

**Clinical trial results:****A Randomised Placebo-Controlled Phase II Study of Continuous Maintenance Treatment with BIBF 1120 Following Chemotherapy in Patients with Relapsed Ovarian Cancer****Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2005-002427-14 |
| Trial protocol           | GB             |
| Global end of trial date | 18 March 2014  |

**Results information**

|                                   |                                                         |
|-----------------------------------|---------------------------------------------------------|
| Result version number             | v2 (current)                                            |
| This version publication date     | 15 May 2019                                             |
| First version publication date    | 01 August 2015                                          |
| Version creation reason           | • Changes to summary attachments<br>Updates in synopsis |
| Summary attachment (see zip file) | Synopsis (1199.9_U10-2880-01-DS_CO.pdf)                 |

**Trial information****Trial identification**

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 1199.9 |
|-----------------------|--------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00710762 |
| 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               | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800243 0127, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800243 0127, clintrriage.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                       | 17 July 2014  |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 18 March 2014 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to estimate the Progression Free Survival Rates (PFS) of patients with relapsed ovarian cancer after 9 months of continuous treatment with either BIBF 1120 or matching placebo.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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                          | 03 March 2006 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 89 |
| Worldwide total number of subjects   | 89                 |
| EEA total number of subjects         | 89                 |

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)      | 59 |
| From 65 to 84 years       | 30 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Of the 84 randomised patients, 43 Nintedanib and 40 placebo treated patients were included in all analyses. 1 patient was excluded from analyses as she had received both trial treatments at different times (she was randomised to placebo but was initially treated for 1 treatment cycle with Nintedanib due to a dispensing error then 2 treatment cycles)

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Treatment period (overall period)                             |
| Is this the baseline period? | Yes                                                           |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Nintedanib |

Arm description:

Patients were treated with 250mg nintedanib twice daily.  
43 patients were included in the analyses instead of 44 patients in nintedanib arm as one patient was excluded after drug administration due to important protocol violation. Consequently, number of subjects that started is 44 but only 43 reported (to match the numbers in the baseline characteristics)

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

Dosage and administration details:

Patients were treated with 250mg nintedanib twice daily

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Patients were treated with matching placebo twice daily

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Placebo       |
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

Patients were treated with matching placebo twice daily

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Nintedanib | Placebo |
|-----------------------------------------------------|------------|---------|
| Started                                             | 43         | 40      |
| Completed                                           | 5          | 0       |
| Not completed                                       | 38         | 40      |
| Adverse Event other disease worsening               | 2          | 1       |
| Other Adverse Event                                 | 7          | 7       |
| Reason other than those listed                      | 1          | 2       |
| Lost to follow-up                                   | 1          | -       |
| Progressive disease                                 | 27         | 30      |

Notes:

[1] - 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: Baseline characteristics are based on the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Nintedanib |
|-----------------------|------------|

Reporting group description:

Patients were treated with 250mg nintedanib twice daily.

43 patients were included in the analyses instead of 44 patients in nintedanib arm as one patient was excluded after drug administration due to important protocol violation. Consequently, number of subjects that started is 44 but only 43 reported (to match the numbers in the baseline characteristics)

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients were treated with matching placebo twice daily

| Reporting group values | Nintedanib | Placebo | Total |
|------------------------|------------|---------|-------|
| Number of subjects     | 43         | 40      | 83    |
| Age categorical        |            |         |       |
| Units: Subjects        |            |         |       |

|                                              |       |       |    |
|----------------------------------------------|-------|-------|----|
| Age continuous                               |       |       |    |
| One patient in the placebo arm has been excl |       |       |    |
| Units: years                                 |       |       |    |
| arithmetic mean                              | 58.4  | 61.3  |    |
| standard deviation                           | ± 9.5 | ± 9.1 | -  |
| Gender categorical                           |       |       |    |
| Units: Subjects                              |       |       |    |
| Female                                       | 43    | 40    | 83 |
| Male                                         | 0     | 0     | 0  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                           |            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                     | Nintedanib |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                              |            |
| Patients were treated with 250mg nintedanib twice daily.<br>43 patients were included in the analyses instead of 44 patients in nintedanib arm as one patient was excluded after drug administration due to important protocol violation. Consequently, number of subjects that started is 44 but only 43 reported (to match the numbers in the baseline characteristics) |            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                     | Placebo    |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                              |            |
| Patients were treated with matching placebo twice daily                                                                                                                                                                                                                                                                                                                   |            |

### Primary: PFS Rate at 36 Weeks (After 9 Months)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | PFS Rate at 36 Weeks (After 9 Months) <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                      |
| The rate (probability) of being progression free at Week 36. Progression Free Survival (PFS) was defined according to RECIST version 1.0 from the time of first study drug administration to the first time of either objective tumour progression, the appearance of $\geq 1$ new tumour lesion(s), occurrence or significant progression of malignant ascites, tumour related death, or the time when patients were censored at last known follow up. The rate is the Kaplan- Meier estimated percent probability. |                                                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Primary                                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                      |
| 36 weeks (after 9 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                      |

Notes:

[1] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test were tested.

| End point values                  | Nintedanib         | Placebo           |  |  |
|-----------------------------------|--------------------|-------------------|--|--|
| Subject group type                | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed       | 43 <sup>[2]</sup>  | 40 <sup>[3]</sup> |  |  |
| Units: percent probability of PFS |                    |                   |  |  |
| median (confidence interval 95%)  | 15.6 (3.8 to 27.3) | 2.9 (0 to 8.4)    |  |  |

Notes:

[2] - Treated set.

[3] - Treated set.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Tumour Progression

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Time to Tumour Progression |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                            |
| Time to Tumour Progression according to RECIST version 1.0 , CA-125 (ovarian tumour marker) levels and RECIST + CA-125 levels.<br>For CA-125, progressive disease was defined on the basis of progressive serial elevations of CA-125 according to the following criteria:<br>Patients with elevated CA-125 pre-treatment and normalisation of CA-125 had to show evidence of CA-125 levels $\geq 2 \times$ ULN on 2 occasions at least 1 week apart, or Patients with elevated CA-125 pre- |                            |

treatment that never normalised had to show evidence of CA-125 levels  $\geq 2 \times$  the nadir value on 2 occasions at least 1 week apart. or Patients with CA-125 in the normal range pre-treatment had to show evidence of CA-125 levels  $\geq 2 \times$  ULN on 2 occasions at least 1 week apart.  
Composite (RECIST+CA-125) endpoint is the RECIST progressive disease (PD) if it occurred or the CA-125 PD if it occurred in the absence of RECIST PD.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 9 months             |           |

| End point values                 | Nintedanib        | Placebo           |  |  |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type               | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed      | 43 <sup>[4]</sup> | 40 <sup>[5]</sup> |  |  |
| Units: days                      |                   |                   |  |  |
| median (confidence interval 95%) |                   |                   |  |  |
| according to RECIST and CA-125   | 83 (78 to 149)    | 84 (78 to 87)     |  |  |
| according to CA-125              | 85 (79 to 149)    | 86 (67 to 113)    |  |  |
| according to RECIST              | 143 (82 to 175)   | 85 (78 to 89)     |  |  |

Notes:

[4] - Treated set

[5] - Treated set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Death

|                                                                         |               |
|-------------------------------------------------------------------------|---------------|
| End point title                                                         | Time to Death |
| End point description:                                                  |               |
| This end point was not determined as no patients died during the trial. |               |
| End point type                                                          | Secondary     |
| End point timeframe:                                                    |               |
| 9 months                                                                |               |

| End point values                 | Nintedanib       | Placebo          |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 0 <sup>[6]</sup> | 0 <sup>[7]</sup> |  |  |
| Units: days                      |                  |                  |  |  |
| median (confidence interval 95%) | ( to )           | ( to )           |  |  |

Notes:

[6] - This end point was not determined as no patients died during the trial.

[7] - This end point was not determined as no patients died during the trial.

## Statistical analyses

No statistical analyses for this end point



## Secondary: Incidence and Intensity of Adverse Events With Grading According CTCAE

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Incidence and Intensity of Adverse Events With Grading According CTCAE |
|-----------------|------------------------------------------------------------------------|

End point description:

Incidence and intensity of Adverse Events with grading according to the Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First drug administration until 28 days after last drug administration, up until 309 days

| End point values                  | Nintedanib        | Placebo           |  |  |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type                | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed       | 43 <sup>[8]</sup> | 40 <sup>[9]</sup> |  |  |
| Units: percentage of participants |                   |                   |  |  |
| number (not applicable)           |                   |                   |  |  |
| CTCAE grade 1                     | 2.3               | 25                |  |  |
| CTCAE grade 2                     | 34.9              | 42.5              |  |  |
| CTCAE grade 3                     | 53.5              | 25                |  |  |
| CTCAE grade 4                     | 7                 | 2.5               |  |  |
| CTCAE grade 5                     | 0                 | 0                 |  |  |

Notes:

[8] - Treated set

[9] - Treated set

## Statistical analyses

No statistical analyses for this end point

## Secondary: PFS Rate at 12 Weeks (After 3 Months) and 24 Weeks ( After 6 Months)

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | PFS Rate at 12 Weeks (After 3 Months) and 24 Weeks ( After 6 Months) |
|-----------------|----------------------------------------------------------------------|

End point description:

The rate (probability) of being progression free at Week 12 and Week 24. Progression Free Survival (PFS) was defined according to RECIST version 1.0 from the time of first study drug administration to the first time of either objective tumour progression, the appearance of  $\geq 1$  new tumour lesion(s), occurrence or significant progression of malignant ascites, tumour related death, or the time when patients were censored at last known follow up. The rate is the Kaplan- Meier estimated percent probability.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks (after 3 months) and 24 weeks ( after 6 months)

| End point values                  | Nintedanib          | Placebo             |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 43 <sup>[10]</sup>  | 40 <sup>[11]</sup>  |  |  |
| Units: percent probability of PFS |                     |                     |  |  |
| median (confidence interval 95%)  |                     |                     |  |  |
| at 24 weeks ( after 6 months)     | 26.7 (12.5 to 40.8) | 17.3 (5.2 to 29.4)  |  |  |
| at 12 weeks (after 3 months)      | 45.3 (29.5 to 61.2) | 46.2 (30.5 to 61.8) |  |  |

Notes:

[10] - Treated set

[11] - Treated set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Relevant Abnormalities for Laboratory Parameters

|                        |                                                                                                                                                            |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Clinical Relevant Abnormalities for Laboratory Parameters                                                                                                  |
| End point description: | Clinical Relevant Abnormalities for laboratory parameters. Any new or clinically relevant worsening of baseline conditions was reported as Adverse Events. |
| End point type         | Secondary                                                                                                                                                  |
| End point timeframe:   | First drug administration until 28 days after last drug administration, up until 309 days                                                                  |

| End point values                             | Nintedanib         | Placebo            |  |  |
|----------------------------------------------|--------------------|--------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed                  | 43 <sup>[12]</sup> | 40 <sup>[13]</sup> |  |  |
| Units: Percentage of participants            |                    |                    |  |  |
| number (not applicable)                      |                    |                    |  |  |
| Alanine aminotransferase increased           | 37.2               | 7.5                |  |  |
| Gamma-glutamyltransferase increased          | 30.2               | 2.5                |  |  |
| Aspartate aminotransferase increased         | 25.6               | 2.5                |  |  |
| Blood alkaline phosphatase increased         | 7                  | 5                  |  |  |
| Blood lactate dehydrogenase increased        | 4.7                | 0                  |  |  |
| Blood alkaline phosphatase                   | 0                  | 2.5                |  |  |
| Blood alkaline phosphatase abnormal          | 2.3                | 2.5                |  |  |
| Lymphocyte count decreased                   | 0                  | 2.5                |  |  |
| Vitamin B12 decreased                        | 0                  | 2.5                |  |  |
| Alanine aminotransferase abnormal            | 2.3                | 0                  |  |  |
| Blood lactate dehydrogenase abnormal         | 2.3                | 0                  |  |  |
| Gamma-glutamyltransferase abnormal           | 2.3                | 0                  |  |  |
| Neutrophil count decreased                   | 2.3                | 0                  |  |  |
| White blood cells urine positive             | 2.3                | 0                  |  |  |
| Blood pressure increased                     | 0                  | 2.5                |  |  |
| Electrocardiogram T wave amplitude decreased | 0                  | 2.5                |  |  |
| Liver function test abnormal                 | 2.3                | 0                  |  |  |

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Notes:

[12] - Treated set

[13] - Treated set

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### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First drug administration until 28 days after last drug administration, up until 309 days

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Nintedanib |
|-----------------------|------------|

Reporting group description:

Patients were treated with 250mg nintedanib twice daily

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients were treated with matching placebo twice daily

| Serious adverse events                            | Nintedanib       | Placebo          |  |
|---------------------------------------------------|------------------|------------------|--|
| Total subjects affected by serious adverse events |                  |                  |  |
| subjects affected / exposed                       | 14 / 43 (32.56%) | 10 / 40 (25.00%) |  |
| number of deaths (all causes)                     | 0                | 0                |  |
| number of deaths resulting from adverse events    | 0                | 0                |  |
| Investigations                                    |                  |                  |  |
| Alanine aminotransferase increased                |                  |                  |  |
| subjects affected / exposed                       | 1 / 43 (2.33%)   | 0 / 40 (0.00%)   |  |
| occurrences causally related to treatment / all   | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Aspartate aminotransferase increased              |                  |                  |  |
| subjects affected / exposed                       | 1 / 43 (2.33%)   | 0 / 40 (0.00%)   |  |
| occurrences causally related to treatment / all   | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Blood alkaline phosphatase increased              |                  |                  |  |
| subjects affected / exposed                       | 1 / 43 (2.33%)   | 0 / 40 (0.00%)   |  |
| occurrences causally related to treatment / all   | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Gamma-glutamyltransferase increased               |                  |                  |  |

|                                                                     |                |                |  |
|---------------------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                                         | 1 / 43 (2.33%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |  |
| Lung neoplasm                                                       |                |                |  |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Neuroendocrine tumour                                               |                |                |  |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Vascular disorders                                                  |                |                |  |
| Deep vein thrombosis                                                |                |                |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders                                |                |                |  |
| Pancytopenia                                                        |                |                |  |
| subjects affected / exposed                                         | 0 / 43 (0.00%) | 1 / 40 (2.50%) |  |
| 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                |                |                |  |
| Pyrexia                                                             |                |                |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                                          |                |                |  |
| Abdominal distension                                                |                |                |  |
| subjects affected / exposed                                         | 1 / 43 (2.33%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Abdominal pain                                                      |                |                |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 43 (9.30%)  | 2 / 40 (5.00%)  |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites                                         |                 |                 |  |
| subjects affected / exposed                     | 6 / 43 (13.95%) | 5 / 40 (12.50%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 43 (6.98%)  | 0 / 40 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 43 (4.65%)  | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |

|                                                 |                 |                |  |
|-------------------------------------------------|-----------------|----------------|--|
| subjects affected / exposed                     | 5 / 43 (11.63%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Pleuritic pain                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pulmonary embolism                              |                 |                |  |
| subjects affected / exposed                     | 0 / 43 (0.00%)  | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Psychiatric disorders                           |                 |                |  |
| Abnormal behaviour                              |                 |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Agitation                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Confusional state                               |                 |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Delusion                                        |                 |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Depression                                      |                 |                |  |
| subjects affected / exposed                     | 0 / 43 (0.00%)  | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Mood altered                                    |                |                |  |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Catheter related infection                      |                |                |  |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lower respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 40 (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              |                |                |  |
| Anorexia                                        |                |                |  |
| subjects affected / exposed                     | 1 / 43 (2.33%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 0 / 43 (0.00%) | 1 / 40 (2.50%) |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Nintedanib       | Placebo          |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 42 / 43 (97.67%) | 37 / 40 (92.50%) |  |
| Investigations                                        |                  |                  |  |
| Alanine aminotransferase increased                    |                  |                  |  |
| subjects affected / exposed                           | 16 / 43 (37.21%) | 3 / 40 (7.50%)   |  |
| occurrences (all)                                     | 20               | 3                |  |
| Aspartate aminotransferase increased                  |                  |                  |  |
| subjects affected / exposed                           | 10 / 43 (23.26%) | 1 / 40 (2.50%)   |  |
| occurrences (all)                                     | 12               | 1                |  |



|                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                  |                                                                                                                                     |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--|
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                    | 12 / 43 (27.91%)<br>12                                                                                                           | 1 / 40 (2.50%)<br>1                                                                                                                 |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)<br><br>Hot flush<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                | 5 / 43 (11.63%)<br>5<br><br>3 / 43 (6.98%)<br>3                                                                                  | 2 / 40 (5.00%)<br>2<br><br>3 / 40 (7.50%)<br>3                                                                                      |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Lethargy<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 4 / 43 (9.30%)<br>4<br><br>6 / 43 (13.95%)<br>6<br><br>4 / 43 (9.30%)<br>4<br><br>1 / 43 (2.33%)<br>1<br><br>0 / 43 (0.00%)<br>0 | 4 / 40 (10.00%)<br>4<br><br>4 / 40 (10.00%)<br>4<br><br>4 / 40 (10.00%)<br>4<br><br>4 / 40 (10.00%)<br>4<br><br>3 / 40 (7.50%)<br>3 |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                           | 12 / 43 (27.91%)<br>17<br><br>1 / 43 (2.33%)<br>1                                                                                | 11 / 40 (27.50%)<br>12<br><br>3 / 40 (7.50%)<br>3                                                                                   |  |
| Ear and labyrinth disorders<br>Tinnitus                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                  |                                                                                                                                     |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 43 (6.98%)<br>3 | 1 / 40 (2.50%)<br>1 |  |
| Gastrointestinal disorders                       |                     |                     |  |
| Abdominal distension                             |                     |                     |  |
| subjects affected / exposed                      | 3 / 43 (6.98%)      | 1 / 40 (2.50%)      |  |
| occurrences (all)                                | 3                   | 1                   |  |
| Abdominal pain                                   |                     |                     |  |
| subjects affected / exposed                      | 23 / 43 (53.49%)    | 15 / 40 (37.50%)    |  |
| occurrences (all)                                | 36                  | 17                  |  |
| Constipation                                     |                     |                     |  |
| subjects affected / exposed                      | 9 / 43 (20.93%)     | 11 / 40 (27.50%)    |  |
| occurrences (all)                                | 10                  | 13                  |  |
| Diarrhoea                                        |                     |                     |  |
| subjects affected / exposed                      | 33 / 43 (76.74%)    | 14 / 40 (35.00%)    |  |
| occurrences (all)                                | 105                 | 22                  |  |
| Dyspepsia                                        |                     |                     |  |
| subjects affected / exposed                      | 3 / 43 (6.98%)      | 1 / 40 (2.50%)      |  |
| occurrences (all)                                | 4                   | 1                   |  |
| Flatulence                                       |                     |                     |  |
| subjects affected / exposed                      | 5 / 43 (11.63%)     | 4 / 40 (10.00%)     |  |
| occurrences (all)                                | 5                   | 4                   |  |
| Nausea                                           |                     |                     |  |
| subjects affected / exposed                      | 32 / 43 (74.42%)    | 13 / 40 (32.50%)    |  |
| occurrences (all)                                | 65                  | 21                  |  |
| Rectal haemorrhage                               |                     |                     |  |
| subjects affected / exposed                      | 3 / 43 (6.98%)      | 1 / 40 (2.50%)      |  |
| occurrences (all)                                | 4                   | 1                   |  |
| Stomatitis                                       |                     |                     |  |
| subjects affected / exposed                      | 5 / 43 (11.63%)     | 1 / 40 (2.50%)      |  |
| occurrences (all)                                | 6                   | 1                   |  |
| Vomiting                                         |                     |                     |  |
| subjects affected / exposed                      | 23 / 43 (53.49%)    | 9 / 40 (22.50%)     |  |
| occurrences (all)                                | 52                  | 10                  |  |
| Respiratory, thoracic and mediastinal disorders  |                     |                     |  |

|                                                                       |                      |                      |  |
|-----------------------------------------------------------------------|----------------------|----------------------|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)             | 6 / 43 (13.95%)<br>6 | 1 / 40 (2.50%)<br>1  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)          | 5 / 43 (11.63%)<br>6 | 3 / 40 (7.50%)<br>3  |  |
| Skin and subcutaneous tissue disorders                                |                      |                      |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)          | 0 / 43 (0.00%)<br>0  | 6 / 40 (15.00%)<br>6 |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)          | 2 / 43 (4.65%)<br>2  | 4 / 40 (10.00%)<br>5 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)              | 3 / 43 (6.98%)<br>3  | 5 / 40 (12.50%)<br>6 |  |
| Psychiatric disorders                                                 |                      |                      |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)           | 2 / 43 (4.65%)<br>2  | 4 / 40 (10.00%)<br>4 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 43 (0.00%)<br>0  | 3 / 40 (7.50%)<br>3  |  |
| Musculoskeletal and connective tissue disorders                       |                      |                      |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)        | 5 / 43 (11.63%)<br>7 | 6 / 40 (15.00%)<br>6 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)         | 2 / 43 (4.65%)<br>2  | 8 / 40 (20.00%)<br>8 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)     | 2 / 43 (4.65%)<br>2  | 4 / 40 (10.00%)<br>6 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 4 / 43 (9.30%)<br>4  | 2 / 40 (5.00%)<br>2  |  |

|                                                                                                    |                        |                      |  |
|----------------------------------------------------------------------------------------------------|------------------------|----------------------|--|
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 6 / 43 (13.95%)<br>6   | 2 / 40 (5.00%)<br>2  |  |
| Infection<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 43 (6.98%)<br>4    | 1 / 40 (2.50%)<br>2  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)              | 4 / 43 (9.30%)<br>4    | 3 / 40 (7.50%)<br>3  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 43 (9.30%)<br>5    | 4 / 40 (10.00%)<br>4 |  |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all) | 11 / 43 (25.58%)<br>14 | 6 / 40 (15.00%)<br>6 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 October 2005 | Amendment no. 1, documented new preclinical (phototoxicity) data that had become available since the preparation of the original study protocol.                                                                                                   |
| 04 January 2006 | Amendment no. 2, documented a rewording of inclusion criteria for clarification, following the suggestion of a study investigator, and the correction of a typographical error with regard to the description of the packages of study medication. |
| 26 January 2006 | Amendment no. 3, documented administrative changes and a clarification of the data collection procedures for patients who continued into the treatment extension period and the subsequent analyses of such data.                                  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

From Nov2009-Mar2014,there was 1 patient who continued taking Nintedanib on compassionate use programme,but due to limited data collected for compassionate use patients,no further analyses/reanalyses were deemed necessary and no new AE data recorded

Notes: