Drug-Drug Interaction Study of Nintedanib (Ofev®) and the Combination of Ethinylestradiol and Levonorgestrel (Microgynon®) in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

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Introduction

- Nintedanib is a tyrosine kinase inhibitor[1] approved for the treatment of idiopathic pulmonary fibrosis (IPF), SSc-ILD, and other chronic fibrosing ILDs with a progressive phenotype.
- After oral administration, maximum plasma concentrations of nintedanib are reached in approximately 2–4 hours; steady state is reached within 7 days.[2]
- As nintedanib may cause fetal harm, patients taking nintedanib should avoid pregnancy.
- Microgynon® (a combination of ethinylestradiol and levonorgestrel) is a commonly used oral contraceptive.

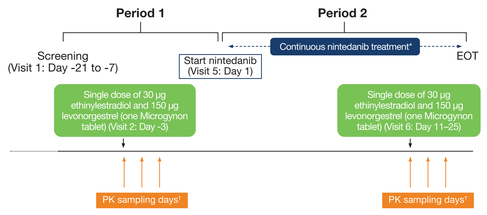
Aim

- To investigate the pharmacokinetics (PK) of Microgynon® (ethinylestradiol and levonorgestrel) alone and in combination with nintedanib in female patients with SSc-ILD.

Methods

Study design

- This was an open-label, two-period, fixed-sequence, drug–drug interaction study (NCT03675581).
- Female patients aged ≥18 years, with SSc and ≥10% extent of fibrotic ILD on a high-resolution computed tomography (HRCT) scan were eligible to participate.



EOT, end of treatment.
*Patients received a stable dose of nintedanib 150 mg bid over a period of ≥14 days to approximately 28 days.
†Blood samples for PK evaluation were collected on the days of ethinylestradiol and levonorgestrel administration (pre- and post-dose) and on the following 2 days.

Endpoints

- Primary PK endpoints
  - Areas under the concentration–time curve of ethinylestradiol and levonorgestrel in plasma over the time interval from 0 to the last quantifiable data point ($AUC_{0\text{-}tz}$)
  - Maximum measured concentrations of ethinylestradiol and levonorgestrel in plasma (C_{max}).
- Secondary PK endpoint
  - Areas under the concentration–time curve of ethinylestradiol and levonorgestrel in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$).

Analyses

- PK analyses were performed in subjects who received ≥1 dose of study drug and provided ≥1 value for ≥1 primary or secondary endpoint without important protocol violations or non-evaluability relevant to the evaluation of pharmacokinetics.
- Relative exposure to ethinylestradiol and levonorgestrel when administered alone versus in combination with nintedanib was assessed using an ANOVA model with subject included as a random effect and treatment included as a fixed effect.

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https://www.usscicomms.com/respiratory/ACR2020/Vonk

Results

Subjects

- Seventeen subjects were treated and all completed the study. PK data could be analyzed from 15 subjects.

Baseline characteristics (n=17)

Mean age 59.1 years

Mean BMI 27.1 kg/m²

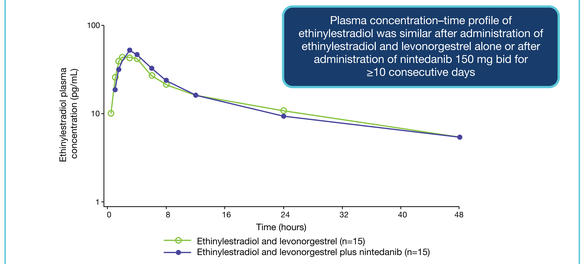
88.2% white

Pharmacokinetics

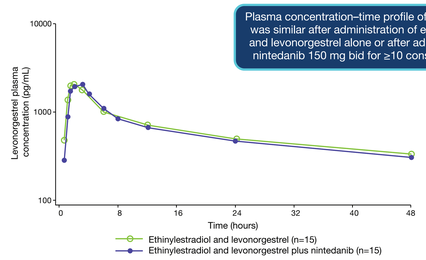
PK of ethinylestradiol and levonorgestrel after single dose administration of ethinylestradiol and levonorgestrel alone or after administration of nintedanib 150 mg bid for ≥10 consecutive days

Parameter	Ethinylestradiol		Levonorgestrel	
	Ethinylestradiol and levonorgestrel alone (n=15)	Ethinylestradiol and levonorgestrel with nintedanib (n=15)	Ethinylestradiol and levonorgestrel alone (n=15)	Ethinylestradiol and levonorgestrel with nintedanib (n=15)
$AUC_{0\text{-}tz}$ [pg·h/mL]	610 (65.6)	618 (57.3)	33100 (81.8)	31900 (81.1)
C_{max} [pg/mL]	54.7 (35.6)	63.9 (44.7)	3120 (55.6)	3150 (54.6)
$AUC_{0\text{-}\infty}$ [pg·h/mL]	750 (60.2)	759 (51.5)	56300 (102)	49600 (97.2)
$AUC_{0\text{-}24}$ [pg·h/mL]	490 (46.8)	517 (43.7)	22800 (76.8)	22200 (75.5)
$AUC_{tz\text{-}\infty}$ [%]	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). $AUC_{0\text{-}24}$, area under the concentration-time curve of ethinylestradiol and levonorgestrel in plasma over the time interval from 0 to 24 h. $AUC_{tz\text{-}\infty}$, percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation. tz, time point of the last quantifiable plasma concentration. t_{max}, time from (last) dosing to the maximum measured concentration of ethinylestradiol and levonorgestrel in plasma. $t_{1/2}$, terminal half-life of ethinylestradiol and levonorgestrel in plasma.



Data are gMean plasma concentration–time profiles of ethinylestradiol after a single oral administration of ethinylestradiol and levonorgestrel alone (Period 1) or after a single oral administration of ethinylestradiol and levonorgestrel with nintedanib 150 mg bid for ≥10 consecutive days (Period 2) on a semi-logarithmic scale.



Data are gMean plasma concentration–time profiles of levonorgestrel after a single oral administration of ethinylestradiol and levonorgestrel alone (Period 1) or after a single oral administration of ethinylestradiol and levonorgestrel after oral administrations of nintedanib 150 mg bid for ≥10 consecutive days (Period 2) on a semi-logarithmic scale.

Total exposure to ethinylestradiol ($AUC_{0\text{-}tz}$ and $AUC_{0\text{-}\infty}$) was similar when ethinylestradiol and levonorgestrel were administered alone or after administration of nintedanib 150 mg bid for ≥10 consecutive days

Peak exposure to ethinylestradiol (C_{max}) slightly increased (by approximately 17%) after administration of nintedanib 150 mg bid for ≥10 consecutive days

Parameter	Adjusted gMean (gSE)		Adjusted gMean ratio, % (90% confidence interval)
	Ethinylestradiol and levonorgestrel with nintedanib (n=15)	Ethinylestradiol and levonorgestrel alone (n=15)	
Ethinylestradiol			
$AUC_{0\text{-}tz}$ [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)
$AUC_{0\text{-}\infty}$ [pg·h/mL]	759.0 (1.1)	749.7 (1.1)	101.2 (94.0, 109.1)

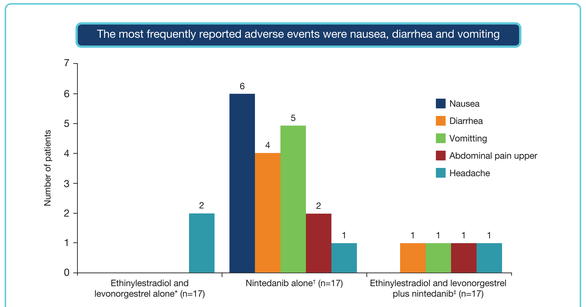
Data are adjusted gMeancomparisons of exposure to ethinylestradiol after single oral administration of ethinylestradiol and levonorgestrel alone (Period 1) and after oral administrations of nintedanib 150 mg bid for ≥10 consecutive days (Period 2).

No differences in total or peak exposure to levonorgestrel ($AUC_{0\text{-}tz}$ or C_{max}) were observed when ethinylestradiol and levonorgestrel were administered alone or after administration of nintedanib 150 mg bid for ≥10 consecutive days

Parameter	Adjusted gMean (gSE)		Adjusted gMean ratio, % (90% confidence interval)
	Ethinylestradiol and levonorgestrel with nintedanib (n=15)	Ethinylestradiol and levonorgestrel alone (n=15)	
Levonorgestrel			
$AUC_{0\text{-}tz}$ [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)
$AUC_{0\text{-}\infty}$ [pg·h/mL]	49605.4 (1.2)	56311.7 (1.2)	88.1 (80.0, 97.0)

Data are adjusted gMean comparisons of exposure to levonorgestrel after single oral administration of ethinylestradiol and levonorgestrel alone (Period 1) and after oral administrations of nintedanib 150 mg bid for ≥10 consecutive days (Period 2).

Adverse events



Adverse events were coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Data are number of patients with ≥1 such adverse event. *Adverse events reported from date of administration of ethinylestradiol and levonorgestrel in Period 1 plus 3 days. †Adverse events reported from first administration of nintedanib in Period 2 until the date of administration of ethinylestradiol and levonorgestrel in Period 2. ‡Adverse events reported from the date of administration of ethinylestradiol and levonorgestrel in Period 2 plus 3 days.

Conclusions

- **Pharmacokinetic results from this open-label, drug–drug interaction study indicated that there was no relevant effect of nintedanib 150 mg bid on the plasma exposure to ethinylestradiol and levonorgestrel in female patients with SSc-ILD.**
- **The adverse event profile of nintedanib combined with ethinylestradiol and levonorgestrel was consistent with the adverse event profile of nintedanib alone in patients with SSc-ILD.[3]**

References

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