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Early View

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No relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone

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Abstract

Nintedanib and pirfenidone are approved treatments for idiopathic pulmonary fibrosis (IPF). This open-label, two-group trial investigated the pharmacokinetic drug-drug interaction between these two drugs in patients with IPF.

Subjects not treated with antifibrotics at screening (Group 1, n=20) received a single nintedanib dose (150 mg) followed by pirfenidone (titrated to 801 mg thrice-daily) for 3 weeks, with a further single nintedanib dose (150 mg) on the last day (day 23). Subjects treated with pirfenidone at screening (Group 2, n=17) continued to receive pirfenidone alone (801 mg thrice-daily) for 7 days, then co-administered with nintedanib (150 mg twice-daily) for a further 7 days, before single doses of both treatments on day 16.

In Group 1, adjusted geometric mean (gMean) ratios (with/without pirfenidone) were 88.6% and 80.6% for nintedanib area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}), respectively. In Group 2, gMean ratios (with/without nintedanib) were 97.2% and 99.5% for pirfenidone AUC and C_{max}, respectively. For all parameters, the 90% confidence intervals included 100%, suggesting similar exposure for administration alone and when co-administered. Both treatments were well tolerated.

These data indicate there is no relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when co-administered in IPF patients.

Lay summary

Nintedanib and pirfenidone are two drugs approved for patients with idiopathic pulmonary fibrosis (IPF). Since nintedanib and pirfenidone act in different ways, combining them is a potentially attractive treatment option. Our study sought to confirm that these drugs do not adversely affect the concentration of each other when given together in patients with IPF. Our analysis confirmed that the concentration of each drug does not change when they are given in combination. Further studies will be required to evaluate the clinical benefit of using these drugs in combination.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing form of interstitial lung disease of unknown aetiology resulting in progressive worsening of dyspnoea and lung function [1,2]. IPF has a poor prognosis and, until recently, no treatment for IPF was proven to be effective or approved for clinical use [1,3].

In the last few years, two novel antifibrotic treatments, nintedanib and pirfenidone, have received regulatory approval in several countries after pivotal trials showed each was effective in slowing disease progression in patients with IPF [4,5]. Both treatments have subsequently received positive recommendations in international evidence-based guidelines [6].Given that nintedanib and pirfenidone are both effective at slowing disease progression, but neither halts nor reverses this ultimately fatal disease, there remains an unmet need for further therapeutic development [7].

With the availability of two antifibrotic drugs, and the existence of multiple signalling pathways involved in the pathogenesis of IPF, it is anticipated that combination therapy is likely to be a key focus of future IPF treatment development, similar to the management of several other chronic progressive diseases such as pulmonary arterial hypertension [2,7-11]. Although pirfenidone's mechanism of action has not been fully elucidated, it is thought to act upon several targets including glioma-associated oncogene homolog 2–mediated transforming growth factor-β–triggered events [12-14]. Conversely, nintedanib acts on platelet-derived, fibroblast and vascular growth factor receptor tyrosine kinases to inhibit intracellular signalling [15,16]. This suggests that therapy with both compounds may offer additive or synergistic effects, resulting in greater clinical benefits than either treatment alone [7,9]. However, there is also some overlap in the tolerability profiles of pirfenidone and nintedanib in patients with IPF in terms of increases in liver enzymes and gastrointestinal events [5,17,18]. As combination therapy is a potential option for clinicians and patients, it follows that data on potential drug-drug interactions and the overall benefit/risk profile of

combined nintedanib and pirfenidone treatment are urgently required in order to inform clinical decision-making [7].

Pirfenidone and nintedanib have different metabolic profiles. Pirfenidone is metabolised by various cytochrome P450 (CYP) enzymes, primarily CYP1A2 with minor contributions from CYP2C9, CYP2C19, CYP2D6 and CYP2E1, and predominantly excreted via the urine as the metabolite 5-carboxy-pirfenidone [19,20]. Co-administration of the antidepressant fluvoxamine, a strong inhibitor of CYP1A2 and other CYP isoenzymes, has been associated with a statistically significant increase in pirfenidone exposure, and pirfenidone is contraindicated in patients with concomitant use of fluvoxamine [19,20]. In contrast, the metabolism of nintedanib is via hydrolytic ester cleavage, resulting in the formation of the free acid moiety that is subsequently glucuronidated and excreted in the faeces [21]. Nintedanib has a low potential for drug-drug interactions via CYP enzymes [22].

At the time of planning this trial, nintedanib and pirfenidone combination treatment had only been tested in a Phase II trial in Japanese patients with IPF [18]. This was a double-blind, randomised, placebo-controlled trial, in which 50 patients were treated with nintedanib on top of standard medical care with stratification according to pirfenidone use. The results indicated a trend towards lower nintedanib exposure in the presence of steady-state pirfenidone and raised the question of a potential pharmacokinetic drug-drug interaction. However, solid conclusions from the study could not be drawn as the study design served a different purpose, exposure to nintedanib could only be compared between-patient groups (inter-individually), and the number of evaluable pharmacokinetic observations (<12 per treatment group) was not deemed sufficient to assess the pharmacokinetic drug-drug interaction.

To provide further clarification, this study was designed to investigate the pharmacokinetic drug-drug interaction of nintedanib and pirfenidone when co-administered in individuals with

IPF. The primary objective was to investigate the effects of steady-state pirfenidone on the pharmacokinetics of a single nintedanib dose, and to investigate the effect of steady-state nintedanib on the pharmacokinetics of pirfenidone at steady-state in patients with IPF. A secondary objective was to evaluate the safety of combination treatment.

Material and methods

This was an open-label, multi-dose, two-group trial in individuals with IPF (EudraCT 2015-000732-15; NCT02606877). Subjects were not randomised. Eligible individuals who were not on nintedanib or pirfenidone treatment at study entry were assigned to Group 1, whereas those currently receiving full-dose pirfenidone entered Group 2. Each group had a fixed-sequence design (**Fig. 1**). The study protocol was approved by an independent ethics committee (London-Surrey Borders Research Ethics Committee, London, UK) and competent authority (Medicines and Healthcare Products Regulatory Agency, London, UK). The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all subjects before study entry. The trial was undertaken at 9 hospitals in the UK between May 2016 and March 2017.

Subjects

Subjects eligible for inclusion were men and women aged ≥40 years, with IPF diagnosed according to current international guidelines [1] and a chest high-resolution computed tomography scan performed prior to screening. Suitable individuals were required to have a forced vital capacity ≥50% of predicted and diffusing capacity of the lung for carbon monoxide 30-79% of predicted. Key exclusion criteria are included: elevated liver enzymes (>1.5 times the upper limit of the normal range); increased bleeding risk (e.g. requiring therapeutic anticoagulation or high-dose antiplatelet therapy); current smoking; history of a thrombotic event within 12 months of screening; and severe renal impairment. Individuals

who had previously received nintedanib in the past 2 weeks, had previous treatment with pirfenidone in the past 3 months (Group 1 only), or had previously discontinued nintedanib or pirfenidone due to adverse events were excluded. For full exclusion criteria see the online supplementary material.

Study design and treatments

Fig. 1 shows the study design and treatments received in the two groups. Group 1 received a single dose of nintedanib 150 mg on day 1, pirfenidone (uptitrated from 267 mg three times daily [tid] to 801 mg tid) from days 2 to 23, with a single dose of nintedanib 150 mg on the last day (day 23). Group 2 received pirfenidone alone (801 mg tid) for 7 consecutive days (from day 1 to 8) and then co-administered with nintedanib 150 mg twice-daily [bid] for another 7 consecutive days (from day 9 to 15); with single doses of pirfenidone 801 mg and nintedanib 150 mg on day 16. A safety follow-up visit was arranged at least 28 days after last drug intake.

Nintedanib was supplied as 150 mg soft gelatine capsules (Ofev®, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany), and pirfenidone as 267 mg hard capsules (Esbriet®, Roche Pharma AG, Grenzach-Wyhlen, Germany). In both groups, oral doses of nintedanib and pirfenidone were administered with food. Treatment interruption and dose reductions were permitted for management of adverse events.

Pharmacokinetic evaluation

In Group 1, venous blood samples for measurement of nintedanib and pirfenidone plasma concentrations were collected in potassium-EDTA-anticoagulant tubes up to 24 h after dosing on days 1 (nintedanib only) and 23 (see **Fig. 1**). In Group 2, blood samples for measurement of nintedanib and pirfenidone plasma concentrations were collected up to 6 h after dosing on days 8 (pirfenidone only) and 16. Plasma concentrations of nintedanib and pirfenidone (in the form of their free bases) were analysed using a validated liquid

chromatography-mass spectrometry assay (Nuvisan GmbH & Co. KG, Neu-Ulm, Germany). The calibration curves for nintedanib and pirfenidone plasma in undiluted samples covered ranges of 0.05-50.0 $ng \cdot mL^{-1}$ and 100-50,000 $ng \cdot mL^{-1}$, respectively.

Safety evaluation

The safety of nintedanib and pirfenidone was assessed by 12-lead ECG, vital signs (pulse, blood pressure), spirometry, routine laboratory assessments, physical examination, adverse event reporting and assessment of tolerability by the investigator. For details see the online supplementary material.

Statistical and pharmacokinetic analysis

The sample size determination was not based on a power calculation. A sample size of at least 12 subjects with both evaluable pharmacokinetic assessments in each Group was judged adequate to achieve the aims of this exploratory trial, in agreement with regulatory guidance [23]. Accounting for possible dropouts it was planned to recruit up to 34 subjects with the aim of entering 16 subjects in Group 1 and 18 in Group 2.

Standard non-compartmental methods were used to calculate plasma pharmacokinetic parameters. Area under the plasma concentration-time curve was calculated using the log-linear trapezoidal rule from time zero (pre-dose) up to the time of the last quantifiable concentration ($AUC_{0\text{-}tz}$) and extrapolated to infinity ($AUC_{0\text{-}\infty}$).

The aim of the study was to estimate 1) the relative bioavailability of nintedanib when administered alone or co-administered with pirfenidone in Group 1, and 2) the relative bioavailability of pirfenidone when administered alone or co-administered with nintedanib in Group 2. Pharmacokinetics were assessed using an intra-individual comparison, whereby treatment comparisons were made within subjects rather than between subjects, avoiding inter-subject variability [24]. The primary endpoints in Group 1 were nintedanib $AUC_{0\text{-}tz}$ and

maximum plasma concentration (C_{max}); $AUC_{0-\infty}$ was a secondary endpoint. In Group 2, the primary endpoints were steady-state pirfenidone AUC over a dosing interval τ ($AUC_{\tau,ss}$) and C_{max} at steady-state ($C_{max,ss}$). The natural log-transformed AUC and C_{max} values for nintedanib and pirfenidone were compared between groups using an analysis of variance (ANOVA) model. The primary analyses compared test treatment (nintedanib and pirfenidone co-administered) and reference treatment (mono-treatment with either nintedanib or pirfenidone) using the ANOVA model to evaluate the effect of treatment (fixed effect) and subjects (random effect) as sources of variation. This meant that individuals who had pharmacokinetic data for test and/or reference periods were used for the test/reference ratio estimate. For the pairwise comparison between the groups, the difference between the expected means was estimated by the difference in the corresponding least square means (point estimate); the 90% two-sided confidence intervals (CI) based on the t-distribution were also computed. These values were then back-transformed to the original scale to provide the point estimate (geometric mean) and interval estimates for the ratio of test and reference group. The main focus of the study was to estimate the magnitude of effects; as such, no hypothesis was tested and no equivalence range was specified. Sensitivity analyses were conducted based on the ANOVA model with treatment and subjects as fixed effects. This meant that only subjects with evaluable data in both treatment periods (test and reference) were used for the test/reference ratio estimate and 90% CIs, although all observations were entered into the model.

Other parameters were presented as descriptive statistics (arithmetic and geometric means [gMean], standard deviation, and geometric coefficient of variation [gCV]). Non-compartmental analysis of plasma concentration-time data was performed using Phoenix WinNonlin® (Pharsight Corporation, Cary, NC, USA). Statistical analyses were performed using SAS® (SAS Institute Inc., Cary, NC, USA).

Results

Of 51 screened subjects, 37 were eligible and entered the trial (**Fig. 2**). Of these, 20 entered Group 1, and 17 entered Group 2 (**Table 1**). As expected, there were more males than females in the study and most individuals were white and older than 60 years. More than half of the subjects had previously smoked. In Groups 1 and 2, 18 (90.0%) and 15 (88.2%) of patients had ≥1 concomitant diagnosis at baseline, respectively. The majority of patients in Group 1 (90.0%) and Group 2 (100.0%) took at least 1 concomitant therapy on-treatment. Further details of concomitant diagnoses and treatments are given in the online supplementary material. All entered subjects were treated. In each group, 16 subjects completed trial medication and all of these completed a follow-up visit.

Pharmacokinetics of nintedanib

In Group 1, 3 subjects prematurely discontinued trial medication due to adverse events and 1 for other reasons. Data from 17 subjects were evaluable for pharmacokinetic analysis of the reference treatment, with 12 of these evaluable for pharmacokinetic analysis of the test group on day 23. The summarised pharmacokinetic parameters are given in **Table 2**.

In both treatment periods, absorption of nintedanib was relatively rapid, with C_{max} reaching a median of ~2 h after administration with and without pirfenidone. Following peak absorption, plasma concentrations of nintedanib declined moderately fast until ~6-10 h, followed by a slower terminal phase (data not shown). The gMean terminal half-life of nintedanib was unaffected by co-administration with pirfenidone. Inter-individual variability in exposure was moderate-to-high for C_{max} (gCV 65-103%) and moderate for AUC (gCV 59-70%) in both treatment periods.

A graphical representation of the individual and gMean values for the primary endpoints shows no clear trend when nintedanib was given alone or co-administered with pirfenidone (**Fig. 3**). Comparing the individual exposure estimates in the two treatment periods, two

subjects had a more pronounced decrease from reference to test, 3 showed a more pronounced increase from reference to test, and all other individuals showed comparable exposure estimates. Three subjects with the highest individual C_{max} values in the reference period had no value in the test period. These subjects did not appear to have any noteworthy demographic characteristics at baseline compared with other individuals.

The point estimates for adjusted gMean ratios of nintedanib exposure when co-administered with pirfenidone *versus* administration alone were 80.6%, 88.6% and 89.5% for C_{max}, $AUC_{0\text{-}tz}$, and $AUC_{0\text{-}\infty}$, respectively (**Table 2**). For all parameters, the 90% CIs included 100%, suggesting a similar exposure for administration alone and when co-administered with pirfenidone. The intra-individual variability was moderate-to-high (gCV 44-75%) which was reflected by the wide 90% CIs.

A sensitivity analysis that considered only the 12 subjects with evaluable pharmacokinetic data in both treatment periods showed point estimates for the gMean ratios of nintedanib exposure of 92.8%, 95.9% and 97.5% for C_{max}, $AUC_{0\text{-}tz}$, and $AUC_{0\text{-}\infty}$, respectively.

Pharmacokinetics of pirfenidone

In Group 2, one patient prematurely discontinued trial medication and one was not evaluable during the reference treatment period due to protocol non-compliance. Data from 15 subjects were included in the pharmacokinetic analysis of the reference treatment with 13 subjects included in the test group. The summarised pharmacokinetic parameters are given in **Table 3**.

Steady-state gMean plasma concentration-time profiles of pirfenidone after multiple dosing before and after concomitant multiple dosing with nintedanib were comparable between the treatment groups (data not shown). Pirfenidone plasma levels peaked at ~1 h and then declined rapidly and steadily throughout the dosing interval.

The extent of pirfenidone exposure as indicated by $C_{max,ss}$ and $AUC_{\tau,ss}$ was comparable whether pirfenidone was administered alone or in the presence of nintedanib. In line with this, no trend towards increased or decreased exposure could be delineated from the comparison of individual and gMean $C_{max,ss}$ or $AUC_{\tau,ss}$ values (**Fig. 4**).

The point estimates for adjusted gMean ratios of pirfenidone exposure when co-administered with nintedanib (both at steady-state) *versus* pirfenidone alone were 97.2% for $AUC_{\tau,ss}$ and 99.5% for $C_{max,ss}$ (**Table 3**). The corresponding 90% CIs covered 100% and were within the standard 80-125% bioequivalence acceptance range for $AUC_{\tau,ss}$ (88-108%) and for $C_{max,ss}$ (88-113%). Intra-individual variability was low (gCV values between 14.1% and 17.4%). A sensitivity analysis that considered only the 12 subjects with evaluable pharmacokinetic data in both groups showed similar results.

Safety

In the two groups, 29 (78.4%) subjects reported one or more adverse events (**Table 4**). The most common adverse events were diarrhoea, nausea, lower respiratory tract infections, vomiting, headache and dyspepsia. Diarrhoea was the most frequently reported adverse event in both groups (Group 1: 30.0%, Group 2: 23.5%). Nausea and vomiting were reported with a frequency >10% in each group. All reported adverse events were considered by the investigator to be mild or moderate apart from 2 cases of severe intensity in Group 1. One of these subjects treated with pirfenidone 267 mg threes time daily felt weak and giddy. The patient interrupted treatment at the time of the event and later permanently discontinued pirfenidone. Another subject treated with pirfenidone 267 mg three times daily reported a tooth infection of severe intensity. Neither of these two events was considered drug-related by the investigator and both subjects recovered from their events. All diarrhoea, nausea, and vomiting events were NCI-CTCAE grade 1. A total of 19 (51.4%) subjects had possible drug-related adverse events. Eight of these individuals experienced diarrhoea and 7 subjects had nausea. Dyspepsia, headache and fatigue were experienced by a further 4 subjects each,

and 3 individuals reported vomiting. Three subjects permanently discontinued pirfenidone treatment due to adverse events (diarrhoea: 2 subjects; vomiting: 1 subject; asthenia, 1 subject). No serious adverse events were reported.

Discussion

The approval of two novel antifibrotic drugs, pirfenidone and nintedanib, has transformed the management of IPF in recent years. As we search for further improvements in clinical outcomes in this patient population, nintedanib and pirfenidone combination therapy is an attractive therapeutic option to consider in view of their availability and differing mechanisms of action [7], but to date little is known about the potential for unanticipated drug-drug interactions or additive/synergistic efficacy or adverse events.

The results of the present study suggest that there is no relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone in patients with IPF. In the primary analysis of Group 1, gMean values of nintedanib exposure (based on $AUC_{0\text{-}tz}$ and C_{max}) decreased by 12–19% when nintedanib was co-administered with pirfenidone. However, the primary analysis used data from all 17 subjects with evaluable pharmacokinetic observations to estimate the gMean ratios, and included 5 individuals who had high exposure values in the reference treatment period (with no noteworthy demographic characteristics), but no value for the test treatment. The sensitivity analysis that only included data from the 12 subjects with evaluable pharmacokinetic observations in both treatment periods resulted in gMean ratios of total and peak exposure that were close to 100%. This suggests that the slight decrease in exposure of nintedanib observed in the primary analysis was primarily due to the unbalanced pharmacokinetic comparison combined with its known high inter-patient pharmacokinetic variability [25,26].

Visual inspection of the individual nintedanib exposure values ($AUC_{0\text{-}tz}$ and C_{max}) provides further support for a lack of a pharmacokinetic drug-drug interaction. There was no obvious

pattern for change in exposure between the test and reference treatments, and variability (both intra- and especially inter-individual) was high in the both groups. The pronounced inter-individual variability was also observed in other nintedanib studies [25,26], including a prior trial of Japanese patients with IPF [18]. In the study enrolling Japanese patients, the pharmacokinetic assessment, due to the parallel-group design, was hampered by the inter-patient variability and, thus, did not provide a definitive conclusion about the effect of pirfenidone co-treatment on nintedanib exposure.

In Group 2, pirfenidone exposure (based on $AUC_{\tau,ss}$ and $C_{max,ss}$) was similar whether pirfenidone was administered with or without steady-state nintedanib. The 90% CIs were within the standard 80–125% bioequivalence acceptance range and the sensitivity analysis supported the primary analysis findings. The results for pirfenidone were consistent with the results from the previously described trial in Japanese IPF patients [18].

Supportive information about the drug-drug interaction of nintedanib and pirfenidone in IPF patients has also recently been generated in the 12-week INJOURNEY trial. This trial focused on safety and tolerability, and only included sparse pharmacokinetic sampling [9]. Similar nintedanib trough plasma concentrations were observed when it was administered alone or with add-on pirfenidone.

Because the adverse reaction profiles of nintedanib and pirfenidone partially overlaps, especially in terms of gastrointestinal events and liver enzyme elevations [15,20], there is also a potential for additive adverse effects when combining both treatments. Nintedanib and pirfenidone were well tolerated in this study when administered alone and when co-administered. Most gastrointestinal events were of mild to moderate intensity and similarly distributed between the two treatment groups. Overall, 23 of 37 subjects (62.2%) across the two groups reported diarrhoea, nausea, or vomiting events (all of which were classified as NCI-CTCAE grade 1), which was similar to that reported in previous studies [9,18].

While the present data and previous studies [9,18] suggest that there is no relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when co-administered in patients with IPF, further research is recommended to address some of limitations of the existing studies. Firstly, it may be informative to examine the activity of pirfenidone's major metabolite 5-carboxy-pirfenidone, as available *in vitro* data suggest some pharmacologically relevant activity of this compound at concentrations in excess of peak plasma concentrations in IPF patients [20]. Secondly, this study investigated in Group 1 the effect of pirfenidone as the perpetrator drug at steady-state on the pharmacokinetics of nintedanib, the victim drug, after a single dose rather than at steady-state. However, as there was no clinically relevant drug-drug interaction in this 'worst case scenario', it is strongly assumed that this finding similarly applies to steady-state dosing of nintedanib (the victim drug), as supported by the pharmacokinetic findings from the INJOURNEY study [9]. Thirdly, although data on the long-term use of nintedanib and pirfenidone monotherapy in patients with IPF are available [27,28], there are currently only very limited data on the chronic use of combination therapy. A small Phase II study in 20 Japanese patients with IPF has reported successful long-term treatment with nintedanib and pirfenidone together; the mean (SD) duration of exposure in the extension was 27.0 (15.8) months and the safety and tolerability profile remained in line with the adverse event profiles for each drug, with no new safety signals identified [29]. In addition, concomitant treatment with nintedanib and pirfenidone for 12 weeks in the INJOURNEY trial was feasible with no new safety signals emerging [9]. However, no definite conclusions on the safety and tolerability of combination treatment can be drawn based on the small number of patients in these studies, and larger and longer trials investigating the long-term safety and tolerability of nintedanib given in addition to pirfenidone are required.

In conclusion, these data indicate that there is no relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when administered as combination therapy in patients with IPF. The plasma concentrations of the two drugs were similar when

administered alone or in combination. The safety results of this trial were also consistent with the known adverse event profiles of the individual drugs.

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Table 1 Baseline characteristics and demographics[#]

	Group 1 (n=20)	**Group 2 (n=17)**
Males	11 (55.0)	15 (88.2)
Age years	71.5 ± 7.8	68.3 ± 7.4
<65	4 (20.0)	4 (23.5)
≥65 to <75	11 (55.0)	11 (64.7)
≥75	5 (25.0)	2 (11.8)
BMI kg·m^{-2}	28.4 ± 4.5	28.0 ± 3.4
Race		
White	18 (90.0)	16 (94.1)
Asian	2 (10.0)	1 (5.9)
Time since IPF diagnosis, years		
≤1	17 (85.0)	4 (23.5)
>1 to ≤3	2 (10.0)	7 (41.2)
>3 to ≤5	1 (5.0)	3 (17.6)
>5	0	3 (17.6)
Smoking status		
Former	14 (70.0)	9 (52.9)
Never	6 (30.0)	8 (47.1)
D_{LCO}, % predicted[¶]	49.6 ± 10.2	43.3 ± 9.5

Data are presented as mean ± standard deviation or n (%). BMI: body mass index; D_{LCO}: diffusing capacity of the lung for carbon monoxide; IPF: idiopathic pulmonary fibrosis.

[#]: In treated population.

[¶]: Corrected for haemoglobin at baseline

Table 2 Pharmacokinetic parameters of nintedanib after single oral administration of 150 mg nintedanib alone (reference), and together with steady-state pirfenidone 801 mg tid (test)[#]

Parameter and unit	Nintedanib 150 mg		Adjusted[¶] gMean ratio[†], % (90% CI)	Intraindividual gCV [%]
	Alone (n=17) (reference)	+ pirfenidone 801 mg (n=12) (test)		
Primary endpoints				
AUC_{0-tz} $ng \cdot h \cdot mL^{-1}$	169.7	150.3	88.6 (65.4-120.0)	45.1
C_{max} $ng \cdot mL^{-1}$	28.6	23.0	80.6 (51.3-126.8)	74.6
Secondary endpoint				
$AUC_{0-\infty}$ $ng \cdot h \cdot mL^{-1}$	195.6	175.0	89.5 (66.3-120.7)	44.3
Other endpoints				
t_{max} h	2.0 (0.5-6.0)	2.5 (2.0-6.0)		
Half-life h	9.3 (22.8)	8.7 (30.0)		
Sensitivity analyses				
AUC_{0-tz} $ng \cdot h \cdot mL^{-1}$	169.7	162.7	95.9 (69.9-131.5)[§]	45.1
C_{max} $ng \cdot mL^{-1}$	28.6	26.5	92.8 (56.8-151.3)[§]	75.0
$AUC_{0-\infty}$ $ng \cdot h \cdot mL^{-1}$	195.6	190.7	97.5 (71.7-132.5)[§]	43.8

Data are presented as adjusted geometric mean (gMean), apart from half-life (presented as gMean [gCV%]) and t_{max} (presented as median [range]). AUC_{0-tz}: area under the plasma concentration-time curve from time 0 to time of the last quantifiable drug plasma concentration $AUC_{0-\infty}$: area under the concentration-time curve from time 0 extrapolated to infinity; C_{max} maximum observed plasma concentration; CI: confidence interval; CV: gCV [%]: geometric coefficient of variation (%); tid: three times daily; t_{max}: time to reach C_{max}

[#]: In pharmacokinetic population.

[¶]: gMean ratio adjusted for 'treatment' as a fixed effect. 'Subject' was considered as a random effect.

[†]: Ratio of test/reference.

[§]: gMean ratio adjusted for 'treatment' and 'subject' as fixed effects.

Table 3 Pharmacokinetic parameters of pirfenidone after multiple oral administration of 801 mg pirfenidone tid alone (reference), and together with steady-state nintedanib 150 mg bid (test)[#]

Parameter and unit	Pirfenidone 801 mg tid		Adjusted[¶] gMean ratio[†], % (90% CI)	Intraindividual gCV [%]
	Alone (n=15) (reference)	+ nintedanib 150 mg bid (n=13) (test)		
Primary endpoints				
$AUC_{\tau,ss}$ $ng \cdot h \cdot mL^{-1}$	40,200	39,000	97.2 (87.8-107.5)	14.1
$C_{max,ss}$ $ng \cdot mL^{-1}$	10,600	10,500	99.5 (87.9-112.6)	17.4
Other endpoints				
$t_{max,ss}$ h	1.00 (0.5-3.0)	1.00 (0.5-4.0)		
Sensitivity analysis				
$AUC_{\tau,ss}$ $ng \cdot h \cdot mL^{-1}$	40,500	38,500	95.2 (85.9-105.5)[§]	14.1
$C_{max,ss}$ $ng \cdot mL^{-1}$	10,700	10,400	97.2 (85.6-110.4)[§]	17.5

Data are presented as adjusted geometric mean (gMean) or median (range). $AUC_{\tau,ss}$: area under the plasma concentration-time curve over a dosing interval τ at steady-state; bid: twice daily; $C_{max,ss}$: maximum measured plasma concentration at steady-state; CI: confidence interval; gCV: geometric coefficient of variation; tid: three times daily; $t_{max,ss}$: time to reach $C_{max,ss}$

[#]: In pharmacokinetic population.

[¶]: gMean ratio adjusted for 'treatment' as a fixed effect. 'Subject' was considered as a random effect.

[†]: Ratio of test/reference.

[§]: gMean ratio adjusted for 'treatment' and 'subject' as fixed effects.

Table 4 Adverse events[#]

Category of event	**Group 1 (n=20)**	**Group 2 (n=17)**
Any adverse event (s)	14 (70.0)	15 (88.2)
Severe adverse events	2 (10.0)	0
Investigator defined drug-related adverse events	12 (60.0)	7 (41.2)
Adverse events leading to permanent dose reduction of pirfenidone	1 (5.0)	0
Adverse events leading to discontinuation of nintedanib	0	0
Adverse events leading to discontinuation of pirfenidone	3 (15.0)	0
Other significant adverse events	3 (15.0)	0
Serious adverse events[¶]	0	0
Adverse events of particular interest		
Diarrhoea[§]	6 (30.0)	4 (23.5)
Nausea[§]	5 (25.0)	3 (17.6)
Vomiting[§]	3 (15.0)	2 (11.8)
Bleeding	0	0

Data are presented as n (%) of subjects. CTCAE: Common Terminology Criteria for Adverse Events.

[#]: In treated population.

[¶]: Adverse events reported for the on-treatment period. There was 1 fatal serious adverse event in the post- study period that was not considered to be drug-related.

[§]: The CTCAE grading was assessed for each event.

Figure Captions

Fig. 1: Study design.

PK pharmacokinetic, tid three times a day, bid twice daily. [#]: Time windows were allowed to reach or to maintain the full pirfenidone dose (Group 1, 6-day time window; Group 2, two 3-day time windows) and to ensure stable 7-day treatment periods (Group 1 and 2, full dose pirfenidone; Group 2, combined treatment with nintedanib and pirfenidone). [¶]: On Day 16 (Visit 3b) subjects took single doses of pirfenidone 801 mg and nintedanib 150 mg only in the morning. PK sampling started 1 h prior to administration of single doses of pirfenidone and nintedanib and continued for 6 h post drug administration.

In Group 1, PK samples were collected before and 0.5, 1, 2, 3, 4, 6, 8, 10, and ~24 h after dosing on days 1 (nintedanib only) and 23. In Group 2, PK samples were collected before and 0.5, 1, 2, 3, 4, and ~6 h after dosing on days 8 (pirfenidone only) and 16.

Fig. 2: Participant disposition.

[#]: 14 subjects (27.5%) were not enrolled since they either did not meet the inclusion criteria or they did meet an exclusion criterion. [¶]: Not due to worsening of disease under study. [§]: Patient misunderstood the instructions for pirfenidone administration.

A pharmacokinetic concentration or parameter collected from a patient was considered to be non-evaluable if, for example, a patient experienced emesis that occurred at or before 2 times median t_{max} of the respective treatment for this treatment period, a patient's pre-dose concentration was >5% of the C_{max} value of that patient, the administered dose (amount of drug) was not in compliance with the clinical trial protocol, or restricted medication was used. In Group 1, data from 17 subjects were considered evaluable for PK analysis of the reference treatment, with 12 of these evaluable for PK analysis of the test group on day 23. In Group 2, data from 15 subjects were evaluable for PK analysis of the reference treatment, with 13 of these evaluable for PK analysis of the test group on day 23. In both treatment

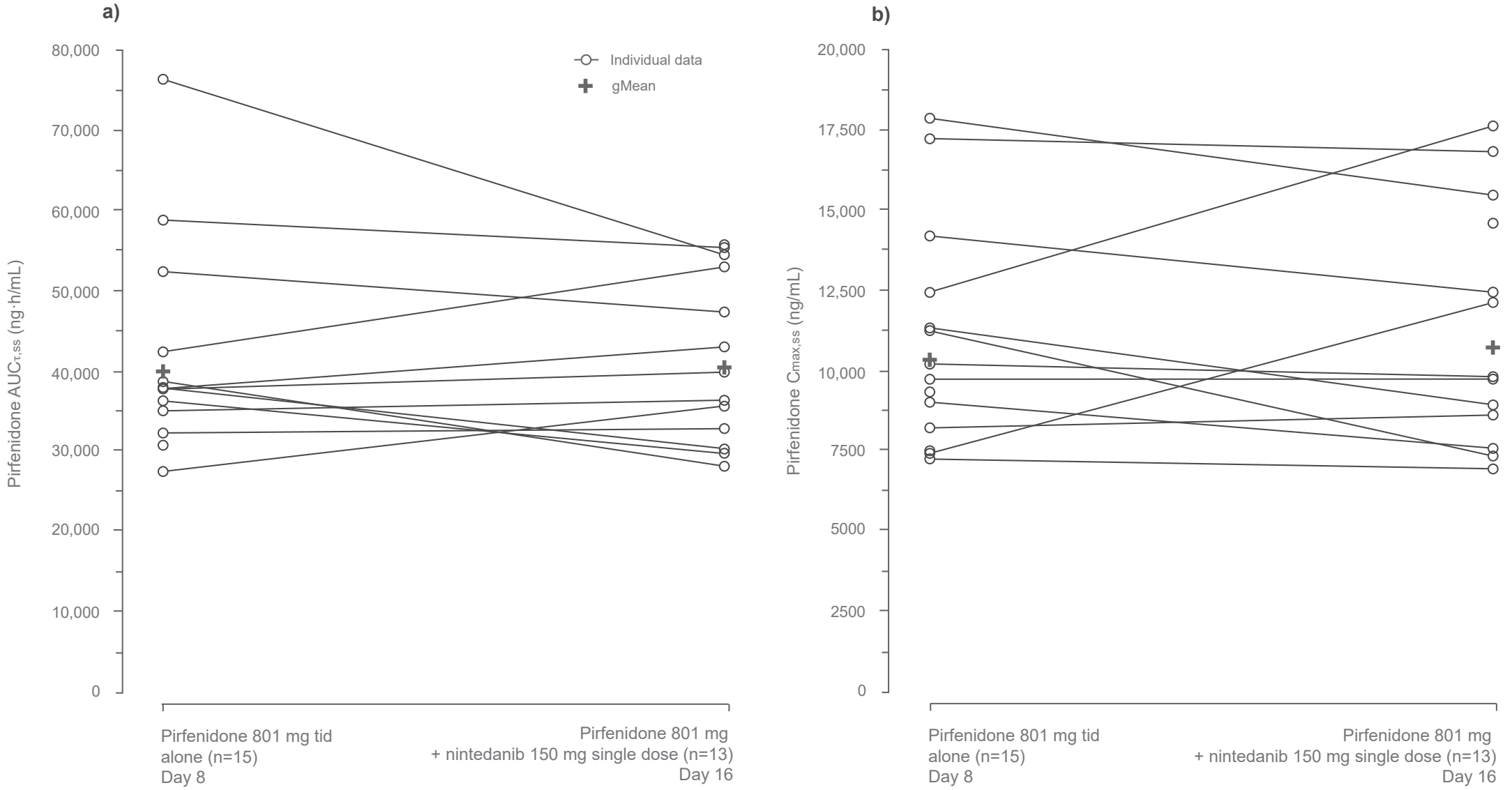
groups, 12 patients had evaluable PK data for the reference and the test treatment (included in the sensitivity analysis), respectively.

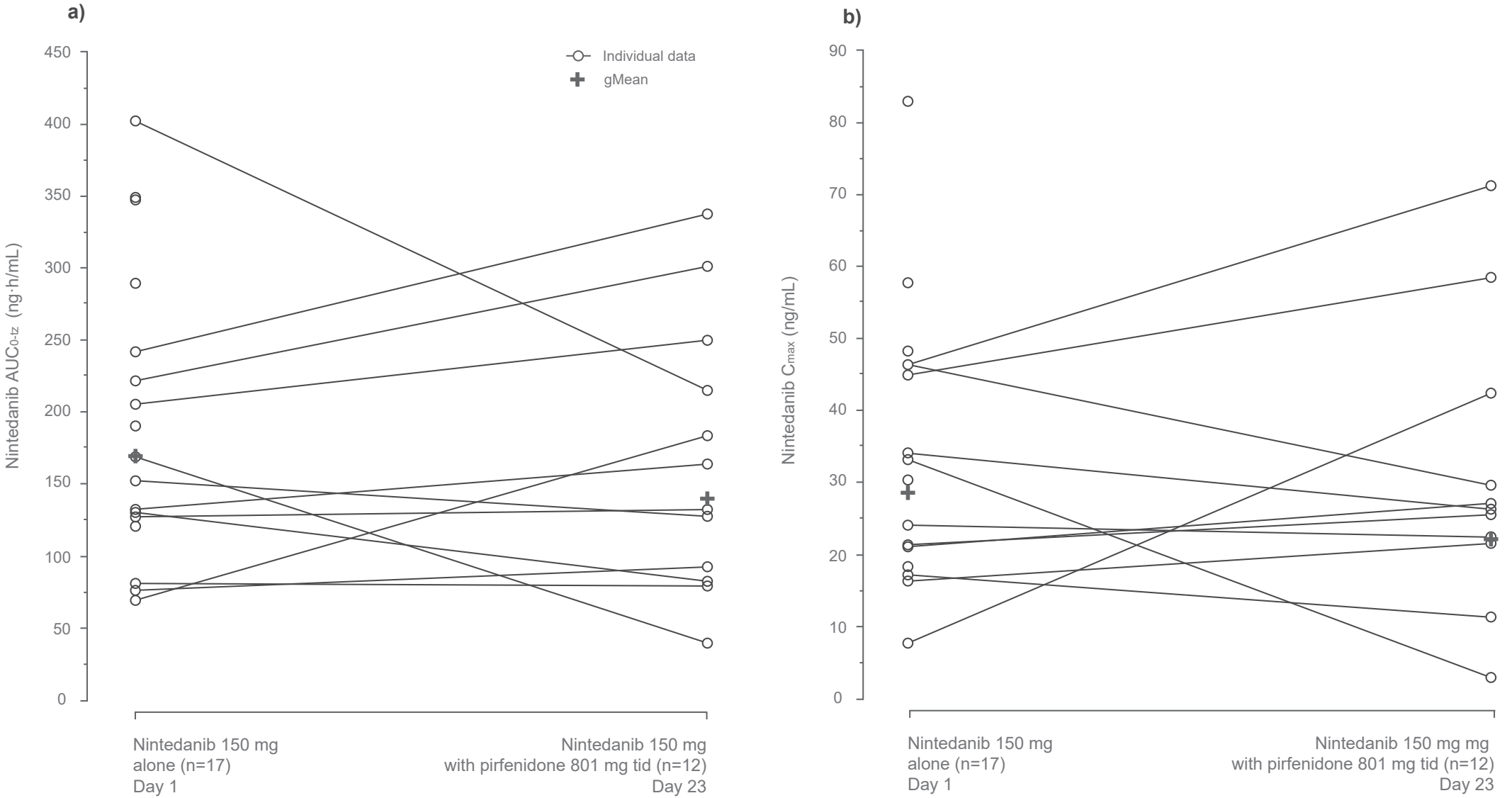
Fig. 3: Comparison of individual and geometric mean nintedanib area under the plasma concentration-time curve from time 0 to the time of the last quantifiable data point (**a**) and maximum concentration in plasma (**b**) after single oral administration of nintedanib 150 mg alone, and together with pirfenidone 801 mg thrice-daily.

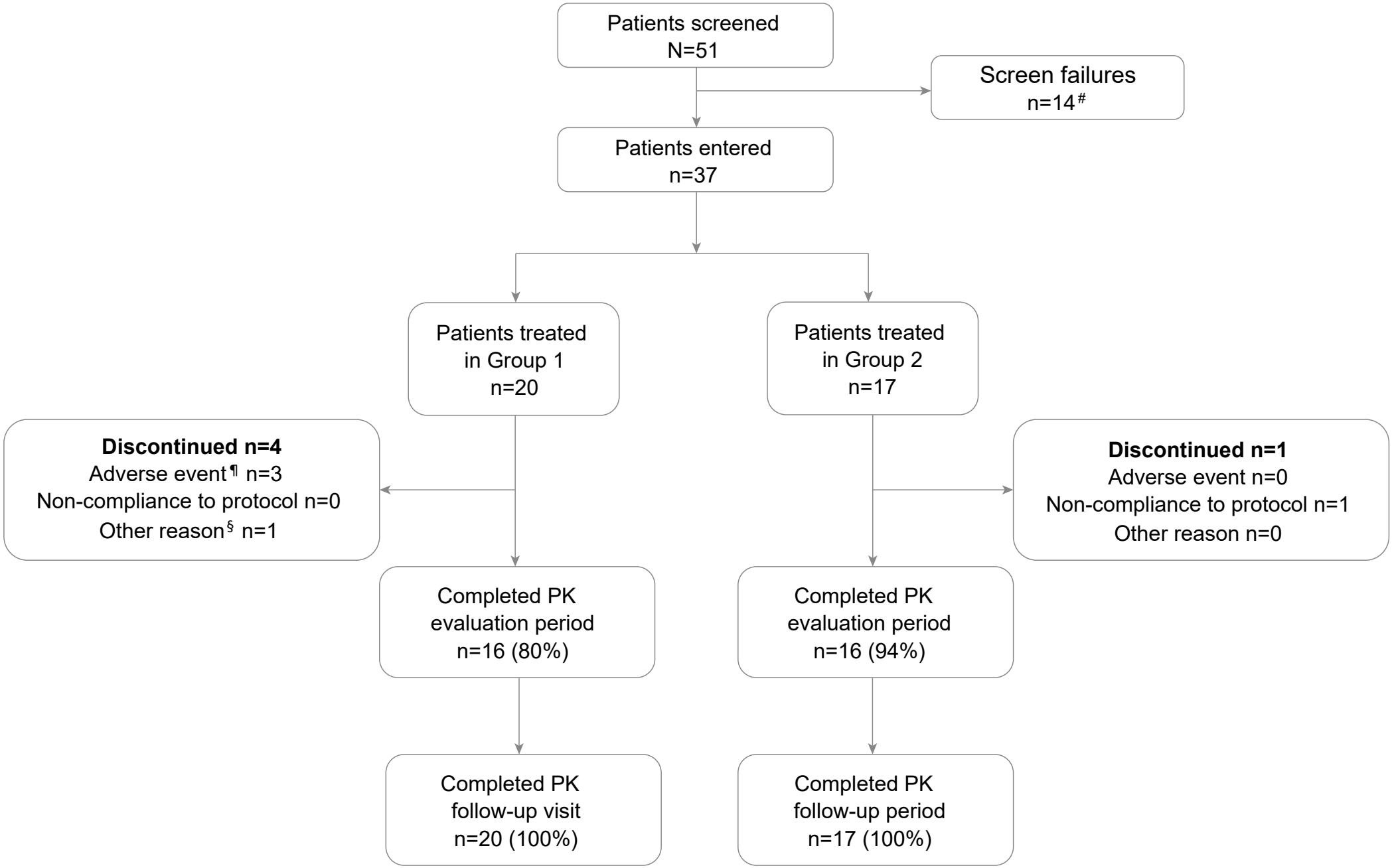
$AUC_{0\text{-}tz}$ area under the nintedanib plasma concentration-time curve from time 0 to the time of the last quantifiable data point, C_{max} maximum nintedanib concentration in plasma, gMean geometric mean.

Fig. 4: Comparison of individual and geometric mean pirfenidone area under the concentration-time curve in plasma at steady-state over a uniform dosing interval τ (**a**) and maximum concentration in plasma (**b**) at steady-state after oral administration of pirfenidone 801 mg thrice-daily alone, and together with nintedanib 150 mg twice-daily.

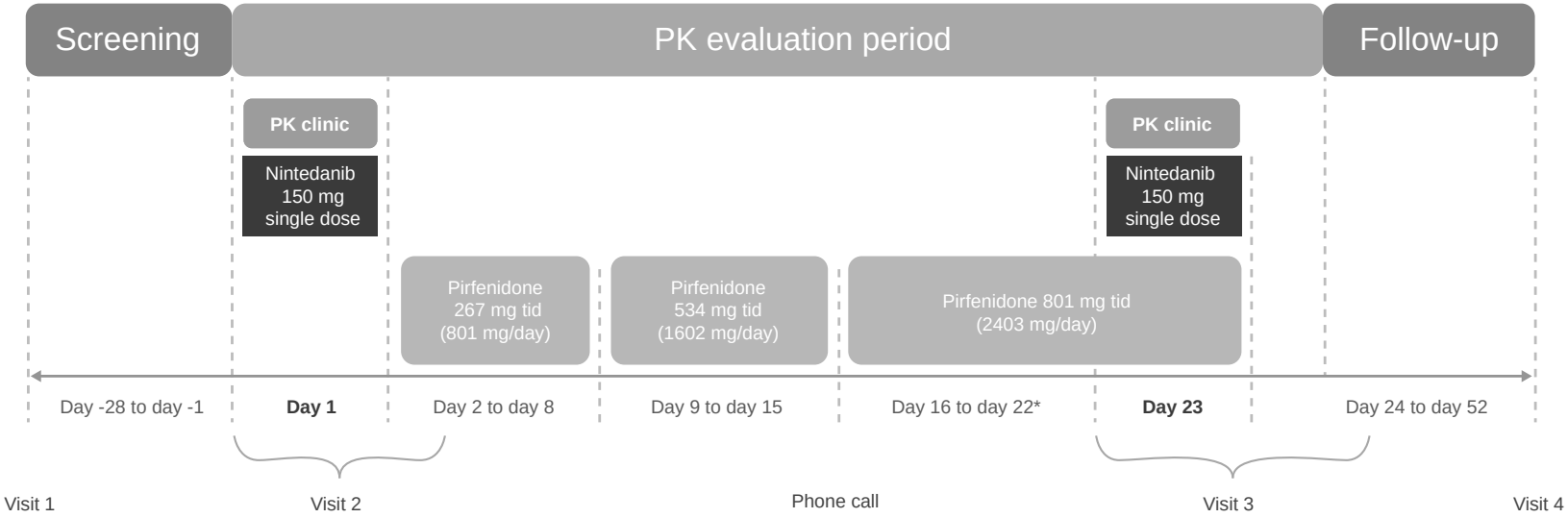
$AUC_{\tau,ss}$ Area under the pirfenidone concentration-time curve in plasma at steady-state over a uniform dosing interval τ, $C_{max,ss}$ maximum pirfenidone concentration in plasma at steady-state, gMean geometric mean.


a)
Individual data
gMean
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
Pirfenidone AUCτ,ss (ng·h/mL)
Pirfenidone 801 mg tid
alone (n=15)
Day 8
Pirfenidone 801 mg
+ nintedanib 150 mg single dose (n=13)
Day 16
b)
20,000
17,500
15,000
12,500
10,000
7500
5000
2500
0
Pirfenidone Cmax,ss (ng/mL)
Pirfenidone 801 mg tid
alone (n=15)
Day 8
Pirfenidone 801 mg
+ nintedanib 150 mg single dose (n=13)
Day 16

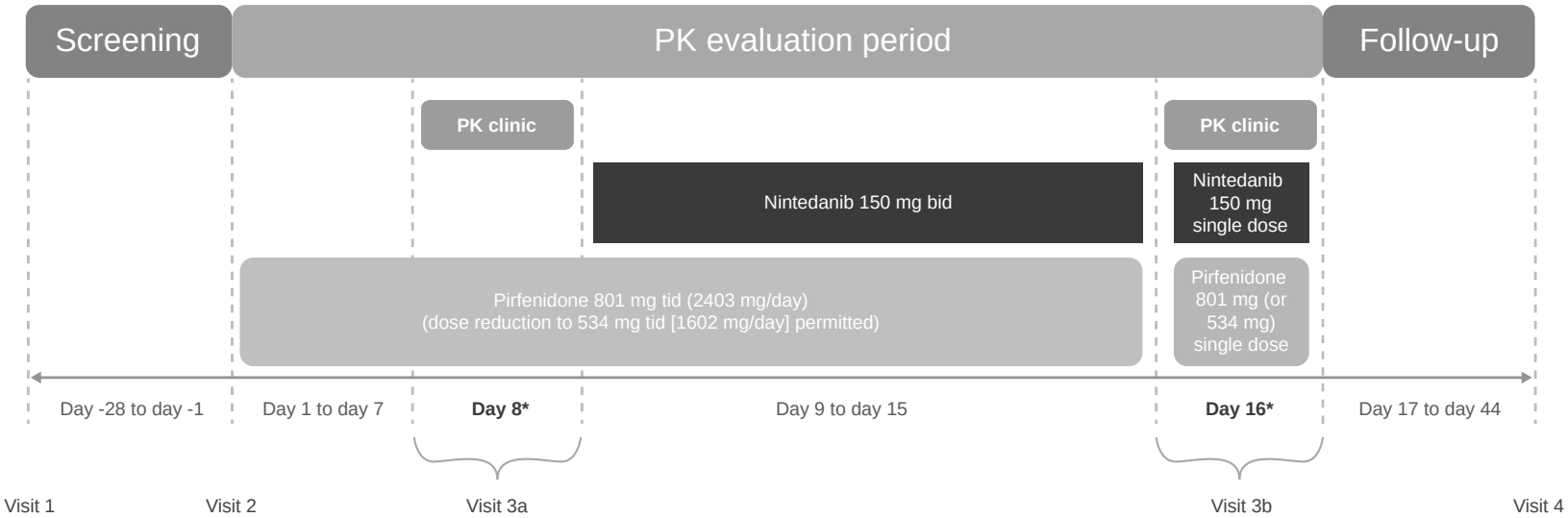

a)
Individual data
gMean
Nintedanib AUC0-tz (ng·h/mL)
450
400
350
300
250
200
150
100
50
0
Nintedanib 150 mg
alone (n=17)
Day 1
Nintedanib 150 mg
with pirfenidone 801 mg tid (n=12)
Day 23
b)
Nintedanib Cmax (ng/mL)
90
80
70
60
50
40
30
20
10
0
Nintedanib 150 mg
alone (n=17)
Day 1
Nintedanib 150 mg mg
with pirfenidone 801 mg tid (n=12)
Day 23


Patients screened
N=51
Screen failures
n=14#
Patients entered
n=37
Patients treated
in Group 1
n=20
Patients treated
in Group 2
n=17
Discontinued n=4
Adverse event¶ n=3
Non-compliance to protocol n=0
Other reason§ n=1
Discontinued n=1
Adverse event n=0
Non-compliance to protocol n=1
Other reason n=0
Completed PK
evaluation period
n=16 (80%)
Completed PK
evaluation period
n=16 (94%)
Completed PK
follow-up visit
n=20 (100%)
Completed PK
follow-up period
n=17 (100%)

Group 1



Group 2



Supplementary Online Material

Exclusion criteria

Patients could not participate in the trial if they met any of the following exclusion criteria:

1. ALT, AST of >1.5-fold upper limit of normal (ULN) at Visit 1
2. Total bilirubin of >1.5-fold ULN at Visit 1
3. Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment). Laboratory parameter could be re-tested within the permitted timeframe, if found abnormal at Visit 1 and thought to be a measurement error or was the result of a temporary and reversible medical condition. It was not required that the Child Pugh classification was performed at screening
4. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC of <0.7 at Visit 1)
5. History of myocardial infarction within 6 months of Visit 1 or unstable angina within 1 month of Visit 1
6. Bleeding risk:
    a. Known genetic predisposition to bleeding
    b. Patients who required fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, heparin, and hirudin) or high dose antiplatelet therapy
        i. Exceptions were prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g., enoxaparin 4000 IU s.c. per day) and prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/d, or clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy)
    c. History of haemorrhagic central nervous system (CNS) event within 12 months prior to Visit 1
    d. History of haemoptysis or haematuria, active gastrointestinal bleeding or ulcers and/or major injury or surgery within 3 months prior to Visit 1
    e. International normalised ratio (INR) of >2 at Visit 1
    f. Prothrombin time (PT) and partial thromboplastin time (PTT) of >150% of institutional ULN at Visit 1
7. Planned major surgery during the trial participation, including lung transplantation, major abdominal or major intestinal surgery (per investigator judgement)
8. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1

9. Severe renal impairment (creatinine clearance of <30 mL/min calculated by Cockcroft–Gault formula at Visit 1) or end-stage renal disease requiring dialysis
10. Treatment with n-acetylcysteine, prednisone of >15 mg daily or of >30 mg every 2 days or equivalent dose of other oral corticosteroids or fluvoxamine within 2 weeks of Visit 2
11. Treatment with azathioprine, cyclophosphamide, cyclosporine as well as any other investigational drug within 8 weeks of Visit 2
12. Previous treatment with pirfenidone in the past 3 months prior to Visit 2 (Group 1)
13. Previous treatment with nintedanib in the past 14 days prior to Visit 2
14. Permanent discontinuation of nintedanib or pirfenidone in the past due to adverse events considered drug-related
15. Known hypersensitivity to nintedanib, pirfenidone, or their excipients; or to peanut or soya
16. A disease or condition which in the opinion of the investigator could have interfered with the testing procedures or put the patient at risk when participating in this trial
17. Alcohol or drug abuse, which in the opinion of the treating physician would have interfered with treatment
18. Women who were pregnant, nursing, or who planned to become pregnant
19. Women of childbearing potential not using highly effective methods of birth control per ICH M3 [R09-1400]. Highly effective methods of birth control were defined as those, alone or in combination, that resulted in a low failure rate of <1% per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomised partner. Barrier contraceptives (e.g. male condom or diaphragm) were acceptable if used in combination with spermicides (e.g. foam, gel). Contraception had to be used for 28 days prior to and 3 months after nintedanib and pirfenidone administration. Women of childbearing potential were defined as any female who has experienced menarche and does not meet the criteria for ‘women not of childbearing potential’ defined as women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
20. Patients not able to understand and follow study procedures including completion of diaries without help
21. Current smoker (vaping and e-cigarettes were acceptable)

Safety evaluation

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0; the intensity of diarrhoea, nausea, and vomiting events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Spirometry and ECG measurements were performed at regular intervals throughout the study. Any abnormalities at screening were captured as a baseline condition. Thereafter they were reported as an adverse event.

Concomitant disease diagnoses at baseline

System organ class/preferred term	**Group 1 n (%)**	**Group 2 n (%)**
Cardiac disorders	**8 (40.0)**	**4 (23.5)**
Vascular disorders	**5 (25.0)**	**4 (23.5)**
Respiratory, thoracic and mediastinal disorders	**5 (25.0)**	**4 (23.5)**

Concomitant therapies on-treatment

The majority of patients in Group 1 and Group 2 took at least 1 concomitant therapy on-treatment. On preferred name level, these primarily included lansoprazole, acetylsalicylic acid, metformin, paracetamol, and levothyroxine.