



A Drug–Drug Interaction Study to Investigate the Effect of Nintedanib on the Pharmacokinetics of Microgynon (Ethinylestradiol and Levonorgestrel) in Female Patients with Systemic Sclerosis–Associated Interstitial Lung Disease

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Abstract

Background and Objectives Nintedanib is a tyrosine kinase inhibitor approved for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD), idiopathic pulmonary fibrosis, and other chronic fibrosing ILDs with a progressive phenotype. As nintedanib may cause foetal harm, patients taking nintedanib should avoid pregnancy. The objective of this study was to investigate the effect of nintedanib co-administration on the pharmacokinetics of Microgynon (ethinylestradiol and levonorgestrel) in female patients with SSc-ILD.

Methods This was an open-label, two-period, fixed-sequence, drug–drug interaction study. Female patients with SSc and $\geq 10\%$ extent of fibrotic ILD on a high-resolution computed tomography scan were eligible to participate. In Period 1, patients received one Microgynon tablet (ethinylestradiol 30 μg and levonorgestrel 150 μg) ≥ 3 days before the first administration of nintedanib in Period 2. In Period 2, patients received one Microgynon tablet following intake of nintedanib 150 mg twice daily for ≥ 10 consecutive days. The primary pharmacokinetic endpoints were the areas under the plasma concentration–time curve of ethinylestradiol and levonorgestrel over the time interval from 0 to the last quantifiable data point (AUC_{0-t_z}) and the maximum measured concentrations of ethinylestradiol and levonorgestrel in plasma (C_{max}). The secondary pharmacokinetic endpoint was the area under the plasma concentration–time curve of ethinylestradiol and levonorgestrel over the time interval from 0 extrapolated to infinity ($\text{AUC}_{0-\infty}$). The relative exposures of ethinylestradiol and levonorgestrel when administered alone and in combination with nintedanib were assessed using an ANOVA model.

Results Seventeen patients were treated. Pharmacokinetic data from 15 patients were analysed. Plasma concentration–time profiles of ethinylestradiol and levonorgestrel were similar following administration of Microgynon before and after administration of nintedanib for ≥ 10 consecutive days. Adjusted geometric mean (gMean) ratios [90% confidence intervals (CIs)] for AUC_{0-t_z} (101.4% [92.8, 110.7]) and $\text{AUC}_{0-\infty}$ (101.2% [94.0, 109.1]) indicated that there was no difference in total ethinylestradiol exposure when Microgynon was administered before or after administration of nintedanib. The adjusted gMean ratio for C_{max} of ethinylestradiol (116.7% [90% CI 107.6, 126.5]) indicated an increase in peak exposure in the presence of nintedanib. Adjusted gMean ratios [90% CIs] for AUC_{0-t_z} (96.4% [91.5, 101.6]) and C_{max} (100.9% [89.9, 113.2]) indicated that there was no difference in total or peak levonorgestrel exposure when Microgynon was administered before or after administration of nintedanib. The adjusted gMean ratio for $\text{AUC}_{0-\infty}$ of levonorgestrel indicated a decrease in total exposure in the presence of nintedanib (88.1% [90% CI 80.0, 97.0]).

Conclusion Pharmacokinetic data indicate that there is no relevant effect of nintedanib on plasma exposure to ethinylestradiol and levonorgestrel in female patients with SSc-ILD.

Trial Registration Clinicaltrials.gov NCT03675581.

Key Points

Pharmacokinetic data indicate that there is no relevant effect of nintedanib on plasma exposure to Microgynon (ethinylestradiol and levonorgestrel) in female patients with systemic sclerosis-associated interstitial lung disease.

Thus, nintedanib is not expected to reduce the effectiveness of contraceptives containing ethinylestradiol and levonorgestrel due to drug–drug interaction.

1 Introduction

Nintedanib is an approved treatment for idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, and systemic sclerosis-associated ILD (SSc-ILD). Nintedanib is an intracellular inhibitor of tyrosine kinases, including the platelet-derived growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor [1, 2]. Non-clinical studies suggest that nintedanib inhibits processes fundamental to the progression of pulmonary fibrosis, including fibroblast activation and the deposition of extracellular matrix [2]. Clinical trials have demonstrated that over 52 weeks, treatment with nintedanib slows the rate of decline in forced vital capacity (FVC) (mL/year) by approximately 50% compared with placebo, with side-effects that are predominantly gastrointestinal in nature [3–5].

Nintedanib is administered orally at a dose of 150 mg twice daily (bid), with dose reductions to 100 mg bid and treatment interruptions recommended to manage adverse events [6]. Maximum plasma concentrations of nintedanib are reached approximately 2–4 h after oral administration, and steady state is reached within 7 days [7]. Nintedanib is metabolised via hydrolytic ester cleavage, resulting in the formation of the free acid moiety, which is glucuronidated and excreted in faeces via the liver [8].

Some patients prescribed nintedanib are of child-bearing age. This includes some patients with SSc-ILD, which occurs mainly in women [9]. As nintedanib may cause foetal harm, patients taking nintedanib should avoid pregnancy [6]. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) recommend that the potential for pharmacokinetic interactions between nintedanib and oral contraceptives should be evaluated. We therefore conducted a drug–drug interaction study to investigate the potential effects of nintedanib on the pharmacokinetics of

Microgynon[®], a commonly used oral contraceptive including ethinylestradiol (a synthetic oestrogen) and levonorgestrel (a progestogen derived from nortestosterone), in female patients with SSc-ILD.

2 Methods

2.1 Study Patients

Female patients aged ≥ 18 years with SSc (based on the American College of Rheumatology/European League Against Rheumatism classification criteria [9]) and $\geq 10\%$ extent of fibrotic ILD on a high-resolution computed tomography (HRCT) scan were eligible to participate. Patients were required to be of non-childbearing potential or, following a protocol amendment, of childbearing potential and using a highly effective method of non-hormonal birth control together with barrier methods. Patients with aspartate transaminase, alanine transaminase and/or bilirubin > 1.5 times the upper limit of normal; clinically relevant anaemia; pre-bronchodilator forced expiratory volume in 1 s/FVC < 0.7 ; significant pulmonary hypertension (previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterisation with a cardiac index ≤ 2 L/min/m², or pulmonary hypertension requiring therapy with parenteral or oral prostacyclins); or at risk of bleeding (e.g., those with a known predisposition to bleeding or those who were taking high-dose antiplatelet therapy or full-dose anticoagulation) were excluded.

2.2 Study Design

This was an open-label, multicentre, two-period, fixed-sequence, drug–drug interaction study to investigate the relative systemic exposure to ethinylestradiol and levonorgestrel alone and in combination with steady-state nintedanib (clinicaltrials.gov NCT03675581; EudraCT 2018-001177-24).

Patients participated in two periods in a fixed sequence (Fig. 1). In Period 1, patients received one Microgynon tablet (Bayer; ethinylestradiol 30 μg and levonorgestrel 150 μg) ≥ 3 days before the first administration of nintedanib (Ofev[®]; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) in Period 2. In Period 2, patients received one Microgynon tablet following intake of nintedanib 150 mg bid for ≥ 10 consecutive days. Patients could receive nintedanib 150 mg bid for a total of 14–28 days to ensure continuous treatment to steady state. Nintedanib dose reduction to 100 mg bid or treatment interruption was permitted to manage adverse events. The maximum period of treatment interruption was 4 weeks for adverse events considered related to the trial drug and 8 weeks for adverse events

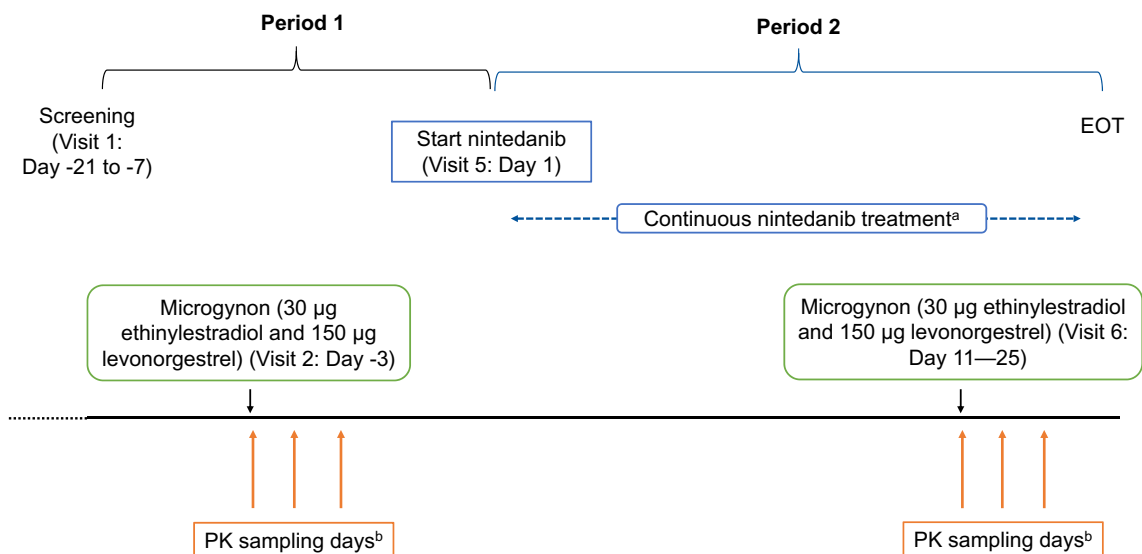


Fig. 1 Study design. ^aPatients received nintedanib 150 mg bid for ≥ 10 consecutive days prior to Microgynon administration in Period 2. Patients received nintedanib 150 mg bid over a period of ≥ 14 days to approximately 28 days. ^bBlood samples for PK evaluation were

collected on the days of Microgynon administration (pre- and post-dose) and on the following 2 days. *EOT* end of treatment, *PK* pharmacokinetic, *bid* twice daily

considered not drug related. Blood samples for pharmacokinetic evaluation were collected on the days of Microgynon administration (pre- and post-dose) and on the following 2 days in both periods. Specifically, pharmacokinetic sampling for ethinylestradiol and levonorgestrel was performed 35 min before and 30 min, 1 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 8 h, 11 h 55 min, 23 h 55 min, and 47 h 55 min after Microgynon administration in Periods 1 and 2. Pharmacokinetic sampling for nintedanib was performed 35 min before and 23 h 55 min and 47 h 55 min after Microgynon administration in Period 2. In Periods 1 and 2, 6 mL of blood was drawn at each time point to prepare the samples for the pharmacokinetic analysis of ethinylestradiol and levonorgestrel. In Period 2, 3 mL of blood was drawn at each of the three time points to prepare the samples for the pharmacokinetic analysis of nintedanib. Blood was collected using tripotassium ethylenediaminetetraacetic acid (K3-EDTA)-containing blood drawing tubes. The tubes were gently inverted ten times and then centrifuged at 2100 *g* for 15 min at 4–25 °C within 60 min of sampling. At least 1.5 mL of plasma was transferred into two cryovials within 30 min of centrifugation (aliquot 1 and back-up aliquot 2) and stored in an upright position at –20 °C or below until shipment to the central laboratory (Nuvisan GmbH) for analysis.

Patients were to be excluded if they had received P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inhibitors or inducers within 7 days prior to the first dose of Microgynon. Use of these medications was not permitted until the last pharmacokinetic sampling day. Patients were to be excluded if they had received mycophenolate (within

2 weeks prior to the first dose of Microgynon), azathioprine (within 8 weeks prior to screening), cyclophosphamide (within 6 months prior to screening) or cyclosporine (within 7 days prior to the first dose of Microgynon). Use of methotrexate was permitted if the dose had been stable for ≥ 6 months prior to screening. Patients were to be excluded if they had received hormone-containing contraceptives < 30 days prior to the first dose of Microgynon. Use of hormone-containing contraceptives was not permitted at any time during the study.

The study was carried out in compliance with the protocol and in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation good clinical practice guideline, and applicable regulatory requirements. All patients provided written informed consent.

2.3 Endpoints

The primary pharmacokinetic endpoints were the area under the plasma concentration–time curve of ethinylestradiol and levonorgestrel over the time interval from 0 to the last quantifiable data point (AUC_{0-t_z}) and the maximum measured concentrations of ethinylestradiol and levonorgestrel in plasma (C_{max}). The secondary pharmacokinetic endpoint was the area under the plasma concentration–time curve of ethinylestradiol and levonorgestrel over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$). Further pharmacokinetic endpoints were the pre-dose (trough) plasma concentration of nintedanib at steady state ($C_{pre,ss}$) and clearance

(CL/F), volume of distribution (V_z/F), time to reach C_{\max} (t_{\max}), terminal rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), and time point of the last quantifiable plasma concentration (t_z) of ethinylestradiol and levonorgestrel. Nintedanib $C_{\text{pre,ss}}$ was assessed to prove exposure on the day of Microgynon administration and on the following 2 days during continuous nintedanib intake.

Safety was assessed based on adverse events, laboratory tests, vital signs, spirometry, physical examination, 12-lead electrocardiogram and echocardiography. Adverse events were reported irrespective of causality and coded using the Medical Dictionary for Regulatory Activities version 22.1. The following phases were defined for the recording of adverse events: adverse events reported from (1) the date of administration of Microgynon in Period 1 plus 3 days, (2) the first administration of nintedanib in Period 2 until the date of administration of Microgynon in Period 2, (3) the date of administration of Microgynon in Period 2 plus 3 days, and (4) the date 3 days after the administration of Microgynon in Period 2 until the day after last contact.

2.4 Bioanalytical Assay

Plasma concentrations of nintedanib, ethinylestradiol and levonorgestrel were determined using a liquid chromatography tandem mass spectrometry assay (LC-MS/MS). The assay method for nintedanib (in the form of its free base, BIBF 1120 BS) involved solid-phase extraction, chromatographic separation on a Phenomenex Luna (C18) column under gradient conditions, and MS/MS detection (MRM-mode) using [2H8]-BIBF 1120 BS as an internal standard. An electrospray ion source (atmospheric pressure ionisation [API]) was used for ionisation. Measurements were performed in the positive ionisation mode. The LC-MS/MS method was validated at Nuvisan GmbH in accordance with internationally accepted standards. The calibration range was 0.05–50 ng/mL and recovery was in the range of 70.1–71.6%. The assay method for ethinylestradiol and levonorgestrel involved liquid-liquid extraction and derivatisation, chromatographic separation on a Waters XBridge BEH18 column under gradient conditions, and MS/MS detection using [2H4]-ethinylestradiol and [2H6]-levonorgestrel as internal standards. An electrospray ion source (API) was used for ionisation. Measurements were performed in the positive ionisation mode. The LC-MS/MS method was validated at Nuvisan GmbH in accordance with internationally accepted standards. The calibration range was 2.5–250 pg/mL for ethinylestradiol and 25–25000 pg/mL for levonorgestrel. Recovery was in the range of 95.4–129.3% for ethinylestradiol and 91.5–112.2% for levonorgestrel. For both assays, performance was assessed by back-calculation of calibration standards, tabulation of the standard curve fit function parameters and measurement of quality control samples. No data were extrapolated. Samples below the lower limit

of quantification (LLOQ) were reported as < LLOQ. There were no samples above the upper limit of quantification.

2.5 Analyses

Pharmacokinetic analyses were performed in patients who received ≥ 1 dose of Microgynon or nintedanib and provided ≥ 1 value for ≥ 1 primary or secondary endpoint without important protocol violations or non-evaluability relevant to the evaluation of pharmacokinetics. Safety analyses were performed in patients who received ≥ 1 dose of Microgynon or nintedanib.

The relative systemic exposures of ethinylestradiol and levonorgestrel alone (reference [R]) and in combination with steady-state nintedanib (test [T]) were assessed using an ANOVA model on a logarithmic scale with patient included as a random effect and treatment included as a fixed effect. Values for AUC_{0-tz} , C_{\max} and $AUC_{0-\infty}$ were log-transformed prior to fitting the model. The difference between the expected means for $\log(T) - \log(R)$ was estimated using the difference in the corresponding least-squares means, and two-sided 90% confidence intervals (CIs) were computed based on the t distribution. Values were back-transformed to the original scale to give the geometric mean (gMean) and two-sided 90% CIs for the ratio between response under T versus R treatment. Further pharmacokinetic endpoints and safety were analysed descriptively.

The observed intra-individual coefficient of variation (gCV) values for ethinylestradiol and levonorgestrel in healthy volunteers have been estimated to be approximately 20% for C_{\max} and 15% for AUC_{0-tz} or $AUC_{t,ss}$. Based on a sample size of 14 patients and assuming a gCV of 20%, the precision of the two-sided 90% CI of the $T:R$ ratio in terms of the upper confidence limit/point estimate would have been approximately 1.19. Thus, a sample size of 14 patients was considered sufficient to achieve the aims of this exploratory study.

Pharmacokinetic parameter calculations were performed using Phoenix[®] WinNonlin[®] 6.3 (or later) and/or SAS[®] software, version 9.4 (or later). For $AUC_{0-\infty}$ calculations, the linear up–log down trapezoidal rule was applied (the linear trapezoidal rule was used for the ascending parts of the concentration–time profiles, and the logarithmic trapezoidal rule was used for the descending parts of the concentration–time profiles).

3 Results

3.1 Patients

A total of 21 patients were screened: 17 were treated and four failed screening. Mean (SD) age was 59.1 (13.2) years and body mass index was 27.1 (4.7) kg/m²; 88.2% of patients were white (Table 1). Median

(minimum–maximum) nintedanib exposure was 15 (13–47) days. One patient had a nintedanib dose reduction. All patients completed the study. Data from two patients were not included in the pharmacokinetic analyses due to protocol violations, i.e., the use of restricted medication.

Table 1 Baseline demographic characteristics of study patients ($n = 17$)

Characteristic	Value
Age, years, mean (SD)	59.1 (13.2)
Body mass index, kg/m ² , mean (SD)	27.1 (4.7)
Race, n (%)	
White	15 (88.2)
Asian	1 (5.9)
Native Hawaiian or other Pacific Islander	1 (5.9)
Time since onset of non-Raynaud symptom, years, mean (SD)	6.1 (4.5)
Systemic sclerosis subtype, n (%)	
Limited cutaneous	14 (82.4)
Diffuse cutaneous	3 (17.6)
Forced vital capacity % predicted, mean (SD)	80.9 (19.5)

3.2 Pharmacokinetics

Ethinylestradiol and levonorgestrel were rapidly absorbed after administration of a single dose of Microgynon. Plasma concentrations of ethinylestradiol and levonorgestrel declined in a bi-exponential manner. Plasma concentration–time profiles of ethinylestradiol and levonorgestrel were similar following administration of Microgynon before and after administration of nintedanib 150 mg bid for ≥ 10 consecutive days (Figs. 2, 3). AUC_{0-tz} , C_{max} and $AUC_{0-\infty}$ of ethinylestradiol and levonorgestrel were similar before and after administration of nintedanib 150 mg bid for ≥ 10 consecutive days (Table 2). Adjusted gMean ratios (90% CIs) for AUC_{0-tz} and $AUC_{0-\infty}$ indicated that there was no difference in total ethinylestradiol exposure when Microgynon was administered before or after administration of nintedanib for ≥ 10 consecutive days. The adjusted gMean ratio (90% CI) for C_{max} of ethinylestradiol indicated an increase in peak exposure in the presence of nintedanib (Table 3). Adjusted gMean ratios (90% CIs) for AUC_{0-tz} and C_{max} indicated that there was no difference in levonorgestrel total or peak exposure when Microgynon was administered before or after administration of nintedanib for ≥ 10 consecutive days. The adjusted gMean ratio (90% CI) for $AUC_{0-\infty}$ of levonorgestrel indicated a decrease in total exposure in the presence of nintedanib (Table 3).

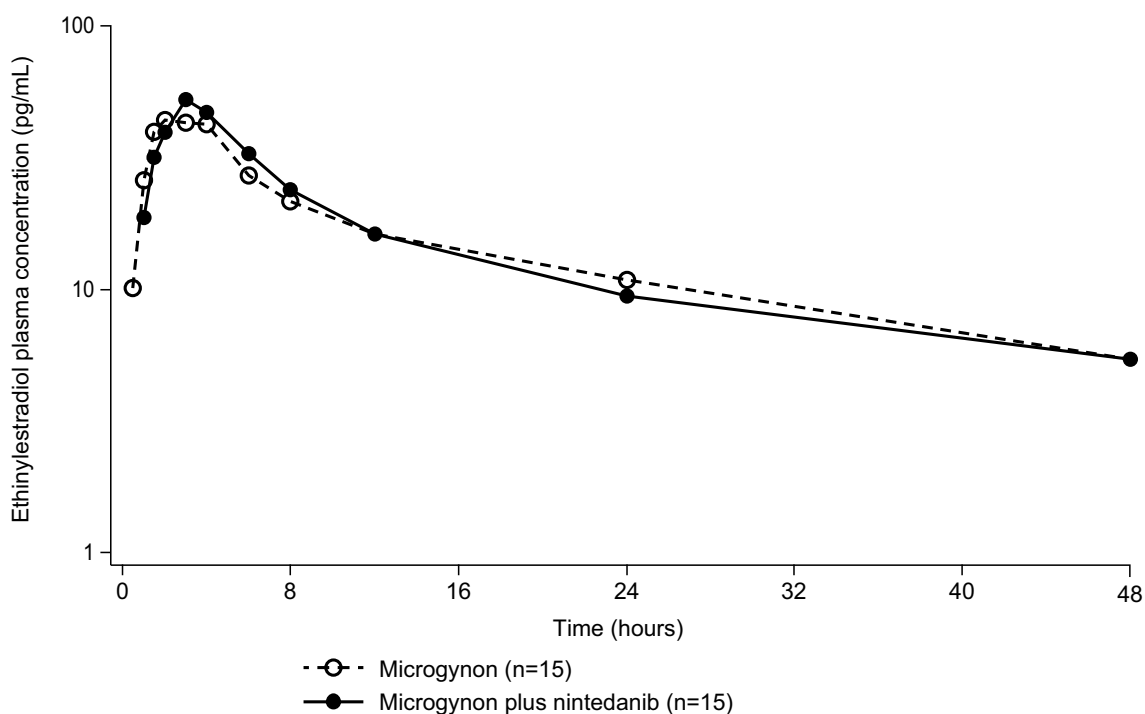


Fig. 2 Geometric mean plasma concentration–time profiles of ethinylestradiol after single-dose administration of Microgynon before (Period 1) and after administration of nintedanib 150 mg bid for ≥ 10 consecutive days (Period 2), plotted on a semi-logarithmic scale

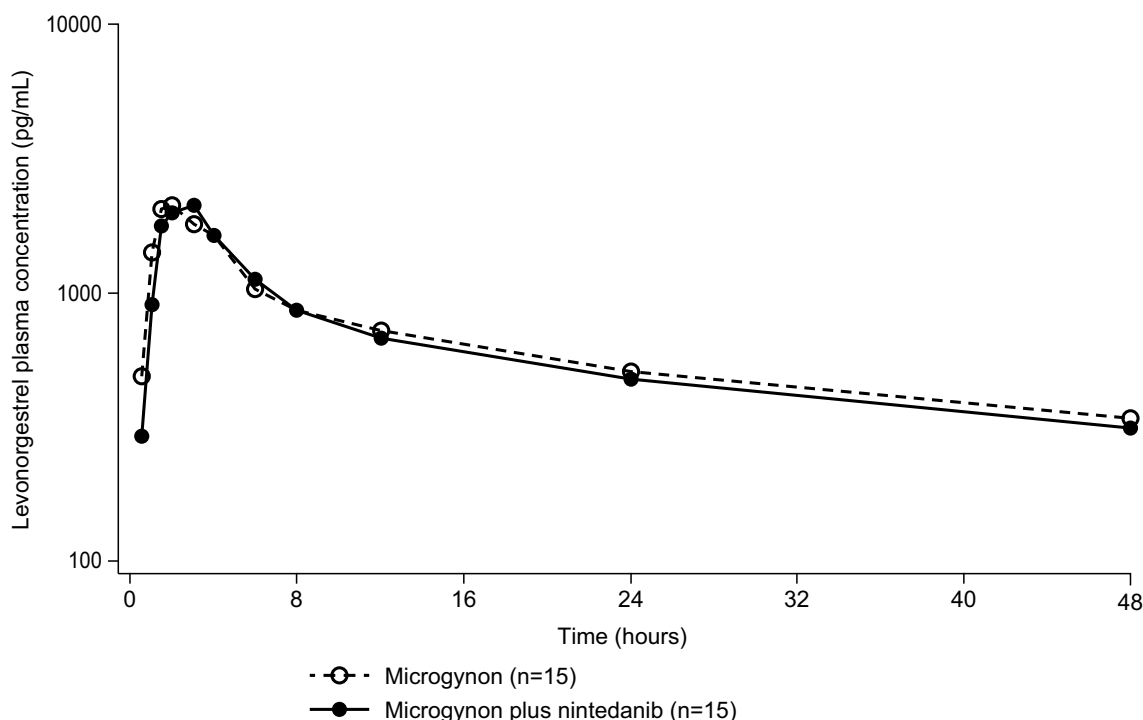


Fig. 3 Geometric mean plasma concentration–time profiles of levonorgestrel after single-dose administration of Microgynon before (Period 1) and after administration of nintedanib 150 mg bid for ≥ 10 consecutive days (Period 2), plotted on a semi-logarithmic scale

Table 2 Pharmacokinetics of ethinylestradiol and levonorgestrel after single dose administration of Microgynon before and after administration of nintedanib 150 mg bid for ≥ 10 consecutive days

Parameter	Ethinylestradiol		Levonorgestrel	
	Microgynon alone ($n = 15$)	Microgynon with nintedanib ($n = 15$)	Microgynon alone ($n = 15$)	Microgynon with nintedanib ($n = 15$)
AUC_{0-t_z} , pg·h/mL	610 (65.6)	618 (57.3)	33,100 (81.8)	31,900 (81.1)
C_{max} , pg/mL	54.7 (35.6)	63.9 (44.7)	3120 (55.6)	3150 (54.6)
$AUC_{0-\infty}$, pg·h/mL	750 (60.2)	759 (51.5)	56,300 (102)	49,600 (97.2)
AUC_{0-24} , pg·h/mL	490 (46.8)	517 (43.7)	22,800 (76.8)	22,200 (75.5)
$AUC_{t_z-\infty}$, %	17.8 (29.5)	17.2 (38.0)	33.9 (56.6)	31.6 (43.8)
t_z , h	47.9 (11.9–48.0)	47.9 (23.8–48.3)	47.9 (47.9–48.0)	47.9 (47.7–48.3)
t_{max} , h	2.0 (1.0–6.0)	3.0 (1.0–5.0)	1.6 (1.0–4.0)	2.0 (1.0–4.0)
$t_{1/2}$, h	17.4 (29.5)	16.7 (27.1)	39.4 (64.2)	35.0 (42.7)

Data are gMean (%gCV) except for t_z and t_{max} , which are median (range)

AUC_{0-t_z} area under the plasma concentration–time curve of ethinylestradiol or levonorgestrel over the time interval from 0 to the last quantifiable data point, C_{max} maximum measured concentration of ethinylestradiol or levonorgestrel in plasma, $AUC_{0-\infty}$ area under the plasma concentration–time curve of ethinylestradiol or levonorgestrel over the time interval from 0 extrapolated to infinity, AUC_{0-24} area under the plasma concentration–time curve of ethinylestradiol or levonorgestrel over the time interval from 0 to 24 h, $AUC_{t_z-\infty}$ $AUC_{0-\infty}$ obtained by extrapolation, t_z time point of the last quantifiable plasma concentration, t_{max} time from (last) dosing to the maximum measured plasma concentration of ethinylestradiol or levonorgestrel, $t_{1/2}$ terminal half-life of ethinylestradiol or levonorgestrel in plasma, gMean geometric mean, gCV geometric coefficient of variation

Eleven patients in Period 1 and 10 patients in Period 2 had extrapolated areas of $> 30\%$ due to pharmacokinetic sampling limited to 48 h.

3.3 Safety

The most frequently reported adverse events were nausea (35.3%), diarrhoea (29.4%) and vomiting (29.4%) (Table 4). One patient had a serious adverse event

Table 3 Relative exposure to ethinylestradiol and levonorgestrel after single dose administration of Microgynon before and after administration of nintedanib 150 mg bid for ≥ 10 consecutive days

Parameter	Adjusted ^a gMean (gSE)		Adjusted gMean ratio, % (90% CI) [T]/[R]
	Microgynon with nintedanib ($n = 15$) [T]	Microgynon alone ($n = 15$) [R]	
Ethinylestradiol			
AUC _{0-tz} , pg-h/mL	618.3 (1.2)	610.0 (1.2)	101.4 (92.8, 110.7)
C _{max} , pg/mL	63.9 (1.1)	54.8 (1.1)	116.7 (107.6, 126.5)
AUC _{0-∞} , pg-h/mL	759.0 (1.1)	749.7 (1.1)	101.2 (94.0, 109.1)
Levonorgestrel			
AUC _{0-tz} , pg-h/mL	31872.5 (1.2)	33062.7 (1.2)	96.4 (91.5, 101.6)
C _{max} , pg/mL	3152.4 (1.1)	3124.5 (1.1)	100.9 (89.9, 113.2)
AUC _{0-∞} , pg-h/mL	49605.4 (1.2)	56311.7 (1.2)	88.1 (80.0, 97.0)

AUC_{0-tz} area under the plasma concentration–time curve of ethinylestradiol or levonorgestrel over the time interval from 0 to the last quantifiable data point, C_{max} maximum measured concentration of ethinylestradiol or levonorgestrel in plasma, AUC_{0-∞} area under the plasma concentration–time curve of ethinylestradiol or levonorgestrel over the time interval from 0 extrapolated to infinity, *T* test, *R* reference, *gMean* geometric mean, *gSE* geometric standard error

^aANOVA model was adjusted for the effects of “patient” and “treatment”

Table 4 Adverse events

Adverse event	Microgynon alone ^a ($n = 17$)	Nintedanib loading phase ^b ($n = 17$)	Microgynon and nintedanib ^c ($n = 17$)	Nintedanib alone after administration of Microgynon ^d ($n = 17$)	Total ($n = 17$)
Any adverse event	3 (17.6)	11 (64.7)	4 (23.5)	2 (11.8)	12 (70.6)
Nausea	0	6 (35.3)	0	0	6 (35.3)
Diarrhoea	0	4 (23.5)	1 (5.9)	0	5 (29.4)
Vomiting	0	5 (29.4)	1 (5.9)	0	5 (29.4)
Abdominal pain upper	0	2 (11.8)	1 (5.9)	0	3 (17.6)
Headache	2 (11.8)	1 (5.9)	1 (5.9)	0	3 (17.6)
Dizziness	1 (5.9)	1 (5.9)	0	0	2 (11.8)
Abdominal pain	0	1 (5.9)	0	0	1 (5.9)
Bronchitis	0	1 (5.9)	0	0	1 (5.9)
Respiratory tract infection	0	1 (5.9)	0	0	1 (5.9)
Rhinitis	0	1 (5.9)	0	0	1 (5.9)
Musculoskeletal pain	0	1 (5.9)	0	0	1 (5.9)
Pain in extremity	0	1 (5.9)	0	0	1 (5.9)
Fatigue	1 (5.9)	0	0	0	1 (5.9)
Malaise	1 (5.9)	0	0	0	1 (5.9)
Drug-induced liver injury	0	0	1 (5.9)	0	1 (5.9)
Increased aspartate transaminase	0	0	0	1 (5.9)	1 (5.9)
Vaginal discharge	0	1 (5.9)	0	1 (5.9)	1 (5.9)

Data are *n* (%) of patients with ≥ 1 such adverse event

^aAdverse events reported from date of administration of Microgynon in Period 1 plus 3 days

^bAdverse events reported from first administration of nintedanib in Period 2 until the date of administration of Microgynon in Period 2

^cAdverse events reported from the date of administration of Microgynon in Period 2 plus 3 days

^dAdverse events reported from the date 3 days after the administration of Microgynon in Period 2 until the day after last contact

(drug-induced liver injury). The onset of the event was after 18 days of continuous intake of nintedanib and before combined administration of Microgynon and nintedanib. The patient was taking an antihistamine to treat rhinitis. This was discontinued the day after onset of liver injury,

and the patient recovered after 10 days. No adverse events led to discontinuation of study medication. There were no clinically relevant changes in electrocardiogram recordings, vital signs, spirometry, or physical examinations.

4 Discussion

Some patients with ILD who are prescribed nintedanib are of child-bearing age and are using hormonal contraception to prevent pregnancy. This is of importance, as nintedanib may cause foetal harm if administered to a pregnant woman [6]. The pharmacokinetic data from this study indicate that there is no relevant effect of nintedanib 150 mg bid on exposure to ethinylestradiol and levonorgestrel in female patients with SSc-ILD. Thus, nintedanib would not be expected to reduce the effectiveness of contraceptives containing ethinylestradiol and levonorgestrel due to drug–drug interaction.

An increase in the peak exposure to ethinylestradiol was observed in the presence of nintedanib. This finding was not considered to be of clinical relevance. Although the AUC_{0–∞} of levonorgestrel indicated a decrease in total exposure in the presence of nintedanib, this observation should be interpreted with caution, given that the majority of patients in both periods had extrapolated areas of > 30% due to pharmacokinetic sampling being limited to 48 h. The AUC_{0–12h} for which no extrapolation was necessary, is considered more reliable.

Ethinylestradiol is metabolised in the liver by hydroxylation, mediated by CYP3A4, while levonorgestrel is metabolised in the liver to sulfate and glucuronide conjugates [10]. Drugs that induce CYP3A4 can cause a decrease in exposure to oral contraceptives, which in turn may reduce their effectiveness [10–12]. Preclinical data have suggested that nintedanib has a low potential to induce CYP3A4 [7, 13]. Therefore, no relevant drug–drug interaction was expected when nintedanib was co-administered with oral contraceptives. This was confirmed in the present study.

The safety profiles of nintedanib and ethinylestradiol and levonorgestrel in this study were generally consistent with the known safety profiles of each drug [6, 10]. There appeared to be no increase in adverse events when nintedanib was combined with ethinylestradiol and levonorgestrel compared with administration alone.

5 Conclusions

Pharmacokinetic data indicate that there is no relevant effect of nintedanib on plasma exposure to ethinylestradiol and levonorgestrel. Nintedanib is therefore not expected to reduce the effectiveness of contraceptives containing ethinylestradiol and levonorgestrel due to drug–drug interaction.

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Declarations

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Conflict of interest MCV reports grants from BI, Ferrer and Janssen-Cilag; fees for serving as an advisor or review panel member for BI and Janssen-Cilag; and speaker fees from BI, Janssen-Cilag, Novartis, Roche. AG-D-C reports consultancy fees from BI and Janssen. MK reports grants from BI and Roche and consultancy fees from BI, Galapagos, Roche. MA, KM, SRM, SW and MG are employees of BI.

Data availability Researchers may request access to de-identified participant clinical study data with documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data would be shared in a secured data-access system for a period of 1 year, which may be extended upon request. Researchers should use the link <https://trials.boehringer-ingelheim.com/> to request access to study data.

Authors' contributions MA, KM, SRM, SW and MG were involved in the design of the study. MCV, AG-D-C and MK were involved in data acquisition. SRM and KM were involved in data analysis. All authors were involved in the interpretation of the data and in the writing and critical review of the manuscript and have approved the final version.

Ethics approval The clinical protocol was approved by an independent ethics committee or institutional review board at each participating centre.

Consent to participate All patients provided written informed consent before study entry.

Consent for publication Not applicable.


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