

Secondary objectives

Secondary objectives included time to disease worsening, progression-free survival as well as selected measures of pulmonary function, quality of life questionnaires and safety parameters

12 Methodology

Prospective phase IIb, randomized, double-blind, placebo-controlled, parallel group, multi-center.

13 Number of patients (planned and analyzed)

Planned number of patients: n=374

Analyzed number of patients: n=127 (for further description see Figure 1).

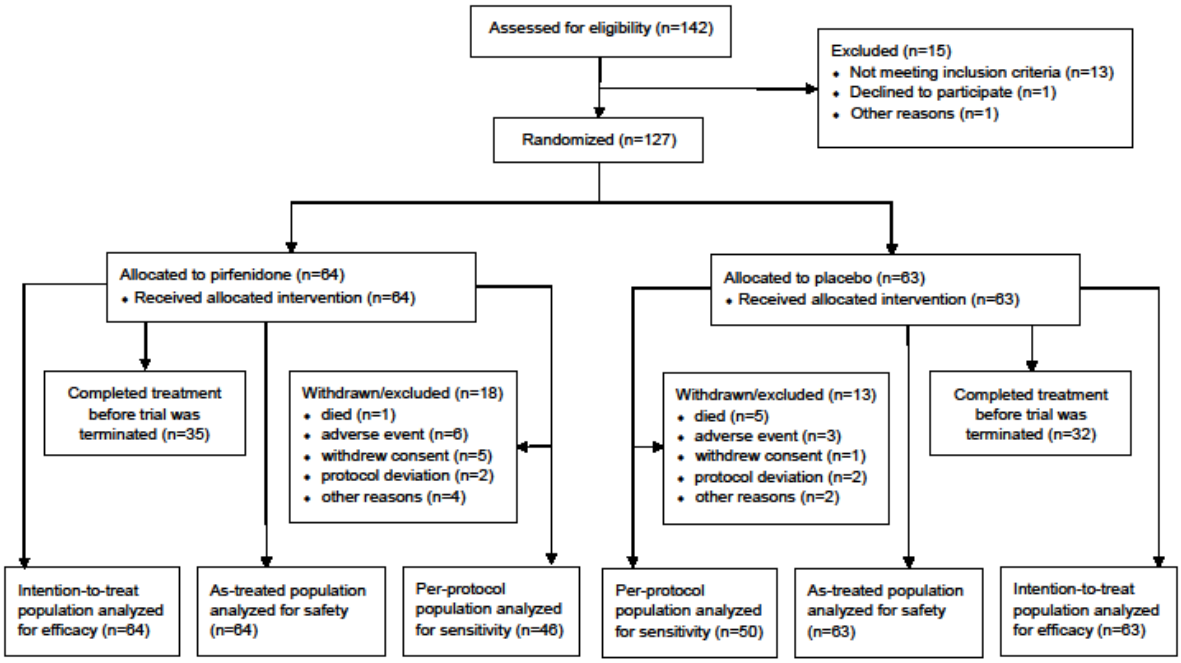

Figure 1 : DZL-RELIEF patient disposition

14 Diagnosis and main criteria for inclusion

Diagnosis:

1. fNSIP - fibrotic Non-Specific Interstitial Pneumonia
2. CVDLF - Lung Fibrosis associated with Collagen / Vascular Disease
3. ALF – Asbestosis-induced Lung Fibrosis
4. chronic HP – chronic Hypersensitivity Pneumonitis

Inclusion criteria:

<u>Confident diagnosis of progressive, non-IPF lung fibrosis due to ALF, CVDLF, chronic HP or fNSIP</u>:
1. Clinical symptoms consistent with ALF, CVDLF, chronic HP or fNSIP, including the insidious onset of otherwise unexplained dyspnea on exertion prior to diagnosis
2. Diagnosis of either ALF, CVDLF, chronic HP or fNSIP based on diagnostic criteria outlined in Table 1, at least 9 months before randomization:

Table 1: Diagnostic criteria for ALF, CVDLF, chronic HP and fNSIP.

(patients need to fulfil all of the listed diagnostic criteria within one of the categories)

Asbestos-induced lung fibrosis
• Existence of asbestos• specific pleural changes in HRCT (pleural plaques)

(patients need to fulfil all of the listed diagnostic criteria within one of the categories)

- Reticular changes in HRCT and restrictive lung function pattern
- History of asbestos exposure
- Absence of an alternative explanation for fibrotic lung disease
- Absence of extensive pleural plaques and/or effusion

Lung fibrosis associated with collagen / vascular diseases

- Diagnosis of progressive systemic sclerosis (PSS), mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), Sjörgen's syndrome, polymyositis/ dermatomyositis on the basis of extrapulmonary symptoms and corresponding proof of auto-antibodies
- Reticular changes in HRCT and restrictive lung function pattern
- Absence of an alternative explanation for fibrotic lung disease

Chronic Hypersensitivity Pneumonitis

- Previous or current respiratory symptoms (dyspnea, coughing) with a temporal or spatial relation to a causative antigen exposure
- Proof of precipitating antibody and/or lymphocytic alveolitis (>30%)
- HRCT consistent with chronic HP
- Restrictive lung function pattern
- Absence of an alternative explanation for fibrotic lung disease

Fibrotic NSIP

- Histological diagnosis of a fibrotic NSIP pattern by open lung biopsy or cryobiopsy
- HRCT consistent with fibrotic NSIP
- Restrictive lung function pattern
- Absence of an alternative explanation for fibrotic lung disease, especially no clinical suspicion of CVD

3. Women of childbearing capacity[1] are required to have a negative serum pregnancy test before treatment and must agree to maintain highly effective methods of contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence is not practiced, then one of the two methods of birth control should be an oral contraceptive (e.g., oral contraception and a spermicide)
4. 18 <= Age <= 80 years

Disease Severity and Progression:

5. Progressive disease in absence of a particular treatment (ALF) or despite a previous or concomitant treatment as outlined in chapter 7.11. Progression prior to study entry must be proven by calculating the slope of a set of at least 3 previous FVC measurements within at least 6 months and at maximum 24 months before screening, showing a (eventually extrapolated) FVC decline of at least 5% (abs. pred.) per year
6. Percent predicted FVC ≥ 40%, but < 90% at the Screening Visit (before randomization)

[1] Definition of women of childbearing potential: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

7. Percent predicted, hemoglobin (Hb)-corrected carbon monoxide diffusing capacity/ carbon monoxide transfer capacity (DLCO) ≥ 10 %, but < 90 % at the Screening Visit
8. Distance walked ≥ 150 meters, with O2 saturation > 83% on ≤ 6L/min of O2
Informed Consent and Protocol Adherence:
9. Able to understand and sign a written informed consent form
10. Able to understand the importance of adherence to study treatment and the study protocol, including the concomitant medication restrictions throughout the study period
Lung transplantation:
11. Patients being considered or on the waiting list for lung transplantation are eligible for participation only if their estimated waiting time is longer than the study period. At the time these patients are placed on the list the date and reason for this placement and the LAS should be collected

15 Test product, dose and mode of administration, batch numbers

Product: Pirfenidone, 267mg/Capsule

Dose: Dosing schedule:
- Days 1 - 7: one capsule TID (801 mg/day)
- Days 8 - 14: two capsules TID (1602 mg/day)
- Day 15 and continuing: three capsules TID (maximum of 9 capsules daily, 2403 mg/day)

Mode of administration: oral; hard-gelatin capsule

Batch numbers: 1304040; 1151196; 1400236; 1151197; 1400228

16 Duration of treatment

Study medication will be administered up to 48 weeks and 2 additional days for down-titration.

17 Reference therapy, dose and mode of administration

Reference product: Placebo

Dose: Dosing schedule:
- Days 1 - 7: one capsule TID
- Days 8 - 14: two capsules TID
- Day 15 and continuing: three capsules TID

Mode of administration: oral; hard-gelatin capsule

18 Criteria for evaluation: Efficacy, Safety

Efficacy criteria:

Primary:
Absolute change in percent predicted FVC from baseline to week 48 in the pirfenidone and placebo group.

Secondary:

Time to disease worsening, defined as time to clinical deterioration, lung fibrosis-related death, lung transplant or respiratory hospitalization, whichever comes first
- Progression-free survival, defined as time to the first occurrence of either of the following (as compared to the patient's baseline):
  - ≥ 10% absolute decline in percent predicted FVC
  - ≥ 15% absolute decline in percent predicted Hb-corrected DLCO
  - death of the patient
- Categorical assessment of relative change from baseline to week 48 in percent predicted FVC
- Change from baseline to week 48 in SGRQ and EQ-5D
- Change from baseline to week 48 in the percent predicted Hb-corrected DLCO/TLCO
- Change from baseline to week 48 in the worst oxygen saturation by pulse oximetry (SpO2) measurement observed during the 6MWT
- Change from baseline to week 48 in distance walked in the 6MWT

Safety criteria:
Number of disease related deaths, adverse events and serious adverse events in pirfenidone- and placebo-group

19 Statistical methods

The sample size was calculated for a two-sided significance level of 5% and a power of 80%. To detect an effect size of 0.3 between the two treatment groups 187 patients per group were needed. One interim analysis was planned according to O'Brien/Fleming after recruitment of 224 patients.
The primary efficacy analysis was performed in the intention-to-treat population. Safety analyses included all randomly assigned patients who received at least 1 dose of study medication. The primary efficacy analysis measured the treatment effect on the absolute change in percent predicted FVC from baseline to week 48 between the pirfenidone and placebo group. Hierarchical testing was applied to test the treatment effect in different groups with regard to diagnosis. Hypotheses were tested consecutively until the p-value of a hypothesis exceeded the 5% significance level, thereby controlling the familywise error rate at the 5% level.
As the primary efficacy endpoint is assumed to be not normally distributed, data were analyzed using a rank analysis of covariance (ANCOVA) model with a classification effect for treatment and diagnosis group and baseline FVC as covariates with a significance level of 5% (two-sided). The treatment effect was tested using the Cochran-Mantel-Haenszel mean score statistic, median treatment differences were estimated according to Hodges-Lehmann. Missing data was imputed sequentially over visits by averaging the non-missing data of those three patients with the smallest sum of squared differences (SSD) at the previous visit (as in the CAPACITY trial). In the rank ANCOVA, patients with missing values due to death were assigned the worst rank according to the time from randomization until death, where the shortest time until death corresponds to the worst rank. In addition the applied rank ANCOVA model was stratified (fixed effect) by diagnosis group. Progression-free survival was defined as either death, a drop of FVC-%-pred. versus the baseline value by more than 10%, or a drop of the percent predicted DLco versus the baseline value by more than 15%. Patients who prematurely withdrew from the study were censored on the day of their last clinic visit before discontinuing the study drug. To compare event time distributions we used Kaplan-Meier methods as well as log-rank tests. We calculated the point estimate and 95% CI of the treatment effect for FVC ml, DLco, TLC, FEV1, and 6MWD using the Hodges–Lehmann method. As sensitivity analyses, we also conducted an analysis applying the last observation carried forward (LOCF) imputation method in order to assess the robustness of our estimates against a different imputation model and/or the exclusion of deceased patients. Additionally, a repeated-measure, mixed linear model for change from baseline in percent predicted FVC is

presented. For this analysis, missing data generally has not been imputed. However, in the case of patients who died, the first missing data value after time of death has been replaced with a FVC-%-pred. of 30. Subsequent values have not been imputed. The mixed model included fixed effects for treatment, diagnosis group and assessment week (divided by 48 for scaling); covariates for baseline FVC-%-pred., and a random intercept for individual patients grouped by trial center. Given the high within-subject correlations of measurements, first order autoregressive covariance matrices for individual patients were specified for the estimation of standard errors. For further checking of the robustness of the derived model estimates, this model has also been fit to the (unimputed) raw data as a post-hoc analysis.
Furthermore, to compare primary and secondary endpoints (as well as TLC and FEV1 in post-hoc analyses) between treatment groups Wilcoxon rank-sum test was applied. However, statistical results reported for secondary endpoints are exploratory and not corrected for multiple testing. Adverse events (AEs) were presented descriptively. All analyses have been carried out with SAS (version 9.4 M3).
Adverse Events (AEs) were presented descriptively.

20 Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

20.1 Efficacy results

Primary endpoint

In the rank ANCOVA analysis, treatment with pirfenidone resulted in a significant between-group difference in the primary endpoint, the change from baseline to week 48 in the percentage of predicted FVC assessed (p=0.04, **Table 2**). Hierarchical testing proceeded after the exclusion of ALF (p=0.03), but was stopped after excluding fNSIP. The (fixed effects) model stratified by diagnosis group showed a quiet similar pattern (p=0.04 in the overall population, p=0.04 when ALF is excluded, and stopped after exclusion of fNSIP). For these pre-specified analyses, missing data was imputed by SSD method and deceased patients were assigned the worst rank as outlined under methods (similar to the statistical analysis applied for the CAPACITY and ASCEND trials of pirfenidone in IPF). If, alternatively to SSD, LOCF imputation method was applied, a similar, significant reduction in the FVC decline was encountered applying the rank ANCOVA analysis (p=0.03 in case of LOCF). The similar effects of imputation of missing values by using either SSD and LOCF are also visible in **Figure 2B** showing the time-dependent change in % predicted FVC for both groups.

Finally, the FVC slopes of both treatment groups were assessed employing the mixed-effect model repeated measures (**Tables 3 and 4**). Such analyses forwarded a significantly reduced decline in the FVC-%-pred. slope in the pirfenidone versus the placebo arm, and this was found to be independent of imputation (p=0.04 with imputation, p<0.05 without imputation).

Analysis of data within the individual subgroups was omitted since meaningful signals cannot be drawn due to small sample size.

The sensitivity analysis conducted in the per-protocol population included 46 patients in the pirfenidone group and 50 in the placebo group (**Figure 1**). Since p exceeded the 5% significance level when testing the overall population (p=0.09 or if stratified for diagnosis group p=0.06, respectively) no further hypotheses on subgroups were tested.

Table 2. Hierarchical testing based on Cochran-Mantel-Haenszel correlations and row mean scores (ANOVA) statistics for the absolute change in % predicted FVC from baseline to week 48 (with deaths ranked worst in predefined imputation method).

	N	Value	DF	P
1. H_0 against H_1 in the overall group	127	4.08	1	0.04
2. H_0 against H_1 when ALF is excluded	121	4.52	1	0.03
After Stratification for Diagnosis Group:				
- **Pooled**	127	4.13	1	0.04
- **Per stratum:**				
Asbestos-Induced Lung Fibrosis	6	0.01	1	0.91
Lung Fibrosis Associated With Collagen / Vascular Diseases	37	0.37	1	0.54
Chronic Hypersensitivity Pneumonitis	57	0.02	1	0.88
Fibrotic NSIP	27	15.05	1	<0.001

Table 3. Slope analysis from the best fit of Mixed Model Repeated Measures for the change in FVC-%-pred. from baseline until week 48 (see methods for model specification and imputation of missing values in case of deceased patients).

LABEL	Estimate	Standard Error	DF	t-Wert	Pr > |t|	Alpha	Lower	Upper
SLOPE, TRT	-1.20	1.17	139	-1.02	0.31	0.05	-3.51	1.12
SLOPE, PLACEBO	-4.73	1.21	140	-3.92	0.0001	0.05	-7.12	-2.35
SLOPE DIFF & CI	3.53	1.68	140	2.10	0.037	0.05	0.21	6.86
INTERCEPT, TRT	1.68	2.32	151	0.73	0.47	0.05	-2.89	6.26
INTERCEPT, PLACEBO	1.07	2.26	145	0.48	0.64	0.05	-3.39	5.54

Table 4. Slope analysis from the best fit of Mixed Model Repeated Measures for the change in FVC-%-pred. from baseline until week 48 after imputed values have been excluded.

LABEL	Estimate	Standard Error	DF	t-Wert	Pr > |t|	Alpha	Lower	Upper
SLOPE, TRT	-0.68	0.97	224	-0.70	0.49	0.05	-2.59	1.23
SLOPE, PLACEBO	-3.46	1.01	227	-3.44	0.001	0.05	-5.45	-1.48
SLOPE DIFF & CI	2.79	1.40	226	1.99	0.0475	0.05	0.03	5.54
INTERCEPT, TRT	1.71	1.97	174	0.87	0.39	0.05	-2.17	5.59
INTERCEPT, PLACEBO	1.25	1.97	170	0.63	0.53	0.05	-2.64	5.14

Secondary Endpoints

No significant difference was found between the treatment groups with regard to progression-free survival (**Figure 3**). A categorical analysis of relative changes from baseline to week 48 in FVC percent predicted revealed a higher proportion of pirfenidone patients in the group of patients with less than 5% relative decline of FVC per year, whereas placebo patients were more frequent in the group of patients experiencing deterioration (FVC decline of more than 10% per year; **Figure 4**). With regard to the other lung function parameters taken together, differences observed for DLCO, FEV1, and TLC (without the imputation of missing values) seem suggestive for a comparable treatment effect of pirfenidone although statistical significance was only found in case of DLCO (**Table 5** and **Figure 5**). Likewise, the loss in 6MWD appeared to be less pronounced in the pirfenidone versus the placebo group (**Table 5** and **Figure 5**). Quality of life was assessed using the SGRQ but no signal occurred (**Table 6**). The condition of “clinical deterioration”, as defined for this study (definition see study protocol in the supplement p 108), was met by two patients (after 84 and 169 days) in the placebo and two patients (after 176 and 182 days) in the pirfenidone arm. Consequently, rescue treatment with pulsed steroids were initiated in these four patients. There were five deaths in the placebo arm, as compared to one death in the pirfenidone arm. Among the five deaths in the placebo arm, three deaths were judged by the Principal Investigators to be respiratory driven. The cause of death of the patient died in the pirfenidone arm was found to be non-respiratory.

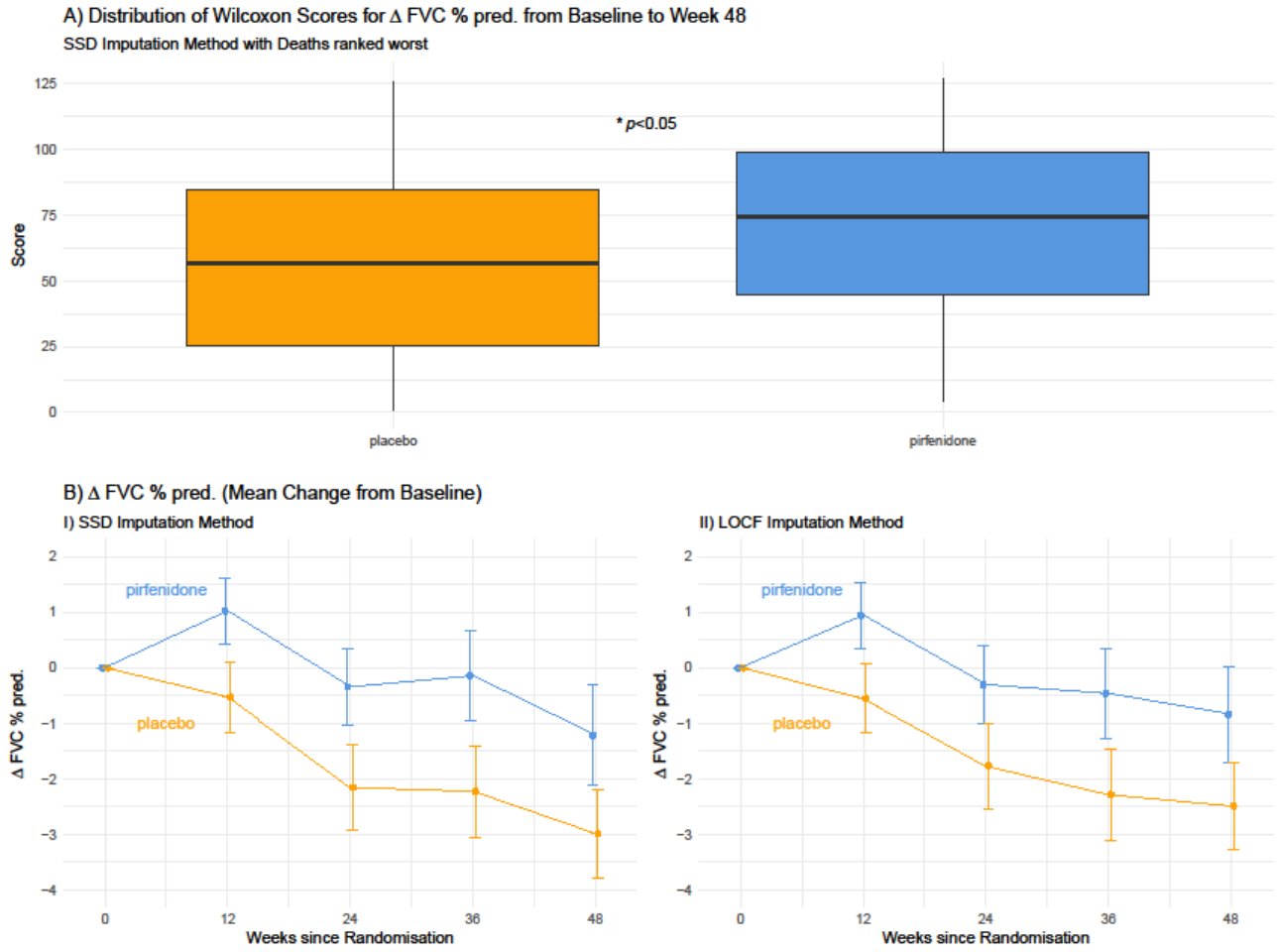

Figure 2. Distribution of Wilcoxon Scores for absolute change in percentage predicted FVC (FVC-%-pred.) and time course of change in mean FVC-%-pred. from baseline to week 48. The top panel (A) shows the distribution of Wilcoxon Scores for the absolute change in FVC-%-pred. from baseline to week 48 in the intention-to-treat population (N = 127) for the placebo and the pirfenidone arm (imputation of missing data by SSD, worst rank assigned to deceased patients). The bottom panel (B) shows mean change from baseline in FVC-%-pred. (with standard errors) over the 48-week trial period in the pirfenidone group and the placebo group after imputation of missing values (including those of deceased patients) according to the prespecified SSD imputation method, or, alternatively, by the LOCF

imputation method.

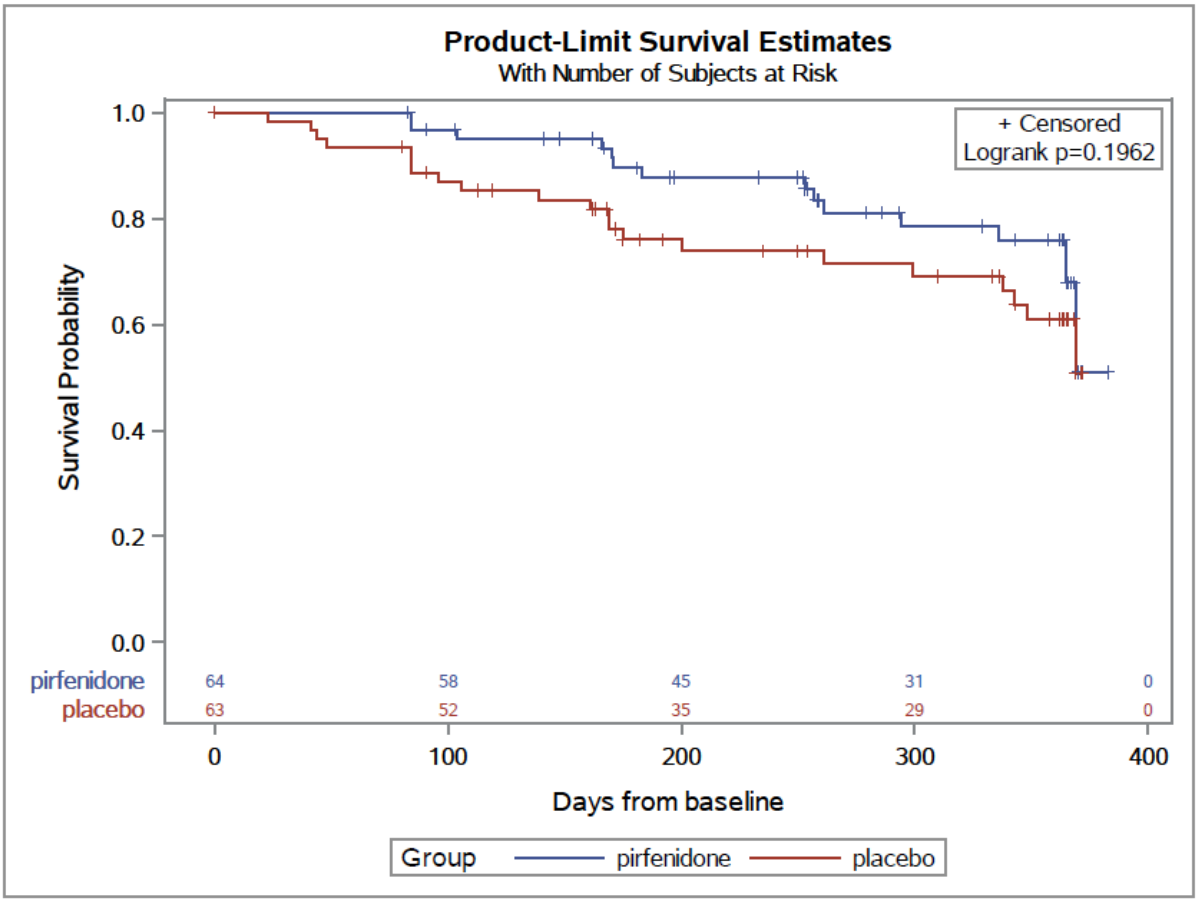

Figure 3. Progression-free survival in the pirfenidone and placebo group over time (ITT population). Progression-free survival was defined as either death, a drop of the percent predicted FVC versus the baseline value by more than 10%, or a drop of the percent predicted DLco versus the baseline value by more than 15%. Patients who prematurely withdrew from the study were censored on the day of their last clinic visit before discontinuing the study drug.

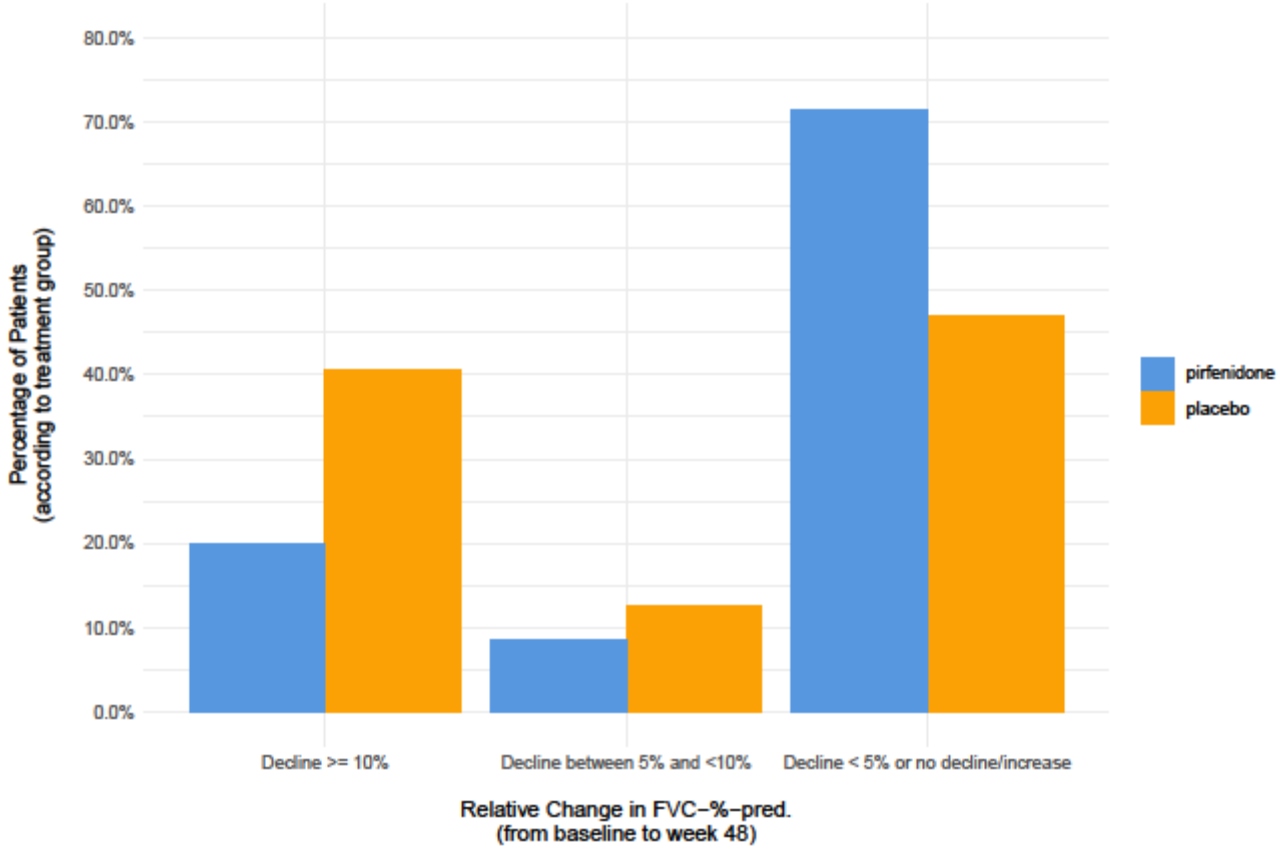

Figure 4. Categorical assessment of relative change in percent predicted forced vital capacity (FVC-%-pred.) from baseline to week 48 without imputation of missing data (N=67). Relative change was defined as the absolute change in FVC-%-pred. divided by FVC-%-pred. at baseline × 100. The numbers account for the proportion of patients within each category according to treatment

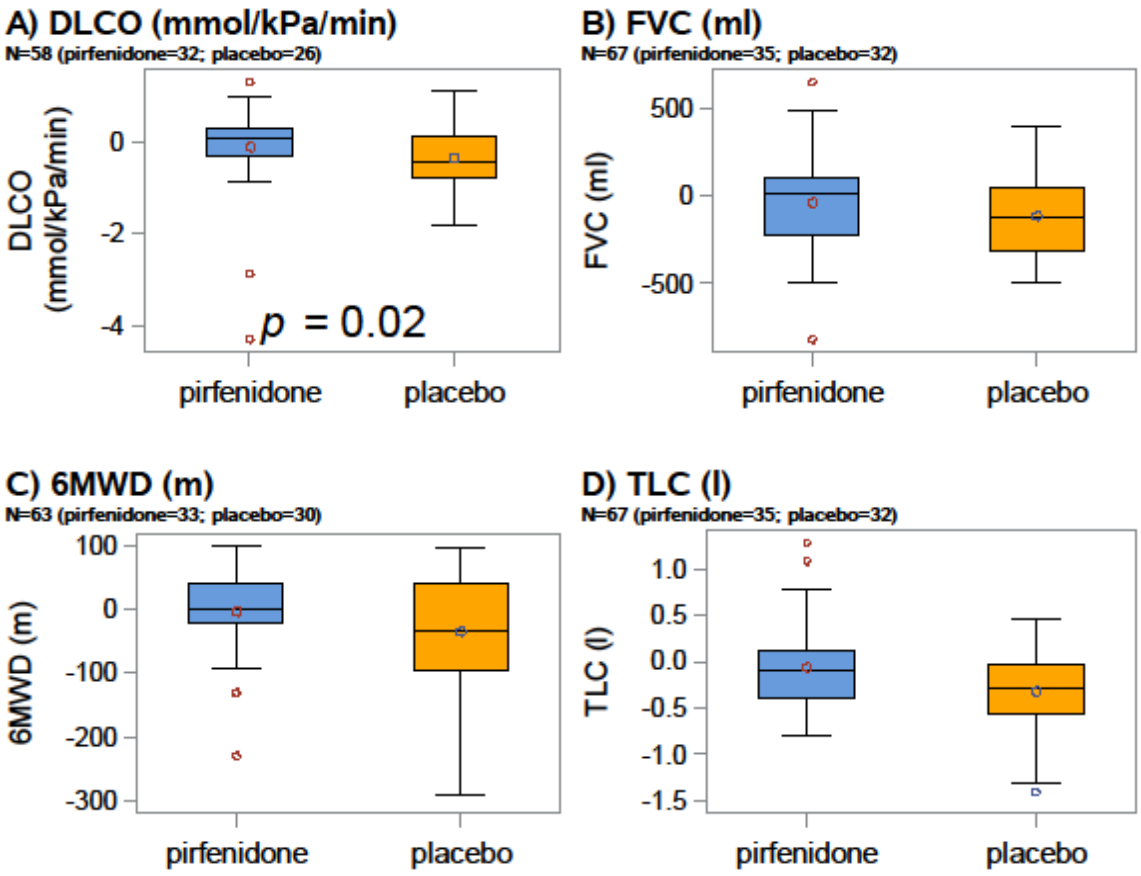

Figure 5. Absolute changes from baseline to week 48 in secondary endpoints without imputation of missing values. Boxes show the interquartile range (IQR) and include median (midline) and mean (point marker). Whiskers show the spread of values beyond the box limits within a distance of 1·5×IQR. Reported p-value is from two-sided Wilcoxon rank sum test (see table 2). DLCO: Diffusing capacity of carbon monoxide/ carbon monoxide transfer factor; FVC: Forced Vital Capacity; 6MWD: 6-minute walk distance; TLC: Total Lung Capacity.

Table 5. Within and between treatment changes in secondary endpoints from baseline to week 48 without imputation of missing values. Given are means with standard deviation at baseline, the absolute changes from baseline to week 48, and Hodges-Lehmann estimates for location shift (compared to pirfenidone as reference category) including asymptotic 95% confidence intervals and two-sided P values from Wilcoxon Test. Note also, that TLC and FEV1 have not been pre-specified and were considered in post-hoc analyses.

	Baseline				Within Treatment Change Baseline to Week 48				Between Treatment Change Baseline to Week 48	
	N	pirfenidone (mean±SD)	N	placebo (mean±SD)	N	pirfenidone (mean±SD)	N	placebo (mean±SD)	Diff. betw. Treatments (95% CI) ^{HL}	P $_{WILCOX}$
FVC (ml)	64	2332.5 (±798.9)	63	2123.0 (±715.7)	35	-36.6 (±281.5)	32	-114.4 (±225.3)	-80.0 (-210.0; 40.0)	0.21
DLco (mmol/kPa/min)	64	3.4 (±1.4)	63	3.2 (±1.2)	32	-0.1 (±1.0)	26	-0.4 (±0.6)	-0.4 (-0.7; -0.1)	0.02
TLC (l)	64	4.1 (±1.2)	63	4.0 (±1.0)	35	-0.1 (±0.5)	32	-0.3 (±0.4)	-0.2 (-0.4; 0.0)	0.09
FEV1 (ml)	64	2004.2 (±636.2)	63	1761.7 (±552.2)	35	-76.9 (±259.3)	32	-103.1 (±182.1)	-50.0 (-140.0; 50.0)	0.27
6MWD (m)	64	357.7 (±99.2)	63	345.2 (±110.0)	33	-2.7 (±74.2)	30	-34.1 (±91.0)	-28.0 (-75.0; 15.0)	0.15

^{HL} Hodges-Lehmann Estimates
^{WILCOX} Wilcoxon Test (two-sided)
* FVC (% pred.) with deaths ranked worst in predefined imputation method

Table 6. Assessment of the St. George's Respiratory Questionnaire (SGRQ). Given are within and between treatment changes in SGRQ scores from baseline to week 48 with Hodges-Lehmann estimates for location shift and two-sided P values from Wilcoxon Test.

	Baseline				Within Treatment Change Baseline to Week 48				Between Treatment Change Baseline to Week 48	
	N	pirfenidone (mean±SD)	N	placebo (mean±SD)	N	pirfenidone (mean±SD)	N	placebo (mean±SD)	Diff. betw. Treatments (95% CI) ^{HL}	P $_{WILCOX}$
Total score	53	50.9 (±16.7)	55	54.7 (±14.5)	23	3.2 (±11.8)	21	5.4 (±13.5)	3.30 (-4.1; 10.7)	0.33
Symptoms	57	64.6 (±21.4)	60	63.0 (±21.3)	29	-3.6 (±15.0)	28	3.2 (±21.1)	4.29 (-3.6; 12.1)	0.32
Activity	57	65.5 (±19.6)	56	72.2 (±16.7)	28	3.1 (±14.7)	23	9.9 (±11.9)	6.68 (-0.6; 13.9)	0.09
Impacts	58	39.7 (±18.8)	58	41.8 (±16.9)	31	5.1 (±14.8)	23	3.8 (±17.6)	0.45 (-7.4; 8.3)	0.75

^{HL} Hodges-Lehmann Estimates
^{WILCOX} Wilcoxon Test (two-sided)

20.2 Safety results

Adverse events were equally distributed between pirfenidone and placebo patients (**Table 7**). Gastrointestinal side effects (nausea, vomiting, dyspepsia, decreased appetite, and weight loss) were slightly more frequent with pirfenidone, while dyspnea and respiratory tract infections occurred slightly less frequently in the pirfenidone arm (**Table 7**).

Table 7. Incidence of Adverse Events (AEs; reported are only AEs that occurred in 5% of all patients at least).

Preferred Term*	**placebo (N=63) Grade 1-2** n (%)	**Grade 3-4** n (%)	**Grade 5** n (%)	**Pirfenidone (N=64) Grade 1-2** n (%)	**Grade 3-4** n (%)	**Grade 5** n (%)	**Total (N=127) Grade 1-5** n (%)
Nausea	9 (14.3)	2 (3.2)		18 (28.1)	2 (3.1)		31 (24.4)
Nasopharyngitis	14 (22.2)			16 (25)			30 (23.6)
Diarrhoea	10 (15.9)			11 (17.2) 1 (1.6)			22 (17.3)
Fatigue	10 (15.9)			10 (15.6)			20 (15.7)
Dyspnoea	10 (15.9)	1 (1.6)		6 (9.4)	1 (1.6)		18 (14.2)
Headache	6 (9.5)			10 (15.6)			16 (12.6)
Cough	6 (9.5)			9 (14.1)			15 (11.8)
Abdominal pain upper	7 (11.1)			7 (10.9)			14 (11)
Dizziness	6 (9.5)			8 (12.5)			14 (11)
Rash	4 (6.3)			7 (10.9)			11 (8.7)
Decreased appetite	2 (3.2)			9 (14.1)			11 (8.7)
Vomiting	4 (6.3)			6 (9.4)			10 (7.9)
Respiratory tract infection	8 (12.7)			2 (3.1)			10 (7.9)
Arthralgia	2 (3.2)			6 (9.4)			8 (6.3)
Dyspepsia	2 (3.2)			6 (9.4)			8 (6.3)
Weight decreased	3 (4.8)			4 (6.3)			7 (5.5)

*All SAEs are listed according to the Medical Dictionary for Regulatory Activities, version 22.1

Serious adverse events occurred more frequently in the placebo arm (58.7%) as compared to pirfenidone (37.5%), with respiratory tract infections (10 vs. 5), disease worsening (7 vs. 2), cardiac disorders (5 vs. 1) and death (4 vs. 1) being more frequent in the placebo arm (**Table 8 and 9**).

Table 8: **Incidence of serious adverse events (SAEs) after aggregation on the level of System Organ Class.** For a full listing of preferred terms, see Table 9.

System Organ Class	**Placebo (n=63) Pts with SAE** *(n, %)* **35 (58.7)**	**Pirfenidone (n=64) Pts with SAE** *(n, %)* **26 (37.5)**	**Count of SAEs** *(n)* **64**	**Total (n=127) Pts with SAE** *(n, %)* **61 (48.0)**
Infections and infestations	10 (16.4)	5 (8.2)	15	15 (24.6)
General disorders and administration site conditions	7 (11.1)	2 (3.2)	10	9 (7.2)
Respiratory, thoracic and mediastinal disorders	4 (6.4)	4 (6.4)	9	8 (4.7)
Surgical and medical procedures	2 (3.2)	4 (6.4)	7	6 (4.8)
Cardiac disorders	5 (8.0)	1 (1.6)	6	6 (4.8)
Neoplasms benign, malignant, and unspecified (w. cysts/polyps)	3 (4.8)	2 (3.2)	5	5 (4.0)
Injury, poisoning and procedural complications	2 (3.2)	1 (1.6)	3	3 (2.4)
Investigations	1 (1.6)	1 (1.6)	2	2 (1.6)
Nervous system disorders	0 (0)	2 (3.2)	2	2 (1.6)

Musculoskeletal and connective tissue disorders	0 (0)	2 (3.2)	2	2 (1.6)
Renal and urinary disorders	1 (1.6)	1 (1.6)	2	2 (1.6)
Gastrointestinal disorders	0 (0)	1 (1.6)	1	1 (0.8)

**All SAEs are listed according to the Medical Dictionary for Regulatory Activities, version 22.1*

Of the total of 64 SAEs, 5 cases had a fatal outcome. However, none of the SAEs with a fatal outcome had a causal relationship with the study medication. The case narratives of the SAEs with fatalities are presented in detail below:

Case - 1)
Initial information for this serious adverse event (SAE-No.: **DE-KKSMR-20160019**) was received on 19.05.2016 from an investigator regarding a 59 year old male patient (Patient-No.: **06001**) who experienced "**Nausea, diarrhea**" while receiving a blinded investigational medicinal product (Pirfenidone vs. Placebo) for Non-IPF Lung Fibrosis. According to MedDRA-coding the preferred term (PT) of this event is "Nausea". The serious criterion of this case is "new in-patient hospitalisation". The patient was enrolled into the Phase II KKS-206 protocol at trial site 06 (Hannover), Germany.
MEDICAL HISTORY:
The patient has a medical history of of a common cold, which started on 24.04.2016 (5 days before the first administration of Pirfenidone vs. Placebo).
CONCOMITANT MEDICATION:
- CellCept, daily dose 500 mg, tablet, oral, started on 12.10.2015, indicated for exogen allergic alveolitis (chronic hypersensitivity pneumonitis).
- Pantoprazole, daily dose unknown, tablet, oral, indicated for prophylaxis of gastroesophageal reflux
STUDY TREATMENT:
The patient started study treatment as follows:
Investigational medicinal product (IMP): Blinded IMP (Pirfenidone vs. Placebo)
- Start date: 29.04.2016; - Route: oral; - Form: Capsules; - Dose per administration at the time of the SAE report: 801 mg; - Frequency: 1-1-1; - Daily dose: 2403 mg; - Date of last dose prior to SAE: 16.05.2015
EVENT DETAILS:
This 59 years old male patient started study medication (Pirfenidone vs. Placebo) at a daily dose of 801 mg on 29.04.2016. According to the dose escalation schedule he has reached the full maintenance daily dose of 2403 mg on 13.05.2016. At this time he developed increasing gastrointestinal problems immediately. The patient went to his local treating lung specialist and was hospitalized there on 17.05.2016. The trial center and investigator was informed by the patient's spouse. The administration of the blinded IMP (Pirfenidone vs. Placebo) was reduced on 16.05.2016 and was stopped on 17.05.2016 because of the gastrointestinal disorder.
Follow-UP- information received on 23.05.2016. The investigator reported that the pre-existing respiratory infection worsened on 17.05.2016. Microbiological testing didn't reveal any infectants. The respiratory infection was treated with antibiotics. Laboratory investigations on 17.05.2016 and 18.05.2016 revealed an increase of the inflammatory parameters and an increased total bilirubin but normal values for AST and ALT. During hospitalization the patient's condition deteriorated and he died in the treating hospital on 21.05.2016 due to a global respiratory insufficiency. The medical term of the serious adverse event was changed by the investigator to "**Global respiratory insufficiency**" and the serious criterion has been changed to "results in death".

Case - 2)
Initial information for this SAE report (SAE-No.: **DE-KKSMR-20160065**) was received on 14.12.2016 from an investigator regarding a 64 year old male patient (Patient-No.: **10001**, trial site 10, Germany) who experienced "**Disc surgery**" while receiving a blinded investigational medicinal product (Pirfenidone vs. Placebo) for Non-IPF Lung Fibrosis. According to MedDRA-coding the preferred term (PT) of this event is "Intervertebral disc operation". The serious criterion of this case is "new in-patient hospitalisation". The patient was enrolled into the Phase II KKS-206 protocol, a phase II randomized, double-blind, placebo controlled, multicenter trial, exploring efficacy and safety of oral Pirfenidone for progressive Non-IPF Lung Fibrosis. The treatment allocation of the subject was not unblinded.
MEDICAL HISTORY:
The patient's past medical history consisted of disc surgery on 16.06.2016. Concomitant medications include Diclofenac on demand.

STUDY TREATMENT:
The patient started study treatment as follows: Investigational medicinal product (IMP): Blinded IMP (Pirfenidone vs. Placebo) - Start date: 04.07.2016;- Route: oral; - Form: Capsules; - Dose per administration at the time of the SAE report: 801 mg; - Frequency: 1-1-1; - Daily dose: 2403 mg; - Date of last dose prior to SAE: 13.12.2016
EVENT DETAILS:
This 64 years old male patient was hospitalised on 13.12.2016 and underwent disc surgery. On 15.12.2016 and 16.12.2016 the investigator reported that the reason for disc surgery was a disc prolapse. The disc surgery was planned. On 19.12.2016 the investigator stated that the disc surgery was planned after enrollment into the clinical trial. On 20.12.2016 the investigator explained that the disc prolapse developed before enrollment into the clinical trial and worsened during study treatment. Because of the worsening of disc prolapse during study treatment a disc surgery was performed on 13.12.2016. The investigator stated that the worsening of the disc prolapse exists since October 2016. On 22.12.2016 the investigator changed the medical term of the event from "disc surgery" into "worsening of disc prolapse". According to MedDRA-coding the preferred term (PT) of this event is "intervertebral disc protrusion".
Follow-Up information (SAE Follow-Up No.1) received on 06.02.2017. The investigator reported that the patient developed "**Inflammation of wound**" after disc surgery. According to investigator, the patient died due to sepsis on 23.12.2016. On 09.02.2017 the investigator stated, that the severity of the serious adverse event should be corrected from CTCAE-Grade 5 to CTCAE-Grade 3.

Case - 3)
This SAE report (SAE-No.: **DE-KKSMR-20170010**) was received on 17.02.2017 from an investigator regarding a 59 year old male patient (Patient-No.: **09003**, trial site 09, Germany) who died due to "**Myocardial infarction**" while receiving a blinded investigational medicinal product (Pirfenidone vs. Placebo) for Non-IPF Lung Fibrosis. The patient was enrolled into the Phase II KKS-206 protocol, a phase II randomized, double-blind, placebo controlled, multicenter trial, exploring efficacy and safety of oral Pirfenidone for progressive Non-IPF Lung Fibrosis. The treatment allocation of the subject was not unblinded.
MEDICAL HISTORY:
The medical history includes respiratory insufficiency due to lung fibrosis, arterial hypertension, allergic vasculitis (personal anamnesis), radial fracture and fracture of the patella. No concomitant medication or past drugs were reported.
STUDY TREATMENT:
The patient started study treatment as follows: Investigational medicinal product (IMP): Blinded IMP (Pirfenidone vs. Placebo); - Start date: 31.05.2016; - Route: oral; - Form: Capsules; - Dose per administration at the time of the SAE report: 801 mg; - Frequency: 1-1-1; - Daily dose: 2403
EVENT DETAILS:
Initial information received on 17.02.2017. The investigator explained that the trial center had a phone call from the patient's wife on 16.02.2017. She reported that her husband (Patient 09003) was admitted to hospital in Riesa (Sachsen) due to worsened dyspnea on 16.02.2017. The patient died shortly after hospitalization, probably due to myocardial infarction or right heart insufficiency. No additional information was available at the time of the initial SAE report.
Additional information received on 30.03.2017. According to the report of the treating hospital the patient was hospitalized on 14.02.2017 for cardiological diagnostics due to thoracic complaints (left side) since two weeks. ECG and laboratory investigations revealed an acute coronary syndrome with NSTEMI and elevated heart enzymes. The patient was transferred to the intensive care unit. During hospitalization the patient had several episodes of cardiac arrest. He was reanimated, intubated and mechanical ventilated. The event was treated with catecholamines and lysis therapy. On 16.02.2017 the patient had another episode of cardiac arrest and died due to acute myocardial infarction.
Additional information received on 12.05.2017. The previously reported event "probably myocardial infarction or right heart insufficiency" was amended to "myocardial infarction". The previously reported event seriousness was amended to "results in death". The previously

reported possible cause of the event "NISP" was amended to "coronary artery disease, possibly a consequence of arterial hypertension". The date of event onset was amended to 14-Feb-2017. The investigator stated that no autopsy was performed and he reported that the event was treated with lysis therapy and stent implantation.

Case - 4)
This clinical case (SAE-No.: **DE-KKSMR-20170034**) was received on 02.05.2017 from an investigator regarding a 69 year old male patient (Patient-No.: **05010**, trial site 05, Germany) who experienced "**Infectious pneumonia**" while receiving a blinded investigational medicinal product (Pirfenidone vs. Placebo) for Non-IPF Lung Fibrosis. The patient was enrolled into the Phase II KKS-206 protocol, a phase II randomized, double-blind, placebo controlled, multicenter trial, exploring efficacy and safety of oral Pirfenidone for progressive Non-IPF Lung Fibrosis. The treatment allocation of the subject was not unblinded.
MEDICAL HISTORY:
The patient's medical history included coronary artery disease (start date unknown), arterial hypertension (start date unknown), aortic valve implantation (unknown date of implantation), implanted DDD Pacemaker (unknown date of implantation). Concomitant medications included ASS (daily dose 100 mg), Simvastatin (daily dose 20 mg), Ramipril (daily dose 10 mg), Torasemid (daily dose 10 mg), Amlodipin (daily dose 5 mg), Metoprolol (daily dose 47,5 mg), and Prednisolon (daily dose 7,5 mg).
STUDY TREATMENT:
The patient started study treatment as follows: Investigational medicinal product: Blinded IMP (Pirfenidone vs. Placebo) - Start date: 03.04.2017;- Route: oral;- Form: Capsules;- Dose per administration at the time of the SAE report: 801 mg;- Frequency: 1-1-1;- Daily dose: 2403 mg;- Date of last dose prior to SAE: 29.04.2017
The blinded IMP (Pirfenidone vs. Placebo) was temporarily stopped on 30.04.2017 (morning and noon) and restarted in the evening of 30.04.2017.
EVENT DETAILS:
Initial information received on 02.05.2017. During participation in the above named clinical trial this 69 year old male patient suffered from progressive exhaustion, fatigue and exercise capacity since 28.04.2017. No significant increase in cough or sputum production was detected. On 30.04.2014 the patient was admitted to hospital due to progressive symptoms. Due to elevated inflammatory signs antibiotic therapy (Piperacillin + Tazobactam 4 g + 0,5 g i.v, 3-times per day) and systemic steroid therapy (Prednisolone 250 mg i.v., once daily for three days) was started on 30.04.2017. No additional information was available at the time of the initial SAE report. The patient did not recover from the event yet.
Follow-up information #1 received 0n 09.05.2017. Patient was treated for an exacerbation of NSIP in University hospital HH-Eppendorf. After initial systemic steroid boost therapy and clinical stabilisation on 08.05. a dramatic and rapid change of the clinical status happened. Due to cardiac arrest, life support was performed. Clinical deterioration was mainly due to pre-existing cardiac insufficiency and coronary artery disease. The patient did not recover from the event yet.
Follow-up information #2 received on 11.05.2017. During participation in the above named clinical trial this 69 year old male patient experienced an **acute myocardial infarction** with acute stenosis of the main coronary artery. Consecutively patient got cardiopulmonary instable and was reanimated for 45 minutes. The event happened while being in hospital and despite intensive care treatment the patient’s life could not be saved. The patient died on 10.05.2017.

Case – 5)
This SAE report (SAE-No.: **DE-KKSMR-20170066**) was received on 25.09.2017 from an investigator regarding a 58 year old male patient (Patient-No.: **07009**, trial site 07, Germany) who experienced "**Acute exacerbation of pulmonary fibrosis**" while receiving a blinded investigational medicinal product (Pirfenidone vs. Placebo) for Non-IPF Lung Fibrosis. According to MedDRA-coding the preferred term (PT) of this event is "Pulmonary fibrosis". The serious criterion of this case is "new inpatient hospitalisation". The patient was enrolled into the Phase II KKS-206 protocol, a phase II randomized, double-blind, placebo controlled,

multicenter trial, exploring efficacy and safety of oral Pirfenidone for progressive Non-IPF Lung Fibrosis. The treatment allocation of the subject was not unblinded.
MEDICAL HISTORY:
The patient's past medical history consists of hypertonia, adipositas, gastro-oesophageal reflux, polyarthritis, coronary three vessel disease and sleep apnoea. Concomitant medications was ASS100mg, Metoprolol 95 mg, and Pantoprazol 20mg.
STUDY TREATMENT:
The patient started study treatment as follows: Investigational medicinal product (IMP): Blinded IMP (Pirfenidone vs. Placebo) - Start date: not reported; - Route: oral; - Form: Capsules; - Dose per administration at the time of the SAE report: 801 mg (3x267mg/capsule); - Frequency: 1-1-1; - Daily dose: 2403 mg; - Date of last dose prior to SAE: 21.09.2017; The administration of the blinded IMP (Pirfenidone vs. Placebo) has not altered.
EVENT DETAILS:
Initial information received on 25.09.2017. During participation in the above named clinical trial this 58 years old male patient was hospitalised on 21.09.2017 due to worsening of shortness of breath from previous weekend (16./17. SEP 2017). The Patient than was admitted to the hospital of trial center 07 on 24.09.2107 for therapy evaluation. Therapy with tazobac and Solu-Medrol i.v. The patient has not yet recovered from the event.
Follow-up information received on 23.10.2017. "Due to acute exacerbation of lung fibrosis the patient died on 29-Sep-2017."

Table 9. Incidence of Serious Adverse Events (SAEs).

System Organ Class	**Preferred Term***	**placebo (N=63) Pts with SAE** n (%) **35 (58.7)**	**Pirfenidone (N=64) Pts with SAE** n (%) **26 (37.5)**	**Total (N=127) Count of SAEs** n **64**	**Pts with SAE** n (%) **61 (48.0)**
Infections and infestations	**Pneumonia**	6 (9.5)	1 (1.6)	7	7 (5.5)
	Atypical pneumonia		1 (1.6)	1	1 (0.8)
	Bronchitis	1 (1.6)		1	1 (0.8)
	Diverticulitis	1 (1.6)		1	1 (0.8)
	Infection	1 (1.6)		1	1 (0.8)
	Influenza	1 (1.6)		1	1 (0.8)
	Nosocomial infection		1 (1.6)	1	1 (0.8)
	Respiratory tract infection		1 (1.6)	1	1 (0.8)
	Upper respiratory tract infection		1 (1.6)	1	1 (0.8)
General disorders and administration site conditions	**Condition aggravated**	6 (9.5)	1 (1.6)	8	7 (5.5)
	Disease progression	1 (1.6)		1	1 (0.8)
	General physical health deterioration		1 (1.6)	1	1 (0.8)

Respiratory, thoracic and mediastinal disorders	**Dyspnoea**	2 (3.2)	2 (3.1)	5	4 (3.1)
	Interstitial lung disease		1 (1.6)	1	1 (0.8)
	Pneumothorax		1 (1.6)	1	1 (0.8)
	Pulmonary fibrosis	1 (1.6)		1	1 (0.8)
	Respiratory failure	1 (1.6)		1	1 (0.8)
Surgical and medical procedures	**Chemotherapy**	1 (1.6)		2	1 (0.8)
	Lung transplant	1 (1.6)	1 (1.6)	2	2 (1.6)
	Knee operation		1 (1.6)	1	1 (0.8)
	Rehabilitation therapy		1 (1.6)	1	1 (0.8)
	Transcatheter aortic valve implantation		1 (1.6)	1	1 (0.8)
Cardiac disorders	**Myocardial infarction**	3 (4.8)		3	3 (2.4)
	Acute coronary syndrome		1 (1.6)	1	1 (0.8)
	Angina pectoris	1 (1.6)		1	1 (0.8)
	Cardiac failure	1 (1.6)		1	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Lung neoplasm malignant**	2 (3.2)		2	2 (1.6)
	Adenocarcinoma		1 (1.6)	1	1 (0.8)
	Metastases to lymph nodes		1 (1.6)	1	1 (0.8)
	Oesophageal carcinoma stage 0	1 (1.6)		1	1 (0.8)
Injury, poisoning and procedural complications	**Femoral neck fracture**	1 (1.6)	1 (1.6)	2	2 (1.6)
	Cervical vertebral fracture	1 (1.6)		1	1 (0.8)
Investigations	**Arteriogram coronary**		1 (1.6)	1	1 (0.8)
	Inflammatory marker increased	1 (1.6)		1	1 (0.8)
Nervous system disorders	**Cerebral ischaemia**		1 (1.6)	1	1 (0.8)
	Cerebrovascular accident		1 (1.6)	1	1 (0.8)

Musculoskeletal and connective tissue disorders	**Intervertebral disc protrusion**		1 (1.6)	1	1 (0.8)
	Musculoskeletal pain		1 (1.6)	1	1 (0.8)
Renal and urinary disorders	**Kidney congestion**		1 (1.6)	1	1 (0.8)
	Renal failure	1 (1.6)		1	1 (0.8)
Gastrointestinal disorders	**Ileus**		1 (1.6)	1	1 (0.8)

*All SAEs are listed according to the Medical Dictionary for Regulatory Activities, version 22.1

Altogether, pirfenidone showed a favorable safety profile, similar to that observed in IPF, despite ongoing anti-inflammatory therapy in the population under study. No new or unexpected adverse events were observed.

Conclusion:

Our data suggests that in interstitial lung disease patients who deteriorate despite conventional therapy addition of pirfenidone may attenuate disease progression.

21 Date of report

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