Clinical trial results:
A randomised, open label, parallel group Phase II study comparing the efficacy and tolerability of BIBF 1120 versus sunitinib in previously untreated patients with Renal Cell Cancer

Summary

EudraCT number	2009-009516-44
Trial protocol	GB HU
Global end of trial date	19 June 2020

Results information

Result version number	v1
This version publication date	02 July 2021
First version publication date	02 July 2021

Trial information

Trial identification

Sponsor protocol code	1199.26

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01024920
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 November 2011
Global end of trial reached?	Yes
Global end of trial date	19 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this trial were to compare the efficacy and safety of nintedanib (BIBF 1120) versus sunitinib in patients with advanced renal cell cancer (RCC) and to investigate the effects of nintedanib on the heart rate corrected QT interval (QTcF).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Ukraine: 56
Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	113
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	81
From 65 to 84 years	31
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

An open-label, 2:1 randomised, parallel-arm comparison of nintedanib versus sunitinib in patients with advanced renal cell cancer (RCC) who had not received prior systemic therapy.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

Period 1 title	Randomised
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study and patients were randomised to receive either nintedanib (BIBF 1120), or sunitinib treatment.
The electrocardiogram and pharmacokinetic (PK) sampleswere identified by patient and study number only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib (BIBF 1120)

Arm description:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively. The dose was continued daily until withdrawal criteria were fulfilled.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	BIBF 1120
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively.

Arm title	Sunitinib

Arm description:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Arm type	Active comparator

Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	Sutent ®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Number of subjects in period 1	Nintedanib (BIBF 1120)	Sunitinib
Started	67	32
Completed	64	32
Not completed	3	0
Not treated	3	-

Period 2

Period 2 title	Treated
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study and patients were randomised to receive either nintedanib (BIBF 1120), or sunitinib treatment.
The electrocardiogram and pharmacokinetic (PK) sampleswere identified by patient and study number only.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib (BIBF 1120)

Arm description:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively. The dose was continued daily until withdrawal criteria were fulfilled.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	BIBF 1120
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval

of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively.

Arm title	Sunitinib

Arm description:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Arm type	Active comparator
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	Sutent ®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 are the randomised subjects, period 2 the treated, baseline characteristics are reported for the treated subjects.

Number of subjects in period 2[2]	Nintedanib (BIBF 1120)	Sunitinib
Started	64	32
Treated	64	32
Completed	0	0
Not completed	64	32
Patient refusal to continue	4	-
Adverse event, non-fatal	8	4
Progressive disease	47	25
Lost to follow-up	-	1
Other than listed	5	1
Protocol deviation	-	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 113 enrolled participants, 96 were treated, which are reported in the baseline characteristics.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib (BIBF 1120)
Reporting group description:	
Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively. The dose was continued daily until withdrawal criteria were fulfilled.	
Reporting group title	Sunitinib
Reporting group description:	
Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.	

Reporting group values	Nintedanib (BIBF 1120)	Sunitinib	Total
Number of subjects	64	32	96
Age categorical			
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	25	67
From 65-84 years	21	7	28
85 years and over	1	0	1
Age Continuous			
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: years			
arithmetic mean	60.4	55.5	
standard deviation	± 9.7	± 11.4	-
Sex: Female, Male			
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units:			
Female	20	10	30
Male	44	22	66
Race (NIH/OMB)			
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	64	32	96
More than one race	0	0	0
Unknown or Not Reported	0	0	0
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at -5 minutes (min) on Day -1 (prior to the first dosing of nintedanib). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	405.2	99999	
standard deviation	± 19.6	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 1 hour (h) on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	406.0	99999	
standard deviation	± 20.3	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were at 2 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	405.3	99999	
standard deviation	± 19.4	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 3 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	406.7	99999	
standard deviation	± 19.4	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 4 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	407.0	99999	
standard deviation	± 17.8	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 5 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	407.2	99999	

standard deviation	± 18.0	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 6 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	405.9	99999	
standard deviation	± 18.3	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 7 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	405.4	99999	
standard deviation	± 19.2	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 10 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	406.6	99999	
standard deviation	± 19.2	± 99999	-
QTcF interval baseline values			
QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) baseline values were measured at 12 h on Day -1 (prior to the first dosing of nintedanib (BIBF 1120)). 99999= Not applicable Full analysis set electrocardiogram (FAS-ECG).			
Units: milliseconds (ms)			
arithmetic mean	406.0	99999	
standard deviation	± 19.2	± 99999	-

End points

End points reporting groups

Reporting group title	Nintedanib (BIBF 1120)

Reporting group description:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively. The dose was continued daily until withdrawal criteria were fulfilled.

Reporting group title	Sunitinib

Reporting group description:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Reporting group title	Nintedanib (BIBF 1120)

Reporting group description:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively. The dose was continued daily until withdrawal criteria were fulfilled.

Reporting group title	Sunitinib

Reporting group description:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Primary: Probability rates of progression-free survival at 9 months

End point title	Probability rates of progression-free survival at 9 months

End point description:

Progression free survival rate at 9 months is the estimated probability of being alive and not having progressive disease at 9 months after randomisation.

Progression was defined using Response Evaluation Criteria In Solid Tumors Criteria version 1.1 (RECIST v1.1), at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since the treatment started together with an absolute increase in the sum of the longest diameters of at least 5 mm, or the appearance of one or more new lesions.
Tumour imaging was made by investigators using Computed tomography (CT)/Magnetic Resonance imaging (MRI) every 12 weeks after the first administration of the trial medication.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Primary

End point timeframe:

At 9 months after randomisation.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[1]	32[2]		
Units: Probability				
number (confidence interval 95%)	0.431 (0.306 to 0.550)	0.452 (0.274 to 0.614)		

Notes:

[1] - TS

[2] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sunitinib v Nintedanib (BIBF 1120)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8531 [3]
Method	Normal approximation test

Notes:

[3] - P−value for comparison of Kaplan−Meier estimates at 9 months using normal approximation test (two−sided).

Primary: Time-matched change from baseline to Day 15 in QTcF (QT interval corrected by the Fridericia formula) at 0 hour (h), at 1 h, at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)

End point title	Time-matched change from baseline to Day 15 in QTcF (QT interval corrected by the Fridericia formula) at 0 hour (h), at 1 h, at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)[4][5]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate by the Fridericia formula. Baseline QTcF measurement at time t was defined as the QTcF measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 15 in QTcF at time t was defined as the QTcF measurement following administration of nintedanib on Day 15 obtained at time t minus baseline QTcF measurement at time t. 0 h is 5 min prior to dosing at Day 15. Time-matched change from baseline to Day 15 in QTcF was modelled using a linear mixed-effects model for repeated measures which included 'time' as repeated measures and the time-matched baseline value as a covariate. Adjusted means with corresponding 2-sided 90% confidence intervals are reported. FAS-ECG.

End point type	Primary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 15. Baseline (Day -1) values were taken at exactly the same time points as on Day 15.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: End point was analyzed only descriptively

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[6]			
Units: milliseconds (ms)				
least squares mean (confidence interval 90%)				
Time-matched change from Day-1 to Day 15 at -5 min	2.6 (-0.7 to 5.9)			
Time-matched change from Day-1 to Day 15 at 1 h	0.4 (-2.8 to 3.7)			
Time-matched change from Day-1 to Day 15 at 2 h	-1.7 (-4.9 to 1.6)			
Time-matched change from DAy -1 to Day 15 at 3 h	-0.5 (-3.8 to 2.8)			
Time-matched change from Day -1 to Day 15 at 4 h	-0.5 (-3.8 to 2.8)			
Time-matched change from Day -1 to Day 15 at 5 h	0.3 (-3.0 to 3.6)			
Time-matched change from baseline to Day 15 at 6 h	2.2 (-1.1 to 5.5)			
Time-matched change from Day -1 to Day 15 at 7 h	3.1 (-0.2 to 6.4)			
Time-matched change from Day -1 to Day 15 at 10 h	0.1 (-3.2 to 3.4)			
Time-matched change from Day-1 to Day 15 at 12 h	1.6 (-1.7 to 4.9)			

Notes:

[6] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression free survival (PFS) from randomisation to the occurrence of disease progression (by RECIST Version 1.1) or death, whichever occurred first.
Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since the treatment started together with an absolute increase in the sum of the longest diameters of at least 5 mm, or the appearance of one or more new lesions.
Tumour imaging was made by investigators using Computed tomography (CT)/Magnetic Resonance imaging (MRI) every 12 weeks after the first administration of the trial medication.
The Kaplan-Meier method was used to calculate the estimates.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From the start of study until the cut-off date for 3 year efficacy analysis, up to 3 years.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[7]	32[8]		
Units: Months				
median (confidence interval 95%)	8.44 (5.59 to 11.10)	8.38 (5.59 to 13.86)		

Notes:

[7] - TS

[8] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A stratified log-rank test (two-sided, 0.05 significance level) was used to test the effect of nintedanib on PFS compared with sunitinib. The test was stratified by Motzer risk score category (low/intermediate or high) and prior nephrectomy surgery for Renal Cell Cancer (yes or no).

Comparison groups	Nintedanib (BIBF 1120) v Sunitinib
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6395
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	1.8

Secondary: Objective response according to RECIST criteria

End point title	Objective response according to RECIST criteria

End point description:

Objective response was defined as complete response (CR, the disappearance of all target and non-target lesions and no new lesions) or partial response (PR, at least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum of the longest diameters and no new lesions) as determined by RECIST Version 1.1. Numbers of participants with objective response are reported.
Tumour imaging was made by investigators using Computed tomography (CT)/Magnetic Resonance imaging (MRI) every 12 weeks after the first administration of the trial medication.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From the start of study until the cut-off date for 3 year efficacy analysis, up to 3 years.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[9]	32[10]		
Units: Participants				
Complete Response	0	1		
Partial response	14	11		

Notes:

[9] - TS

[10] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

A logistic regression model stratified by Motzer risk score category and prior surgery for renal cell cancer (RCC) was used to compare the objective response rate between the two treatment arms. The corresponding odds ratio and 95% CI was also presented. Odds ratio > 1 favours nintedanib.

Comparison groups	Nintedanib (BIBF 1120) v Sunitinib
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1213
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.484
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.193
upper limit	1.212

Secondary: Duration of objective response

End point title	Duration of objective response

End point description:

Duration (months) of objective response was measured from the time of first objective response to the time of disease progression (by RECIST Version 1.1) or death, whichever occurred first.
Objective response was defined as complete response (CR, the disappearance of all target and non-target lesions and no new lesions) or partial response (PR, at least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum of the longest diameters and no new lesions) as determined by RECIST Version 1.1.
Tumour imaging was made by investigators using Computed tomography (CT)/Magnetic Resonance imaging (MRI) every 12 weeks after the first administration of the trial medication. The Kaplan-Meier method was used to calculate the estimates.
99999= Not applicable. Upper Interquartile-Range cannot be estimated based on the current limited data in a small sample−sized study.
Treated set (TS)

End point type	Secondary

End point timeframe:

From the time of first objective response to the time of disease progression or death (whichever comes first), up to 3 years.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[11]	12[12]		
Units: Months				
median (inter-quartile range (Q1-Q3))	19.42 (8.31 to 99999)	11.66 (7.06 to 28.45)		

Notes:

[11] - TS

[12] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was calculated as the time (months) from randomisation to death. Patients for whom there was no evidence of death at the time of analysis were censored on the date that they were last known to have been alive.
The Kaplan-Meier method was used to calculate the estimates.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From randomisation to death, up to 3 years.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[13]	32[14]		
Units: Months				
median (confidence interval 95%)	20.37 (13.86 to 29.01)	21.22 (11.01 to 31.74)		

Notes:

[13] - TS

[14] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by Motzer risk score and previous surgery. Hazard ratio < 1 favours nintedanib.

Comparison groups	Nintedanib (BIBF 1120) v Sunitinib

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7593 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.542
upper limit	1.564

Notes:

[15] - P−value from log−rank stratified by Motzer risk score and previous surgery.

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression is defined as the time period from randomisation to objective tumour progression. Patients with no progression (by RECIST Version 1.1) were censored at the date of the last evaluable imaging.
Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), at least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the longest diameters recorded since the treatment started together with an absolute increase in the sum of the longest diameters of at least 5 mm, or the appearance of one or more new lesions.
Tumour imaging was made by investigators using Computed tomography (CT)/Magnetic Resonance imaging (MRI) every 12 weeks after the first administration of the trial medication. The Kaplan-Meier method was used to calculate the estimates.
Treated set (TS).

End point type	Secondary

End point timeframe:

From randomisation up to objective tumour progression, up to 3 years.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[16]	32[17]		
Units: Months				
median (confidence interval 95%)	8.48 (7.56 to 11.20)	8.54 (5.68 to 13.90)		

Notes:

[16] - TS

[17] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

P−value from log−rank stratified by Motzer risk score and previous surgery.
Hazard ratio from Cox proportional hazards model stratified by Motzer risk score and previous surgery.
Hazard ratio < 1 favours nintedanib.

Comparison groups	Nintedanib (BIBF 1120) v Sunitinib

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5958
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	1.873

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Time to treatment failure was defined as the time from randomisation to objective tumour progression (by RECIST Version 1.1), death, global deterioration of health status requiring treatment discontinuation, or start of new anticancer treatment, whichever came first. Tumour imaging was made by investigators using Computed tomography (CT)/Magnetic Resonance imaging (MRI) every 12 weeks after the first administration of the trial medication.The Kaplan-Meier method was used to calculate the estimates.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From randomisation up to objective tumour progression, up to 3 years.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[18]	32[19]		
Units: Month				
median (confidence interval 95%)	8.44 (5.62 to 10.97)	8.36 (5.55 to 13.86)		

Notes:

[18] - TS

[19] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

P−value from log−rank stratified by Motzer risk score and previous surgery (two−sided).
Hazard ratio from Cox proportional hazards model stratified by Motzer risk score and previous surgery.
Hazard ratio < 1 favours nintedanib.

Comparison groups	Nintedanib (BIBF 1120) v Sunitinib

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5712
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.812

Secondary: Time-matched change from baseline to Day 1 in QTcF (QT interval corrected by the Fridericia formula) at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)

End point title	Time-matched change from baseline to Day 1 in QTcF (QT interval corrected by the Fridericia formula) at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)[20]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate by the Fridericia formula. Baseline QTcF measurement at time t was defined as the QTcF measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 in QTcF at time t was defined as the QTcF measurement following administration of nintedanib on Day 1 obtained at time t minus baseline QTcF measurement at time t.
Time-matched change from baseline to Day 1 in QTcF was modelled using a linear mixed-effects model for repeated measures which included 'time' as repeated measures and the time-matched baseline value as a covariate. Adjusted means with corresponding 2-sided 90% confidence intervals are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1. Baseline (Day -1) values were taken at exactly the same time points as on Day 1.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[21]			
Units: milliseconds (ms)				
least squares mean (confidence interval 90%)				
Time-matched change from baseline to Day 1 at 1 h	-1.6 (-4.4 to 1.2)			
Time-matched change from baseline to Day 1 at 2 h	-3.1 (-6.0 to -0.3)			
Time-matched change from baseline to Day 1 at 3 h	-2.6 (-5.5 to 0.2)			
Time-matched change from baseline to Day 1 at 4 h	-2.6 (-5.4 to 0.3)			

Time-matched change from baseline to Day 1 at 5 h	-1.4 (-4.3 to 1.4)			
Time-matched change from baseline to Day 1 at 6 h	-2.0 (-4.8 to 0.9)			
Time-matched change from baseline to Day 1 at 7 h	-1.5 (-4.4 to 1.3)			
Time-matched change from baseline to Day 1 at 10 h	-3.6 (-6.4 to -0.7)			
Time-matched change from baseline to Day 1 at 12 h	-2.2 (-5.0 to 0.7)			

Notes:

[21] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time-matched change from baseline in QTcF interval (QT interval corrected by the Fridericia formula) at the time of each participant's maximum plasma concentration of nintedanib (BIBF 1120), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time-matched change from baseline in QTcF interval (QT interval corrected by the Fridericia formula) at the time of each participant's maximum plasma concentration of nintedanib (BIBF 1120), calculated separately for Days 1 and 15 of treatment cycle 1[22]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula. Baseline QTcF measurement at time t was defined as the QTcF measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in QTcF at time t was defined as the QTcF measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline QTcF measurement at time t.
For each participant 'Time-matched change from baseline to Day 1 (Day 15) in QTcF' at the time of the participant's maximum nintedanib plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[23]			
Units: milliseconds (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	-2.8 (-5.0 to -0.6)			

Day 15	-3.2 (-5.9 to -0.4)			

Notes:

[23] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in QTcF interval at the time of each patient’s maximum plasma concentration of BIBF 1202 (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in QTcF interval at the time of each patient’s maximum plasma concentration of BIBF 1202 (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1[24]

End point description:

Baseline QTcF measurement at time t was defined as the QTcF measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in QTcF at time t was defined as the QTcF measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline QTcF measurement at time t.
For each participant ‘Time-matched change from baseline to Day 1 (Day 15) in QTcF’ at the time of the participant's maximum BIBF 1202 (a nintedanib (BIBF 1120) metabolite) plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[25]			
Units: milliseconds (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	-2.5 (-4.6 to -0.5)			
Day 15	-1.1 (-3.8 to 1.6)			

Notes:

[25] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in QTcF interval at the time of each patient's maximum plasma concentration of BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in QTcF interval at the time of each patient's maximum plasma concentration of BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1[26]

End point description:

Baseline QTcF measurement at time t was defined as the QTcF measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in QTcF at time t was defined as the QTcF measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline QTcF measurement at time t.
For each participant 'Time-matched change from baseline to Day 1 (Day 15) in QTcF' at the time of the participant's maximum BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite) plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[27]			
Units: milliseconds (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	-2.4 (-4.9 to 0.0)			
Day 15	-1.5 (-4.2 to 1.2)			

Notes:

[27] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Average time-matched changes from baseline in QTcF interval over 1 h to 12 h after dosing on Days 1 and 15 of treatment cycle 1

End point title	Average time-matched changes from baseline in QTcF interval over 1 h to 12 h after dosing on Days 1 and 15 of treatment cycle 1[28]

End point description:

Average time-matched in QTcF interval (QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula) changes over 1 to 12 hours was evaluated using a t-test for paired observation. The mean differences between post-treatment values (Days 1 and 15) and baseline (Day -1) along with two-sided 90% confidence limits are reported.

Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 1 and on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle. Continues in the description.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[29]			
Units: milliseconds (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	-2.2 (-3.5 to -0.8)			
Day 15	0.5 (-1.4 to 2.3)			

Notes:

[29] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time-matched changes from baseline to Day 15 in QT interval at 0 hour (h), at 1 h, at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)

End point title	Time-matched changes from baseline to Day 15 in QT interval at 0 hour (h), at 1 h, at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)[30]

End point description:

QT interval is the electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave. Baseline QT measurement at time t was defined as the QT measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 15 in QT at time t was defined as the QT measurement following administration of nintedanib on Day 15 obtained at time t minus baseline QT measurement at time t. 0 h is 5 min prior to dosing at Day 15.
Time-matched change from baseline to Day 15 in QT was modelled using a linear mixed-effects model for repeated measures which included 'time' as repeated measures and the time-matched baseline value as a covariate. Adjusted means with corresponding 2-sided 90% confidence intervals are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 15. Baseline (Day -1) values were taken at exactly the same time points as on Day 15.

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[31]			
Units: milliseconds (ms)				
least squares mean (confidence interval 90%)				
Time-matched change from Day-1 to Day15 at -5 min	1.0 (-3.6 to 5.6)			
Time-matched change from Day -1 to Day 15 at 1 h	0.5 (-4.1 to 5.1)			
Time-matched change from Day -1 to Day 15 at 2 h	1.6 (-3.0 to 6.2)			
Time-matched change from Day -1 to Day 15 at 3 h	4.4 (-0.2 to 9.0)			
Time-matched change from Day -1 to Day 15 at 4 h	4.7 (0.0 to 9.3)			
Time-matched change from Day-1 to Day 15 at 5 h	5.1 (0.5 to 9.7)			
Time-matched change from Day -1 to Day 15 at 6 h	7.7 (3.1 to 12.3)			
Time-matched change from Day-1 to Day 15 at 7 h	7.1 (2.5 to 11.7)			
Time-matched change from Day-1 to Day 15 at 10 h	3.4 (-1.2 to 8.0)			
Time-matched change from Day-1 to Day 15 at 12 h	4.2 (-0.4 to 8.8)			

Notes:

[31] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time-matched changes from baseline to Day 1 in QT interval at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)

End point title	Time-matched changes from baseline to Day 1 in QT interval at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)[32]

End point description:

QT interval is the electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave. Baseline QT measurement at time t was defined as the QT measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 in QT at time t was defined as the QT measurement following administration of nintedanib on Day 1 obtained at time t minus baseline QT measurement at time t.
Time-matched change from baseline to Day 1 in QT was modelled using a linear mixed-effects model for repeated measures which included 'time' as repeated measures and the time-matched baseline value as a covariate. Adjusted means with corresponding 2-sided 90% confidence intervals are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1. Baseline (Day -1) values were taken at exactly the same time points as on Day 1.

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[33]			
Units: millisecond (ms)				
least squares mean (confidence interval 90%)				
Time−matched change from Day -1 to Day 1 at 1 h	-2.0 (-6.3 to 2.3)			
Time−matched change from Day-1 to Day 1 at 2 h	1.6 (-2.8 to 5.9)			
Time−matched change from Day-1 to Day 1 at 3 h	3.5 (-0.8 to 7.8)			
Time−matched change from Day-1 to Day 1 at 4 h	1.4 (-2.9 to 5.7)			
Time−matched change from Day-1 to Day 1 at 5 h	1.4 (-2.9 to 5.7)			
Time−matched change from Day-1 to Day 1 at 6 h	1.8 (-2.6 to 6.1)			
Time−matched change from Day-1 to Day 1 at 7 h	0.7 (-3.6 to 5.0)			
Time−matched change from Day-1 to Day 1 at 10 h	-1.7 (-6.0 to 2.7)			
Time−matched change from Day-1 to Day 1at 12 h	-2.2 (-6.5 to 2.2)			

Notes:

[33] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in QT interval at the time of each patient’s maximum plasma concentration of nintedanib (BIBF 1120), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in QT interval at the time of each patient’s maximum plasma concentration of nintedanib (BIBF 1120), calculated separately for Days 1 and 15 of treatment cycle 1[34]

End point description:

QT interval is the (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave. Baseline QT measurement at time t was defined as the QT measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in QT at time t was defined as the QT measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline QT measurement at time t.
For each participant ‘Time-matched change from baseline to Day 1 (Day 15) in QT’ at the time of the participant's maximum nintedanib plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 1 and on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[35]			
Units: millisecond (ms)				
arithmetic mean (confidence interval 90%)				
Day 1 Day 15	0.9 (-2.3 to 4.0) -0.4 (-5.0 to 4.1)			

Notes:

[35] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in QT interval at the time of each patient’s maximum plasma concentration of BIBF 1202 (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in QT interval at the time of each patient’s maximum plasma concentration of BIBF 1202 (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1[36]

End point description:

QT interval is the (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave. Baseline QT measurement at time t was defined as the QT measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in QT at time t was defined as the QT measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline QT measurement at time t.
For each participant ‘Time-matched change from baseline to Day 1 (Day 15) in QT’ at the time of the participant's maximum BIBF 1202 (a nintedanib (BIBF 1120) metabolite) plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle. Continues in the description.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[37]			
Units: millisecond (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	1.2 (-1.9 to 4.3)			
Day 15	1.8 (-2.7 to 6.3)			

Notes:

[37] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in QT interval at the time of each patient's maximum plasma concentration BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in QT interval at the time of each patient's maximum plasma concentration BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1[38]

End point description:

QT interval is the (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave. Baseline QT measurement at time t was defined as the QT measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in QT at time t was defined as the QT measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline QT measurement at time t.
For each participant 'Time-matched change from baseline to Day 1 (Day 15) in QT' at the time of the participant's maximum BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite) plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[39]			
Units: millisecond (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	-0.4 (-4.0 to 3.1)			

Day 15	1.3 (-3.2 to 5.9)			

Notes:

[39] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Averaged time-matched changes from baseline in QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) over 1 h to 12 h after dosing on Days 1 and 15 of treatment cycle 1

End point title	Averaged time-matched changes from baseline in QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) over 1 h to 12 h after dosing on Days 1 and 15 of treatment cycle 1[40]

End point description:

Averaged time-matched QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) changes from baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120) to Day 1 (first drug dose nintedanib (BIBF 1120)) and to Day 15 (steady state) over 1 to 12 hours was evaluated using a t-test for paired observation. The mean differences between post-treatment values (Days 1 and 15) and baseline (Day -1) along with two-sided 90% confidence limits are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 1 and on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle.

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[41]			
Units: millisecond (ms)				
arithmetic mean (confidence interval 90%)				
Day 1	0.9 (-1.3 to 3.0)			
Day 15	4.2 (0.6 to 7.7)			

Notes:

[41] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched heart rate (HR) changes from baseline to Day 15 at 0

hour (h), at 1 h, at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)

End point title	Time−matched heart rate (HR) changes from baseline to Day 15 at 0 hour (h), at 1 h, at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)[42]

End point description:

Baseline heart rate (HR) measurement at time t was defined as the HR measurement collected 1 day prior to the day of the first administration of nintedanib (BIBF 1120) at time t. Time-matched change from baseline to Day 15 in HR at time t was defined as the HR measurement following administration of nintedanib (BIBF 1120) on Day 15 obtained at time t minus baseline HR measurement at time t. 0 h is 5 min prior to dosing at Day 15.
Time-matched change from baseline to Day 15 in HR was modelled using a linear mixed-effects model for repeated measures which included 'time' as repeated measures and the time-matched baseline value as a covariate. Adjusted means with corresponding 2-sided 90% confidence intervals are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 15. Baseline (Day -1) values were taken at exactly the same time points as on Day 15.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[43]			
Units: beats per minute (bpm)				
least squares mean (confidence interval 90%)				
Time−matched change from Day-1 to Day15 at -5 min	0.9 (-1.2 to 3.0)			
Time−matched change from Day-1 to Day 15 at 1 h	-0.3 (-2.4 to 1.9)			
Time−matched change from Day-1 to Day 15 at 2 h	-2.0 (-4.2 to 0.1)			
Time−matched change from Day-1 to Day 15 at 3 h	-3.3 (-5.4 to -1.2)			
Time−matched change from Day-1 to Day 15 at 4 h	-3.4 (-5.5 to -1.3)			
Time−matched change from Day-1 to Day 15 at 5 h	-3.1 (-5.2 to -1.0)			
Time−matched change from Day-1 to Day 15 at 6 h	-3.8 (-5.9 to -1.7)			
Time−matched change from Day-1 to Day 15 at 7 h	-2.8 (-4.9 to -0.7)			
Time−matched change from Day-1 to Day 15 at 10 h	-2.4 (-4.5 to -0.5)			
Time−matched change from Day-1 to Day 15 at 12 h	-1.6 (-3.8 to 0.5)			

Notes:

[43] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched heart rate (HR) changes from baseline to Day 1 at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)

End point title	Time−matched heart rate (HR) changes from baseline to Day 1 at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after dosing of nintedanib (BIBF 1120)[44]

End point description:

Baseline heart rate (HR) measurement at time t was defined as the HR measurement collected 1 day prior to the day of the first administration of nintedanib (BIBF 1120) at time t. Time-matched change from baseline to Day 1 in HR at time t was defined as the HR measurement following administration of nintedanib (BIBF 1120) on Day 1 obtained at time t minus baseline HR measurement at time t. Time-matched change from baseline to Day 1 in HR was modelled using a linear mixed-effects model for repeated measures which included 'time' as repeated measures and the time-matched baseline value as a covariate. Adjusted means with corresponding 2-sided 90% confidence intervals are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1. Baseline (Day -1) values were taken at exactly the same time points as on Day 1.

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[45]			
Units: beats per minute (bpm)				
least squares mean (confidence interval 90%)				
Time−matched change from Day-1 to Day 1 at 1 h	-0.0 (-1.9 to 1.8)			
Time−matched change from Day-1 to Day 1 at 2 h	-2.9 (-4.7 to -1.0)			
Time−matched change from Day-1 to Day 1 at 3 h	-3.8 (-5.7 to -2.0)			
Time−matched change from Day-1 to Day 1 at 4 h	-2.5 (-4.3 to -0.6)			
Time−matched change from Day-1 to Day 1 at 5 h	-1.8 (-3.7 to 0.0)			
Time−matched change from Day-1 to Day 1 at 6 h	-2.2 (-4.1 to -0.4)			
Time−matched change from Day-1 to Day 1 at 7 h	-1.4 (-3.3 to 0.4)			
Time−matched change from Day-1 to Day 1at 10 h	-1.3 (-3.2 to 0.6)			
Time−matched change from Day-1 to Day 1at 12 h	0.0 (-1.8 to 1.9)			

Notes:

[45] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in heart rate (HR) at the time of each patient's maximum nintedanib (BIBF 1120) plasma concentration, calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in heart rate (HR) at the time of each patient's maximum nintedanib (BIBF 1120) plasma concentration, calculated separately for Days 1 and 15 of treatment cycle 1[46]

End point description:

Baseline heart rate (HR) measurement at time t was defined as the HR measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in HR at time t was defined as the HR measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline HR measurement at time t.
For each participant 'Time-matched change from baseline to Day 1 (Day 15) in HR' at the time of the participant's maximum nintedanib plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[47]			
Units: beats per minute (bpm)				
arithmetic mean (confidence interval 90%)				
Day 1	-2.0 (-3.4 to -0.7)			
Day 15	-2.1 (-4.3 to 0.1)			

Notes:

[47] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in heart rate (HR) at the time of each patient's maximum plasma concentration of BIBF 1202 (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in heart rate (HR) at the time of each patient's maximum plasma concentration of BIBF 1202 (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1[48]

End point description:

Baseline heart rate (HR) measurement at time t was defined as the HR measurement collected 1 day

prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in HR at time t was defined as the HR measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline HR measurement at time t.
For each participant 'Time-matched change from baseline to Day 1 (Day 15) in HR' at the time of the participant's maximum BIBF 1202 (a nintedanib (BIBF 1120) metabolite) plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[49]			
Units: beats per minute (bpm)				
arithmetic mean (confidence interval 90%)				
Day 1	-2.3 (-3.8 to -0.8)			
Day 15	-2.0 (-4.2 to 0.1)			

Notes:

[49] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Time−matched change from baseline in heart rate (HR) at the time of each patient's maximum plasma concentration of BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Time−matched change from baseline in heart rate (HR) at the time of each patient's maximum plasma concentration of BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite), calculated separately for Days 1 and 15 of treatment cycle 1[50]

End point description:

Baseline heart rate (HR) measurement at time t was defined as the HR measurement collected 1 day prior to the day of the first administration of nintedanib at time t. Time-matched change from baseline to Day 1 (Day 15) in HR at time t was defined as the HR measurement following administration of nintedanib on Day 1 (Day 15) obtained at time t minus baseline HR measurement at time t.
For each participant 'Time-matched change from baseline to Day 1 (Day 15) in HR' at the time of the participant's maximum BIBF 1202-glucuronide (a nintedanib (BIBF 1120) metabolite) plasma concentration was obtained and the mean across all participants calculated. Corresponding two-sided 90% confidence intervals based on the t-distribution are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 1 and on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6

h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of treatment cycle 1. Continues in the description.

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[51]			
Units: beats per minute (bpm)				
arithmetic mean (confidence interval 90%)				
Day 1	-1.2 (-2.6 to 0.3)			
Day 15	-1.6 (-3.6 to 0.4)			

Notes:

[51] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Averaged time−matched heart rate (HR) change from baseline over 1 to 12 hours, calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Averaged time−matched heart rate (HR) change from baseline over 1 to 12 hours, calculated separately for Days 1 and 15 of treatment cycle 1[52]

End point description:

Averaged time-matched heart rate changes from baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120)) to Day 1 (first drug dose nintedanib (BIBF 1120)) and to Day 15 (steady state) over 1 to 12 hours was evaluated using a t-test for paired observation. The mean differences between post-treatment values (Days 1 and 15) and baseline (Day -1) along with two-sided 90% confidence limits are reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 1 and on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15.

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[53]			
Units: beats per minute (bpm)				
arithmetic mean (confidence interval 90%)				

Day 1 Day 15	-1.9 (-2.8 to -1.1) -2.5 (-4.0 to -0.9)			

Notes:

[53] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients with maximum time−matched QTcF interval change from baseline categorized by magnitude of change, calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Frequency of patients with maximum time−matched QTcF interval change from baseline categorized by magnitude of change, calculated separately for Days 1 and 15 of treatment cycle 1[54]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula. Number of patients with maximum time-matched change from baseline in the QTcF interval observed at each point in time, i.e., 9 time points on Day 1 and 10 timepoints on Day 15 is reported. 3 categories of individual QTcF increases from baseline to maximum value were defined:

<= 30 milliseconds (ms)

> 30 to 60 milliseconds (ms)

> 60 milliseconds (ms)
Changes more than 60 ms in the QTcF interval represent notable changes.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[55]			
Units: Participants				
Day 1, 1-12 hours (h)|<= 30 ms	64			
Day 15, -0:05-12 h|<= 30 ms	57			
Day 1, 1-12 hours (h)|> 30 to 60 ms	0			
Day 15, -0:05-12 h|> 30 to 60 ms	6			
Day 1, 1-12 hours (h)|> 60 ms	0			
Day 15, -0:05-12 h|> 60 ms	0			

Notes:

[55] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients with maximum time−matched QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) change from baseline categorized by magnitude of change, Days 1 and 15

End point title	Frequency of patients with maximum time−matched QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) change from baseline categorized by magnitude of change, Days 1 and 15[56]

End point description:

Number of patients with maximum time-matched change from baseline in the QT interval observed at each point in time, i.e., 9 time points on Day 1 and 10 timepoints on Day 15 is reported. 3 categories of individual QTcF increases from baseline to maximum value were defined:

<= 30 milliseconds (ms)

> 30 to 60 milliseconds (ms)

> 60 milliseconds (ms)
Changes more than 60 ms in the QT interval represent notable changes.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[57]			
Units: Participants				
Day 1, 1-12 hour (h)|<= 60 ms	64			
Day 15, -0:05-12 h|<= 60 ms	62			
Day 1, 1-12 hour (h)|> 60 ms	0			
Day 15, -0:05-12 h|> 60 ms	1			

Notes:

[57] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new (not present at any time pre-dose) onset of QTcF ≤450 milliseconds (ms), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Number of participants with new (not present at any time pre-dose) onset of QTcF ≤450 milliseconds (ms), calculated separately for Days 1 and 15 of treatment cycle 1[58]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula. Number of participants with new onset (not present at any time pre-dose) of QTcF ≤450 milliseconds (ms) on Day 1 (first drug dose nintedanib (BIBF 1120)) and Day 15 (steady state) compared to the baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120)) is reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[59]			
Units: Participants				
Day 1	3			
Day 15	2			

Notes:

[59] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new (not present at any time pre-dose) onset of QTcF >450 to 470 milliseconds (ms), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Number of participants with new (not present at any time pre-dose) onset of QTcF >450 to 470 milliseconds (ms), calculated separately for Days 1 and 15 of treatment cycle 1[60]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula. Number of participants with new onset of QTcF >450 to 470 milliseconds (ms) on Day 1 (first drug dose nintedanib (BIBF 1120)) and Day 15 (steady state) compared to the baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120)) is reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of the first treatment cycle. Continues in the description.

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[61]			
Units: Participants				
Day 1	1			
Day 15	1			

Notes:

[61] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new onset of QTcF> 470 to 500 milliseconds (ms), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Number of participants with new onset of QTcF> 470 to 500 milliseconds (ms), calculated separately for Days 1 and 15 of treatment cycle 1[62]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula. Number of participants with new onset of QTcF> 470 to 500 milliseconds (ms) on Day 1 (first drug dose nintedanib (BIBF 1120)) and Day 15 (steady state) compared to the baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120)) is reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle. Continues in the description.

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[63]			
Units: Participants				
Day 1	0			
Day 15	1			

Notes:

[63] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new (not present at any time pre-dose) onset of QTcF> 500 milliseconds (ms) (notable prolongation), calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Number of participants with new (not present at any time pre-dose) onset of QTcF> 500 milliseconds (ms) (notable prolongation), calculated separately for Days 1 and 15 of treatment cycle 1[64]

End point description:

QTcF interval is the QT interval (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) corrected for the effects of heart rate (HR) by the Fridericia formula. Number of participants with new onset of QTcF> 500 milliseconds (ms) (notable prolongation) on Day 1 (first drug dose nintedanib (BIBF 1120)) and Day 15 (steady state) compared to the baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120)) is reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle. Continues in the description.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[65]			
Units: Participants				
Day 1	0			
Day 15	0			

Notes:

[65] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new (not present at any time pre-dose) onset of QT (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) > 500 ms (notable prolongation), Days 1 and 15 of treatment cycle 1

End point title	Number of participants with new (not present at any time pre-dose) onset of QT (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave) > 500 ms (notable prolongation), Days 1 and 15 of treatment cycle 1[66]

End point description:

Number of participants with new onset of QT (electrocardiogram (ECG) interval from the beginning of the QRS complex to the end of the T wave)> 500 milliseconds (ms) (notable prolongation) on Day 1 (first drug dose nintedanib (BIBF 1120)) and Day 15 (steady state) compared to the baseline (Day -1 prior to the first dosing of nintedanib (BIBF 1120)) is reported.
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle. Continues in the description.

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[67]			
Units: Participants				
Day 1	0			
Day 15	0			

Notes:

[67] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values at baseline (Day -1) and Day 1 and changes from baseline to Day 1 at each point in time in PR interval

End point title	Absolute values at baseline (Day -1) and Day 1 and changes from baseline to Day 1 at each point in time in PR interval[68]

End point description:

The PR interval is an electrocardiogram (ECG) interval and is the time from the onset of the P wave to the start of the QRS complex (combination of the Q wave, R wave and S wave). It reflects conduction through the atrioventricular node (AV) node. The normal PR interval is between 120 – 200 milliseconds (ms) (0.12-0.20s) in duration. Absolute values at baseline (Day-1 prior to the first dosing of nintedanib) and at Day 1 (first drug dose of nintedanib (BIBF 1120)) and changes from baseline to Day 1 at each point in time i.e., 10 time points from 0 to 12 in the PR interval are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1. Baseline (Day -1) values were taken at exactly the same time points as on Day 1.

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[69]			
Units: milliseconds (ms)				
arithmetic mean (standard deviation)				
Absolute value on Day -1 at −5 min	164.7 (± 23.8)			
Absolute value on Day -1 at 1 h	165.7 (± 24.9)			
Absolute value on Day −1 at 2 h	166.8 (± 24.9)			
Absolute value on Day −1 at 3 h	166.6 (± 24.0)			
Absolute value on Day −1 at 4 h	168.1 (± 26.9)			
Absolute value on Day −1 at 5 h	167.2 (± 26.3)			
Absolute value on Day −1 at 6 h	168.1 (± 26.4)			

Absolute value on Day −1 at 7 h	168.9 (± 27.5)			
Absolute value on Day −1 at 10 h	168.0 (± 26.7)			
Absolute value on Day −1 at 12 h	170.0 (± 29.4)			
Absolute value on Day 1 at −5 min	165.7 (± 25.6)			
Absolute value on Day 1 at 1 h	167.4 (± 28.2)			
Absolute value on Day 1 at 2 h	169.4 (± 28.2)			
Absolute value on Day 1 at 3 h	170.0 (± 27.3)			
Absolute value on Day 1 at 4 h	170.0 (± 28.2)			
Absolute value on Day 1 at 5 h	169.4 (± 27.5)			
Absolute value on Day 1 at 6 h	170.8 (± 27.9)			
Absolute value on Day 1 at 7 h	169.9 (± 27.0)			
Absolute value on Day 1 at 10 h	169.8 (± 26.3)			
Absolute value on Day 1 at 12 h	171.3 (± 28.7)			
Time-matched change from Day-1 to Day1 at -5 min	0.7 (± 7.6)			
Time-matched change from Day -1 to Day 1 at 1 h	1.7 (± 11.6)			
Time-matched change from Day -1 to Day 1 at 2 h	2.6 (± 10.3)			
Time-matched change from Day -1 to Day 1 at 3 h	3.4 (± 9.1)			
Time-matched change from Day -1 to Day 1 at 4 h	2.2 (± 9.1)			
Time-matched change from Day -1 to Day 1 at 5 h	2.8 (± 10.7)			
Time-matched change from Day -1 to Day 1 at 6 h	3.3 (± 9.8)			
Time-matched change from Day -1 to Day 1 at 7 h	1.6 (± 9.3)			
Time-matched change from Day -1 to Day 1 at 10 h	1.8 (± 8.6)			
Time-matched change from Day -1 to Day 1 at 12 h	0.7 (± 9.4)			

Notes:

[69] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values at baseline (Day -1) and Day 15 and changes from baseline to Day 15 at each point in time in PR interval

End point title	Absolute values at baseline (Day -1) and Day 15 and changes from baseline to Day 15 at each point in time in PR interval[70]

End point description:

The PR interval is an electrocardiogram (ECG) interval and is the time from the onset of the P wave to the start of the QRS complex (combination of the Q wave, R wave and S wave). It reflects conduction through the atrioventricular node (AV) node. The normal PR interval is between 120 – 200 milliseconds (ms) (0.12-0.20s) in duration. Absolute values at baseline (Day-1 prior to the first dosing of nintedanib (BIBF 1120) and at Day 15 (steady state) and changes from baseline to Day 15 at each point in time i.e., 10 time points from 0 to 12 in the PR interval are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 15. Baseline (Day -1) values were taken at exactly the same time points as on Day 15.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[71]			
Units: milliseconds (ms)				
arithmetic mean (standard deviation)				
Absolute value on Day −1 at −5 min	164.7 (± 24.0)			
Absolute value on Day −1 at 1 h	165.7 (± 25.1)			
Absolute value on Day −1 at 2 h	166.8 (± 25.1)			
Absolute value on Day −1 at 3 h	166.5 (± 24.2)			
Absolute value on Day −1 at 4 h	168.0 (± 27.2)			
Absolute value on Day −1 at 5 h	167.2 (± 26.5)			
Absolute value on Day −1 at 6 h	168.3 (± 26.6)			
Absolute value on Day −1 at 7 h	168.9 (± 27.7)			
Absolute value on Day −1 at 10 h	168.1 (± 26.9)			
Absolute value on Day −1 at 12 h	170.1 (± 29.7)			
Absolute value on Day 15 at −5 min	164.5 (± 24.4)			
Absolute value on Day 15 at 1 h	166.1 (± 25.3)			
Absolute value on Day 15 at 2 h	166.8 (± 26.2)			
Absolute value on Day 15 at 3 h	167.4 (± 25.3)			
Absolute value on Day 15 at 4 h	168.7 (± 27.4)			
Absolute value on Day 15 at 5 h	167.7 (± 27.8)			
Absolute value on Day 15 at 6 h	169.3 (± 26.7)			
Absolute value on Day 15 at 7 h	169.0 (± 27.9)			
Absolute value on Day 15 at 10 h	169.1 (± 27.9)			
Absolute value on Day 15 at 12 h	168.8 (± 27.9)			
Time-matched change from Day-1 to Day15 at −5 min	-0.1 (± 10.6)			
Time-matched change from Day -1 to Day 15 at 1 h	0.5 (± 12.5)			
Time-matched change from Day -1 to Day 15 at 2 h	-0.0 (± 12.7)			
Time-matched change from Day -1 to Day 15 at 3 h	0.9 (± 14.6)			
Time-matched change from Day -1 to Day 15 at 4 h	0.9 (± 12.2)			
Time-matched change from Day -1 to Day 15 at 5 h	0.9 (± 13.7)			
Time-matched change from Day -1 to Day 15 at 6 h	1.3 (± 11.8)			
Time-matched change from Day -1 to Day 15 at 7 h	0.6 (± 13.2)			
Time-matched change from Day -1 to Day 15 at 10 h	1.2 (± 11.2)			
Time-matched change from Day -1 to Day 15 at 12 h	-1.5 (± 12.5)			

Notes:

[71] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values at baseline (Day -1) and Day 1 and changes from baseline to Day 1 at each point in time in QRS interval

End point title	Absolute values at baseline (Day -1) and Day 1 and changes from baseline to Day 1 at each point in time in QRS interval[72]

End point description:

QRS interval is an electrocardiogram (ECG) interval and is the time interval from the onset to the end of the QRS complex (combination of the Q wave, R wave and S wave). The normal QRS duration is less than 120 milliseconds (ms). Absolute values and changes from baseline (Day-1 prior to the first dosing of nintedanib) to Day 1 (first drug dose of nintedanib (BIBF 1120)) at each point in time i.e., 10 time points from 0 to 12 in the QRS interval are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1. Baseline (Day -1) values were taken at exactly the same time points as on Day 1.

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[73]			
Units: milliseconds (ms)				
arithmetic mean (standard deviation)				
Absolute value on Day −1 at −5 min	92.4 (± 11.8)			
Absolute value on Day −1 at 1 h	93.7 (± 11.0)			
Absolute value on Day −1 at 2 h	93.2 (± 10.5)			
Absolute value on Day −1 at 3 h	93.6 (± 10.8)			
Absolute value on Day −1 at 4 h	92.7 (± 9.8)			
Absolute value on Day −1 at 5 h	92.6 (± 11.0)			
Absolute value on Day −1 at 6 h	92.5 (± 10.3)			
Absolute value on Day −1 at 7 h	93.0 (± 10.6)			
Absolute value on Day −1 at 10 h	92.8 (± 11.7)			
Absolute value on Day −1, 12 h	92.5 (± 10.4)			
Absolute value on Day 1 at −5 min	92.6 (± 10.1)			
Absolute value on Day 1 at 1 h	93.2 (± 11.0)			
Absolute value in QRS interval on Day 1 at 2 h	93.0 (± 10.4)			
Absolute value on Day 1 at 3 h	93.3 (± 10.3)			
Absolute value on Day 1 at 4 h	93.5 (± 11.1)			
Absolute value on Day 1 at 5 h	93.4 (± 11.5)			
Absolute value on Day 1 at 6 h	93.4 (± 10.7)			
Absolute value on Day 1 at 7 h	93.2 (± 11.3)			
Absolute value on Day 1 at 10 h	92.3 (± 10.6)			
Absolute value on Day 1 at 12 h	92.8 (± 10.9)			
Time-matched change from Day -1 to Day 1 at −5 min	0.7 (± 5.1)			

Time-matched change from Day -1 to Day 1 at 1 h	-0.5 (± 5.2)			
Time-matched change from Day -1 to Day 1 at 2 h	-0.2 (± 4.4)			
Time-matched change from Day -1 to Day 1 at 3h	-0.3 (± 4.4)			
Time-matched change from Day -1 to Day 1 at 4 h	0.2 (± 4.7)			
Time-matched change from Day -1 to Day 1 at 5 h	0.2 (± 5.4)			
Time-matched change from Day -1 to Day 1 at 6 h	0.3 (± 5.6)			
Time-matched change from Day -1 to Day 1 at 7 h	-0.2 (± 4.7)			
Time-matched change from Day -1 to Day 1 at 10 h	-0.5 (± 4.9)			
Time-matched change from Day -1 to Day 1 at 12 h	0.3 (± 4.9)			

Notes:

[73] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values at baseline (Day -1) and Day 15 and changes from baseline to day 15 at each point in time in QRS interval

End point title	Absolute values at baseline (Day -1) and Day 15 and changes from baseline to day 15 at each point in time in QRS interval[74]

End point description:

QRS interval is an electrocardiogram (ECG) interval and is the time interval from the onset to the end of the QRS complex (combination of the Q wave, R wave and S wave). The normal QRS duration is less than 120 milliseconds (ms). Absolute values and changes from baseline (Day-1 prior to the first dosing of nintedanib) to Day 15 (steady state) at each point in time i.e., 10 time points from 0 to 12 in the QRS interval are reported.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 15. Baseline (Day -1) values were taken at exactly the same time points as on Day 15.

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[75]			
Units: milliseconds (ms)				
arithmetic mean (standard deviation)				
Absolute value on Day −1 at −5 minutes (min)	92.5 (± 11.8)			
Absolute value on Day −1 at 1 hour (h)	93.8 (± 11.1)			
Absolute value on Day −1 at 2 h	93.3 (± 10.6)			
Absolute value on Day −1 at 3 h	93.6 (± 10.9)			

Absolute value on Day −1 at 4 h	92.7 (± 9.9)			
Absolute value on Day −1 at 5 h	92.7 (± 11.0)			
Absolute value on Day −1 at 6 h	92.7 (± 10.3)			
Absolute value on Day −1 at 7 h	93.1 (± 10.6)			
Absolute value on Day −1 at 10 h	92.8 (± 11.8)			
Absolute value on Day −1 at 12 h	92.6 (± 10.4)			
Absolute value on Day 15 at −5 min	93.3 (± 11.0)			
Absolute value on Day 15 at 1 h	93.9 (± 10.3)			
Absolute value on Day 15 at 2 h	93.0 (± 11.5)			
Absolute value on Day 15 at 3 h	92.9 (± 11.1)			
Absolute value on Day 15 at 4 h	92.6 (± 11.2)			
Absolute value on Day 15 at 5 h	93.6 (± 10.9)			
Absolute value on Day 15 at 6 h	93.1 (± 11.1)			
Absolute value on Day 15 at 7 h	93.1 (± 11.3)			
Absolute value on Day 15 at 10 h	92.8 (± 10.7)			
Absolute value on Day 15 at 12 h	93.7 (± 11.5)			
Time-matched change from Day -1 to Day15 at −5 min	0.8 (± 5.4)			
Time-matched change from Day -1 to Day 15 at 1 h	0.0 (± 5.1)			
Time-matched change from Day -1 to Day 15 at 2 h	-0.3 (± 5.3)			
Time-matched change from Day -1 to Day 15 at 3 h	-0.8 (± 5.7)			
Time-matched change from Day -1 to Day 15 at 4 h	-0.6 (± 5.4)			
Time-matched change from Day -1 to Day 15 at 5h	0.5 (± 7.3)			
Time-matched change from Day -1 to Day 15 at 6 h	-0.1 (± 5.3)			
Time-matched change from Day -1 to Day 15 at 7 h	-0.4 (± 5.3)			
Time-matched change from Day -1 to Day 15 at 10 h	0.1 (± 5.1)			
Time-matched change from Day -1 to Day 15 at 12 h	1.0 (± 4.7)			

Notes:

[75] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients by clinical electrocardiogram (ECG) measurement interpretation, calculated separately for Days 1 and 15 of treatment cycle 1

End point title	Frequency of patients by clinical electrocardiogram (ECG) measurement interpretation, calculated separately for Days 1 and 15 of treatment cycle 1[76]

End point description:

Based on the interpretation of the electrocardiogram (ECG) patients were classified in 3 categories:
- Normal (a normal ECG reading would be a reading that includes the following normal findings: 1) normal general features; 2) no arrhythmia; 3) no conduction delays;
4) T-wave morphology of normal; and 5) normal U-wave morphology) on Day 1 or on Day 15)
- Not normal and not normal at baseline (an abnormal ECG reading would be a reading that includes one or more of the following abnormal findings: 1) abnormal general features; 2) arrhythmia; 3) conduction delays;
4) T-wave morphology of flat, inverted or biphasic; and 5) abnormal U-wave morphology) on Day 1 or

on Day 15)
- Not normal and new onset of finding
Time frame: Baseline (Day -1) values were taken at exactly the same time points as on Day 15.
FAS-ECG.

End point type	Secondary

End point timeframe:

At 5 minutes (min) before the first dose on Day 15 and at 1 hour (h), at 2 h, at 3 h, at 4 h, at 5 h, at 6 h, at 7 h, at 10 h and at 12 h after the first dose of nintedanib on Day 1 and on Day 15 of first treatment cycle. Continues in the description.

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined and analyzed only for the nintedanib (BIBF 1120) arm.

End point values	Nintedanib (BIBF 1120)			
Subject group type	Reporting group			
Number of subjects analysed	64[77]			
Units: Participants				
Day 1|Normal	39			
Day 15|Normal	37			
Day 1|Not normal and not normal at baseline	24			
Day 15|Not normal and not normal at baseline	25			
Day 1|Not normal and new onset of finding	1			
Day 15|Not normal and new onset of finding	1			

Notes:

[77] - FAS-ECG

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Adverse Events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0

End point title	Frequency of Adverse Events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0

End point description:

The number of participants who experienced adverse events graded according to NCI CTCAE version 3.0, is reported below.The maximum grade of adverse event intesnisty for each type of treatment-related adverse event was recorded for each patient.

Grade 1 - Mild AE
Grade 2 - Moderate AE
Grade 3 - Severe AE
Grade 4 - Life-threatening or disabling AE
Grade 5 - Death related to AE
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[78]	32[79]		
Units: Participants				
Grade 1	11	5		
Grade 2	16	6		
Grade 3	14	16		
Grade 4	10	2		
Grade 5	7	1		

Notes:

[78] - TS

[79] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events leading to dose reduction

End point title	Number of participants with Adverse Events leading to dose reduction

End point description:

Number of participants who experienced Adverse Events which led to dose reduction of the trial medication is reported for each treatment arm.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[80]	32[81]		
Units: Participants	16	8		

Notes:

[80] - TS

[81] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events leading to discontinuation of trial drug

End point title	Number of participants with Adverse Events leading to discontinuation of trial drug

End point description:

Number of participants with Adverse Events which lead to discontinuation of trial medication drug is reported for each treatment arm.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[82]	32[83]		
Units: Participants	11	5		

Notes:

[82] - TS

[83] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events requiring or prolonging hospitalisation

End point title	Number of participants with Adverse Events requiring or prolonging hospitalisation

End point description:

Number of participants who experienced Adverse Events which required or prolonged hospitalisation of patients is reported for each treatment arm.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[84]	32[85]		
Units: Participants	15	10		

Notes:

[84] - TS

[85] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of hospital stays due to Adverse Events requiring or prolonging hospitalisation

End point title	Duration of hospital stays due to Adverse Events requiring or prolonging hospitalisation

End point description:

Duration of hospitalisation in days for each treatment arm is reported for those patients who experienced adverse events which required or prolonged hospitalisation (of the patients).
All patients who were dispensed trial medication and were documented to have taken at least 1 dose of investigational treatment and experienced Adverse Events requiring or prolonging hospitalisation.

End point type	Secondary

End point timeframe:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: days				
arithmetic mean (standard deviation)	11.40 (± 8.56)	13.10 (± 8.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients with possible clinically significant abnormal lab values

End point title	Frequency of patients with possible clinically significant abnormal lab values

End point description:

Number of patients with possible clinically significant abnormal lab values for the lab parameters alkaline phosphatase, activated partial thromboplastin time (APTT), creatinine, haemoglobin, prothrombin time (PT)−international normalized ratio (INR), potassium, lymphocytes, sodium, neutrophils, platelets, aspartate amino transferase (AST), alanine aminotransferase (ALT), bilirubin and white blood cell count is reported. Only lab values with CTCAE rule for possible clinical significance are displayed.
Treated set (TS): All participants who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

End point values	Nintedanib (BIBF 1120)	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[86]	31[87]		
Units: Participants				
Alkaline phosphatase	2	3		
APTT (Activated partial thrombopl. time)	7	0		
Creatinine	4	5		
Haemoglobin	6	6		
PT−INR	5	0		
Potassium	14	4		
Lymphocytes	8	11		
Sodium	14	3		
Neutrophils	3	9		
Platelets	2	3		
Aspartate amino Transferase (AST)	10	1		
Alanine aminotransferase (ALT)	14	3		
Bilirubin, total	4	3		
White blood cell count	0	7		

Notes:

[86] - TS

[87] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug administration up to 28 days after last dose of study drug, up to 121 months.

Adverse event reporting additional description:

Treated set (TS): All patients who were dispensed trial medication and were documented to have taken at least 1 dose of investigational treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Nintedanib (BIBF 1120

Reporting group description:

Participants received orally (swallowed) soft gelatine capsules of nintedanib (BIBF 1120) twice daily (bid) starting with a dose of 200 milligram (mg) bid given continuously in 4-week cycles. Nintedanib was to be swallowed unchewed with about 200 milliliter (mL) of water after food intake with a dosing interval of approximately 12 hours. In case of Adverse Events, the dose was to be reduced to 150 mg bid and 100 mg bid, respectively. The dose was continued daily until withdrawal criteria were fulfilled.

Reporting group title	Sunitinib

Reporting group description:

Participants received orally (swallowed) hard capsule of sunitinib starting with a dose of 50 milligram (mg) once daily (qd). In case of Adverse Events the dose was to be reduced to 37.5 mg once daily and 25 mg once daily, respectively. The daily dosing was performed in 6-week cycles (4 weeks on and 2 weeks off) until withdrawal criteria were fulfilled.

Serious adverse events	Nintedanib (BIBF 1120	Sunitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 64 (31.25%)	11 / 32 (34.38%)	
number of deaths (all causes)	50	25	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			

subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	7 / 64 (10.94%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 6	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 64 (1.56%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 64 (1.56%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incisional hernia, obstructive			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			

subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 64 (0.00%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Jaundice			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nintedanib (BIBF 1120	Sunitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 64 (85.94%)	27 / 32 (84.38%)	
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	2 / 64 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Hypertension			
subjects affected / exposed	2 / 64 (3.13%)	5 / 32 (15.63%)	
occurrences (all)	2	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 64 (7.81%)	2 / 32 (6.25%)	
occurrences (all)	5	2	
Fatigue			
subjects affected / exposed	17 / 64 (26.56%)	8 / 32 (25.00%)	
occurrences (all)	18	12	
Hyperthermia			
subjects affected / exposed	2 / 64 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	2	3	
Mucosal inflammation			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Pain			

subjects affected / exposed	4 / 64 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 64 (3.13%)	3 / 32 (9.38%)	
occurrences (all)	2	7	
Dyspnoea			
subjects affected / exposed	1 / 64 (1.56%)	4 / 32 (12.50%)	
occurrences (all)	1	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 64 (7.81%)	1 / 32 (3.13%)	
occurrences (all)	8	1	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 64 (9.38%)	1 / 32 (3.13%)	
occurrences (all)	7	1	
Blood creatinine increased			
subjects affected / exposed	3 / 64 (4.69%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 64 (12.50%)	1 / 32 (3.13%)	
occurrences (all)	13	1	
Lipase increased			
subjects affected / exposed	2 / 64 (3.13%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Weight decreased			
subjects affected / exposed	8 / 64 (12.50%)	2 / 32 (6.25%)	
occurrences (all)	8	2	
Weight increased			
subjects affected / exposed	2 / 64 (3.13%)	3 / 32 (9.38%)	
occurrences (all)	2	3	

Amylase increased			
subjects affected / exposed	1 / 64 (1.56%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Blood glucose increased			
subjects affected / exposed	2 / 64 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	4	2	
Cardiac disorders			
Aortic valve sclerosis			
subjects affected / exposed	1 / 64 (1.56%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Tachycardia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 64 (4.69%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
Headache			
subjects affected / exposed	7 / 64 (10.94%)	1 / 32 (3.13%)	
occurrences (all)	7	1	
Lethargy			
subjects affected / exposed	3 / 64 (4.69%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 64 (6.25%)	5 / 32 (15.63%)	
occurrences (all)	8	5	
Neutropenia			
subjects affected / exposed	0 / 64 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	4	
Thrombocytopenia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 64 (7.81%)	1 / 32 (3.13%)	
occurrences (all)	7	1	
Abdominal pain upper			
subjects affected / exposed	5 / 64 (7.81%)	2 / 32 (6.25%)	
occurrences (all)	8	6	
Constipation			
subjects affected / exposed	5 / 64 (7.81%)	4 / 32 (12.50%)	
occurrences (all)	5	5	
Diarrhoea			
subjects affected / exposed	40 / 64 (62.50%)	15 / 32 (46.88%)	
occurrences (all)	109	46	
Dry mouth			
subjects affected / exposed	5 / 64 (7.81%)	1 / 32 (3.13%)	
occurrences (all)	5	1	
Dyspepsia			
subjects affected / exposed	3 / 64 (4.69%)	7 / 32 (21.88%)	
occurrences (all)	6	15	
Flatulence			
subjects affected / exposed	4 / 64 (6.25%)	3 / 32 (9.38%)	
occurrences (all)	5	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 64 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	7	
Nausea			
subjects affected / exposed	25 / 64 (39.06%)	8 / 32 (25.00%)	
occurrences (all)	41	13	
Stomatitis			
subjects affected / exposed	0 / 64 (0.00%)	10 / 32 (31.25%)	
occurrences (all)	0	22	
Vomiting			

subjects affected / exposed	10 / 64 (15.63%)	6 / 32 (18.75%)	
occurrences (all)	25	13	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	4	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 64 (0.00%)	10 / 32 (31.25%)	
occurrences (all)	0	42	
Rash			
subjects affected / exposed	1 / 64 (1.56%)	3 / 32 (9.38%)	
occurrences (all)	2	4	
Dry skin			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 64 (7.81%)	0 / 32 (0.00%)	
occurrences (all)	6	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 64 (1.56%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Hypothyroidism			
subjects affected / exposed	2 / 64 (3.13%)	5 / 32 (15.63%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 64 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	6	2	
Osteoarthritis			
subjects affected / exposed	0 / 64 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	2 / 64 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 64 (18.75%)	6 / 32 (18.75%)	
occurrences (all)	17	10	
Hyponatraemia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2010	Global amendment No. 1: Clarified some discrepancies within the trial protocol, namely to adjust the flow charts to the corresponding written paragraphs. Likewise, the time schedule for PK sampling given in Appendix 10 of the trial protocol was corrected to accurately reflect the written parts of the protocol. Moreover, Global Amendment No. 1 stated that a minimisation approach was unnecessary as a stratified randomisation would be sufficient to ensure a 2:1 ratio of the treatment arms overall and within each stratum.
11 July 2017	Global amendment No. 2: Clarified that the follow-up for progressive disease was now no longer required.
11 July 2019	Global amendment No. 3: Clarified the future handling for clinical laboratory assessments, vital signs, physical findings, and other observations related to safety. It also introduced the possibility to remove patients from the trial after completion of the primary efficacy analysis, given that the patient consented and given that the patient had access to the study medication through marketed product.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported