Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-001009-26	
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Title of trial:	Relative bioavailability of nintedanib given alone and in combination with ketoconazole at steady state in healthy male volunteers (an open-label, randomised, two-way cross-over clinical Phase I study)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre, Birkendorfer Str. 65, Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objective:	The objective of this trial was to investigate the relative bioavailability of a single dose of nintedanib when given alone and in combination with steady state ketoconazole in healthy male subjects.
Methodology:	This was a randomised, open-label trial in healthy male subjects with a 2-way cross-over Pilot Part, followed by a 2-way cross-over Main Part. Subjects participated either in the Pilot Part with 2 treatments (A and B) given in 1 of the 2 treatment sequences (A_B and B_A) or in the Main Part with also 2 treatments (C and D) given in 1 of the 2 treatment sequences (C_D and D_C). Nintedanib administrations of the 2 respective treatments (A and B or C and D) were to be separated by a wash-out period of at least 14 days.

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No. of subjects:	
planned:	entered: 34 subjects (8 subjects in the Pilot Part and 26 subjects in the Main Part)
actual:	entered: 34 subjects (8 subjects in the Pilot Part and 26 subjects in the Main Part) Treatment sequence A_B: entered and treated: 4; analysed (for primary endpoint): 4 Treatment sequence B_A: entered and treated: 4; analysed (for primary endpoint): 3 Treatment sequence C_D: entered and treated: 13; analysed (for primary endpoint): 13 Treatment sequence D_C: entered and treated: 13; analysed (for primary endpoint): 11
Diagnosis and main criteria for inclusion:	Healthy male volunteers in the age range of 18 to 55 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.
Test product 1:	Nintedanib soft gelatine capsule
dose:	Pilot Part: 50 mg single dose Main Part: 50 mg single dose Alternatively, a 100 mg single dose could have been administered. The chosen dosing scheme depended on the increase in nintedanib exposure due to ketoconazole co-administration observed in the Pilot Part.
mode of admin.:	Oral administration with 240 mL of water under fed conditions
batch no.:	142597001
Test product 2:	Ketoconazole tablet (Polfarmex®)
dose:	Pilot Part: 400 mg once daily (2 tablets of 200 mg each) Main Part: 400 mg once daily (2 tablets of 200 mg each)
mode of admin.:	Oral administration with 240 mL of water under fed conditions
batch no.:	010212

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Duration of treatment:

Pilot Part:

Treatment A (Reference): Nintedanib (50 mg) was given as a single dose on Day 1.

Treatment B (Test): Ketoconazole (400 mg) was given once daily for 3 days starting on Day -2 and nintedanib (50 mg) was given as a single dose 1 h after the ketoconazole administration on Day 1, with ketoconazole under steady-state conditions.

Main Part:

Treatment C (Reference): Nintedanib (50 mg) was given as a single dose on Day 1.
Alternatively, nintedanib (100 mg) could have been given. The chosen dosing scheme depended on the increase in nintedanib exposure due to ketoconazole co-administration observed in the Pilot Part.

Treatment D (Test): Ketoconazole (400 mg) was given once daily for 3 days starting on Day -2 and nintedanib (50 mg) was given as a single dose 1 h after the ketoconazole administration on Day 1, with ketoconazole under steady-state conditions.
Alternatively, nintedanib (100 mg) could have been given as a single dose 1 h after the ketoconazole administration or 4 h before the ketoconazole administration on Day 1. The chosen dosing scheme depended on the increase in nintedanib exposure due to ketoconazole co-administration observed in the Pilot Part.

Eight subjects participated in the Pilot Part receiving treatments A and B in the order of their respective treatment sequence. Twenty-six different subjects participated in the Main Part receiving treatments C and D in the order of their respective treatment sequence. Nintedanib administrations of the 2 respective treatments (A and B or C and D) were to be separated by a wash-out period of at least 14 days. Furthermore, the last pharmacokinetic sampling on Day 4 of the Pilot Part and the first drug administration on Day 1 of the Main Part were to be separated by at least 3 weeks to allow enough time for the interim pharmacokinetic analysis.

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Criteria for evaluation:

Clinical pharmacology:

The following pharmacokinetic parameters were analysed as primary endpoints: $AUC_{0-\infty}$ and C_{max} of nintedanib.

The following pharmacokinetic parameter was assessed as secondary endpoint: AUC_{0-tz} of nintedanib.

In addition, the following pharmacokinetic parameters were calculated as appropriate:
t_{max}, AUC_{0-24}, CL/F, V_z/F, $t_{1/2}$, λ_z, MRT_{po}, and $\%AUC_{tz-\infty}$ for nintedanib, and AUC_{0-tz}, $AUC_{0-\infty}$, C_{max}, t_{max}, AUC_{0-24}, $t_{1/2}$, λ_z, MRT_{po}, and $\%AUC_{tz-\infty}$, for the 2 clinically relevant nintedanib metabolites (BIBF 1202 and BIBF 1202-glucuronide).

Furthermore, plasma concentrations of ketoconazole at 1 h before ketoconazole administration as well as 1 h and 2 h after ketoconazole administration were determined on Day 1 of treatments B and D.

Safety:

Safety and tolerability were determined based on monitoring of adverse events, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory assessments (haematology, clinical chemistry, and urinalysis), and physical examination.

Statistical methods:

Point estimators (geometric means) of the median intrasubject ratios of $AUC_{0-\infty}$ and C_{max} of nintedanib and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model used was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. The 2-sided 90% CIs were computed based on the t-distribution.

An exploratory interaction analysis between treatment and P-glycoprotein (P-gp) as well as Cytochrome (CYP) 3A4 genotype were to be carried out, if the number of subjects with polymorphism in these genes allowed it. Descriptive statistics were calculated for all endpoints.

According to Protocol Amendment 2 (dated 15 Nov 2012), pharmacokinetic and statistical evaluations could be conducted based on the data of subjects from the Pilot Part and the Main Part together, as the nintedanib dose used in each of the 2 trial parts was identical.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

In this trial, 34 subjects (8 subjects in the Pilot Part and 26 subjects in the Main Part) received trial medication and 29 subjects (7 subjects in the Pilot Part and 22 subjects in the Main Part) completed the trial according to the clinical trial protocol. The remaining 5 subjects were withdrawn prematurely from the trial due to ALT/GPT or bilirubin measurements which were slightly outside the reference range (in accordance with exclusion criterion No. 23). The trial population consisted of healthy male white subjects, with the exception of 1 healthy male black subject in the Main Part. The mean age was 35.9 years, ranging from 18 to 53 years, and the mean BMI was 25.2 kg/m^2, ranging from 19.8 to 29.7 kg/m^2.

As the subjects in the Main part received the same dose of nintedanib (50 mg) as the subjects in the Pilot Part, all analyses could be based on the pooled data from both trial parts. Pharmacokinetic parameters of nintedanib after single dose administration without and with steady state ketoconazole are listed in Table 1.

Table 1 Pharmacokinetic parameters of nintedanib after administration of a single 50 mg nintedanib dose alone and following multiple administrations of 400 mg ketoconazole once daily for 3 days in the Pilot Part + Main Part

	Nintedanib alone (reference) (N=31)		Nintedanib + ketoconazole (test) (N=29)	
	gMean	gCV [%]	gMean	gCV [%]
$AUC_{0-\infty}$ [ng·h/mL]	38.6	42.5	61.3	40.4
AUC_{0-tz} [ng·h/mL]	35.7	47.8	59.4	40.8
C_{max} [ng/mL]	4.19	71.0	7.13	44.4
t_{max} [1] [h]	4.00	3.00 – 6.00	3.00	1.00 – 6.00
$t_{1/2}$ [h]	18.1	34.9	15.6	38.3
CL/F [mL/min]	21600	42.5	13600	40.4
V_z/F [L]	33900	62.1	18400	42.8

[1] For t_{max}, the median and range are given instead of gMean and gCV.

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Clinical pharmacology results (continued):

Compared with the administration of nintedanib alone, co-administration with steady state ketoconazole (test treatment) resulted in increased exposure to nintedanib. The apparent oral clearance and apparent volume of distribution were higher during administration of nintedanib alone than during co-administration. Other pharmacokinetic parameters were similar between both treatments, indicating an effect on the bioavailability rather than on elimination or disposition. Ketoconazole had similar effects on the pharmacokinetic parameters of BIBF 1202 and of BIBF 1202-glucuronide as on those of nintedanib.

Statistical comparison of primary and secondary endpoints for the treatments showed that the relative bioavailability of nintedanib was larger when ketoconazole was concomitantly administered than when nintedanib was administered alone. The 90% CIs were outside the bioequivalence acceptance criteria of 80 to 125% (see Table 2). A sensitivity analysis yielded comparable results as the primary analysis.

Table 2 Primary analysis of relative bioavailability of nintedanib after single oral administration of nintedanib alone or co-administration with steady state ketoconazole in the Pilot Part + Main Part

Pharmacokinetic parameter	Adjusted gMean ratio of test to reference treatment [%][1]	90% CI of gMean ratio		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	160.5	148.2	173.7	17.9
AUC_{0-tz} [ng·h/mL]	168.1	155.3	182.0	17.9
C_{max} [ng/mL]	179.6	157.6	204.8	29.9

[1] For the calculation of the adjusted gMean, the data of 29 subjects for the test treatment and of 31 subjects for the reference treatment were used.

The P-gp genotyping analysis revealed no change in $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} in the reference treatment or in $RAUC_{0-\infty,T/R}$, $RAUC_{0-tz,T/R}$, and $RC_{max,T/R}$ values for nintedanib, BIBF 1202 and BIBF 1202-glucuronide in subjects with base exchanges in the P-gp gene as compared to subjects with wild-type P-gp gene.

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Safety results:

Of the 34 entered subjects, 29 subjects received 400 mg ketoconazole once daily for 3 days and 2 single doses of 50 mg nintedanib, as planned. Three subjects received only 1 single dose of 400 mg ketoconazole, before being withdrawn from the trial, and 2 subjects received a single dose of 50 mg nintedanib as well as 1 or 2 single doses of 400 mg ketoconazole, before discontinuing the trial.

In this trial, a total of 14 out of 34 subjects (41.2%) reported at least 1 adverse event during the treatment periods of the trial. The frequency of subjects with treatment-emergent adverse events was comparable under treatment with nintedanib alone and under the combined treatment of nintedanib and ketoconazole, with 8 out of 31 subjects and 8 out of 29 subjects (corresponding to 25.8% and 27.6%, respectively). The frequency was somewhat lower under treatment with ketoconazole alone (3 out of 34 subjects, 8.8%). The most frequently reported adverse events overall at the system organ class (SOC) level were nervous system disorders (9 out of 34 subjects, 26.5%), followed by infections/infestations (3 out of 34 subjects, 8.8%). The most frequent adverse event by preferred term was headache (9 out of 34 subjects, 26.5%). Nasopharyngitis was reported by 3 out of 34 subjects (8.8%), while back pain was reported by 2 out of 34 subjects (5.9%). All other adverse events were reported by 1 out of 34 subjects (2.9%) each. The frequency of subjects with headache was higher under treatment with nintedanib alone and under the combined treatment of nintedanib and ketoconazole (5 out of 31 subjects and 5 out of 29 subjects, corresponding to 16.1% and 17.2%, respectively) than under treatment with ketoconazole alone (2 out of 34 subjects, 5.9%). No other clustering of any specific adverse event during any treatment was apparent.

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Safety results (continued):	The investigator classified adverse events of 7 out of 34 subjects (20.6%) as possibly related to the trial medication. The majority of the drug-related adverse events (4 cases of headache and 1 case of fatigue) were reported under treatment with nintedanib alone, while 1 case of headache and 1 case of upper abdominal pain were considered drug-related under treatment with ketoconazole alone and 2 cases of back pain were considered drug-related under the combined treatment of ketoconazole with nintedanib. All other adverse events were judged as not drug-related. No death, no other serious or severe adverse events, no adverse events of special interest, and no adverse events leading to discontinuation of trial medication occurred in this trial. There were no clinically relevant findings with respect to safety laboratory measurements, ECG recordings, physical examinations, and vital sign measurements.
Conclusions:	Inhibition of P-gp by steady state ketoconazole resulted in an increased nintedanib exposure following administration of single-dose nintedanib in the presence of steady state ketoconazole compared with administration of single-dose nintedanib alone. The adjusted gMean ratios of T/R treatments for $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} were 160.5%, 168.1% and 179.6%, respectively. Median t_{max} and $t_{1/2}$ were comparable between both treatments, indicating no substantial alteration in elimination kinetics of nintedanib. No difference in $AUC_{0-\infty}$, AUC_{0-tz}, C_{max} in the reference treatment (nintedanib alone) or in $RAUC_{0-\infty,T/R}$, $RAUC_{0-tz,T/R}$, and $RC_{max,T/R}$ values was observed for nintedanib, BIBF 1202, or BIBF 1202-glucuronide in subjects with base exchanges in the P-gp gene as compared to subjects with wild-type P-gp gene. Administration of nintedanib alone or in combination with ketoconazole was generally safe and well tolerated by the healthy male subjects in this trial.

Trial Synopsis - Appendix

The results tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables complement the results for the primary and secondary endpoints as summarized below.

Results for	**presented in**
$AUC_{0-\infty}$ (primary endpoint)	Table 15.5.1.1: 2
C_{max} (primary endpoint)	Table 15.5.1.2: 2
AUC_{0-tz} (secondary endpoint)	Section 16.1.9.3. Table 1.3.5

Table 15.5.1.1: 2 Adjusted by-treatment geometric means and relative bioavailability
comparison NIN+KTZ : NIN
AUCinfpred [ng*h/mL] for BIBF 1120 BS (PLASMA EDTA)
Treated set

NIN+KTZ N	NIN+KTZ gMean	NIN N	NIN gMean	Ratio NIN+KTZ : NIN [%]	gSE	90% Confidence interval [%]	[%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
29	61.843	31	38.535	160.48	1.048	148.245	173.736	17.9	1.0000

Table 15.5.1.2: 2 Adjusted by-treatment geometric means and relative bioavailability
comparison NIN+KTZ : NIN
Cmax [ng/mL] for BIBF 1120 BS (PLASMA EDTA)
Treated set

NIN+KTZ N	NIN+KTZ gMean	NIN N	NIN gMean	Ratio NIN+KTZ : NIN [%]	gSE	90% Confidence interval [%]		Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
29	7.469	31	4.158	179.62	1.080	157.557	204.779	29.9	1.0000

Table 1.3.5 Adjusted by-treatment geometric means and relative bioavailability
comparison NIN+KTZ : NIN
AUClast [ng*h/mL] for BIBF 1120 BS (PLASMA EDTA)
Treated set

NIN+KTZ N	NIN+KTZ gMean	NIN N	NIN gMean	Ratio NIN+KTZ : NIN [%]	gSE	90% Confidence interval [%]		Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
29	59.923	31	35.650	168.09	1.048	155.252	181.981	17.9	1.0000