

**Clinical trial results:****A Randomized Discontinuation, Blinded, Placebo-Controlled, Phase II Study of Sorafenib in Patients with Chemo-naïve Metastatic Uveal Melanoma (Sorafenib Treatment of Metastatic Uveal Melanoma)****Summary**

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-022687-12   |
| Trial protocol           | DE               |
| Global end of trial date | 16 December 2016 |

**Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 13 December 2021 |
| First version publication date | 13 December 2021 |

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

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | STREAM |
|-----------------------|--------|

**Additional study identifiers**

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

Notes:

**Sponsors**

|                              |                                                                                                                                                                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Department of Medical Oncology, West German Cancer Center, University Medicine Essen, Germany                                                                                                                                         |
| Sponsor organisation address | Hufelandstrasse 55, Essen, Germany, 45147                                                                                                                                                                                             |
| Public contact               | ClinAssesss GmbH<br>, Department of Medical Oncology, West German Cancer Center, University Medicine Essen, Germany, +49 2171363360, info@clinassess.de                                                                               |
| Scientific contact           | Monitoring was performed by:<br>ClinAssess GmbH<br>Dr med. Burkhard Deuß<br>51379 Leverkusen, Department of Medical Oncology, West German Cancer Center, University Medicine Essen, Germany, +49 20172384140, WTZI-Studie@uk-essen.de |
| Sponsor organisation name    | Bayer Vital GmbH                                                                                                                                                                                                                      |
| Sponsor organisation address | Kaiser-Wilhelm-Allee 70, Leverkusen, Germany, 51368                                                                                                                                                                                   |
| Public contact               | Bayer Vital GmbH, Bayer Vital GmbH, 0049 021430 51 348, uwephillip.strauss@bayer.com                                                                                                                                                  |
| Scientific contact           | Dr. med. Uwe Philipp Strauss, Bayer Vital GmbH supported us financially and with sorafenib- was not direct sponsor, 0049 0214 30-51952, uwephillip.strauss@bayer.com                                                                  |

Notes:

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**Paediatric regulatory details**

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|                                                                      |    |
|----------------------------------------------------------------------|----|
| 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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 04 November 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 04 November 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 16 December 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine progression free survival (PFS) of sorafenib versus placebo after random assignment (randomized subset only).

Protection of trial subjects:

clearly planned management of side effects e.g. treatment-associated skin toxicity, prophylactic supportive measures to prevent the development of HFSR  
clearly defined management of treatment-associated hypertension, of treatment-associated diarrhea, of hematological toxicities and non-hematologic toxicities

Background therapy:

prophylactic and therapeutic supportive measures before/after development of HFSR  
all medication which was considered necessary for the patient's welfare and which were not expected to interfere with the evaluation of the study drug were allowed

Evidence for comparator:

all patient received sorafenib within the first 56 days- no comparators in that initial time given  
There are no approved systemic treatment options for patients with metastatic uveal melanoma.  
Patients achieving stable disease after a 56-days run-in phase of sorafenib 400 mg bid were randomly assigned, in a 1:1 ratio, to blinded sorafenib (S) or placebo (P).

|                                                           |                                       |
|-----------------------------------------------------------|---------------------------------------|
| Actual start date of recruitment                          | 16 June 2011                          |
| Long term follow-up planned                               | Yes                                   |
| Long term follow-up rationale                             | Safety, Efficacy, Scientific research |
| Long term follow-up duration                              | 1 Years                               |
| Independent data monitoring committee (IDMC) involvement? | Yes                                   |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 147 |
|--------------------------------------|--------------|

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 147 |
| EEA total number of subjects       | 147 |

Notes:

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**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)                      | 86 |
| From 65 to 84 years                       | 59 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details:

randomized placebo-controlled discontinuation study was conducted at three centers from June 2011 until December, 2016 in accordance with the standards of each site's independent ethics committees, the Declaration of Helsinki, and GCP guidelines. In total 147 consecutive patients were enrolled in the run-in period, which was completed by 117 pat.

### Pre-assignment

Screening details:

Chemonaïve, patients (aged  $\geq 18$  years) with metastatic uveal melanoma with at least one measurable metastasis were eligible. Additional inclusion criteria included an ECOG performance status of 0, 1 or 2, a life expectancy of at least 12 weeks, and adequate hematologic, hepatic, and renal function.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | first 56 days = run-in      |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                                        |              |
|----------------------------------------|--------------|
| <b>Arm title</b>                       | run-in phase |
| Arm description: -                     |              |
| Arm type                               | Experimental |
| Investigational medicinal product name | Sorafenib    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

400mg BID every day

| <b>Number of subjects in period 1</b> | run-in phase      |
|---------------------------------------|-------------------|
| Started                               | 147               |
| patients without staging at day 56    | 30 <sup>[1]</sup> |
| evaluable patients on day 56          | 117               |
| Completed                             | 117               |
| Not completed                         | 30                |
| Consent withdrawn by subject          | 4                 |
| Physician decision                    | 3                 |
| death                                 | 5                 |
| Adverse event, non-fatal              | 4                 |
| missing compliance                    | 1                 |
| early PD                              | 13                |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: that is correct:

147 patients fulfilled inclusion criteria and entered the run-in phase

30 of them dropped out during this run in phase and could not receive a restaging on day 56

evaluable patients at the end of this run-in phase at day 56: 117

## Period 2

|                              |                                |
|------------------------------|--------------------------------|
| Period 2 title               | randomization phase            |
| Is this the baseline period? | No                             |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator, Monitor |

Blinding implementation details:

for patients who experience progression (either clinical progression according to RECIST) at any time during the randomization phase, the blind should be broken- patients having received placebo should be offered continuing treatment with sorafenib

## Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | No            |
| <b>Arm title</b>             | Sorafenib Arm |

Arm description:

In patients who completed the run-in period, tumor response was classified according to RECIST. Patients with partial response (PR) were continued on sorafenib, patients with progression (PD) were taken off study and patients with stable disease (SD) were randomly assigned to sorafenib (2 x 200 mg bid) or matching placebo in a double-blind fashion without stratification.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | sorafenib    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

sorafenib (2 x 200 mg bid) daily use

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

Arm description:

control arm with placebo

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

Dosage and administration details:

BID

| <b>Number of subjects in period 2</b> | Sorafenib Arm | Placebo |
|---------------------------------------|---------------|---------|
| Started                               | 39            | 39      |
| blinded placebo                       | 39            | 39      |
| blinded sorafenib                     | 39            | 39      |
| Completed                             | 39            | 39      |

## Baseline characteristics

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | first 56 days = run-in |
|-----------------------|------------------------|

Reporting group description: -

| Reporting group values                                                                          | first 56 days = run-in | Total |  |
|-------------------------------------------------------------------------------------------------|------------------------|-------|--|
| Number of subjects                                                                              | 147                    | 147   |  |
| Age categorical                                                                                 |                        |       |  |
| Units: Subjects                                                                                 |                        |       |  |
| Adults (18-64 years)                                                                            | 86                     | 86    |  |
| From 65-84 years                                                                                | 59                     | 59    |  |
| 85 years and over                                                                               | 2                      | 2     |  |
| Gender categorical                                                                              |                        |       |  |
| Units: Subjects                                                                                 |                        |       |  |
| Female                                                                                          | 60                     | 60    |  |
| Male                                                                                            | 87                     | 87    |  |
| patients enrolled                                                                               |                        |       |  |
| patients fulfilling the inclusion criteria versus patients who could not enter the run-in phase |                        |       |  |
| Units: Subjects                                                                                 |                        |       |  |
| patients enrolled                                                                               | 147                    | 147   |  |
| not recorded                                                                                    | 0                      | 0     |  |
| Age                                                                                             |                        |       |  |
| age of patients                                                                                 |                        |       |  |
| Units: years                                                                                    |                        |       |  |
| median                                                                                          | 62                     |       |  |
| full range (min-max)                                                                            | 23 to 88               | -     |  |

### Subject analysis sets

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | treated in run-in phase |
|----------------------------|-------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

patients entering run in phase and receiving study medication in not blinded phase

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | not evaluable at day 56 |
|----------------------------|-------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

patient that entered run-in phase but not being evaluable at the end of this phase

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | evaluable on day 56 |
|----------------------------|---------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

patients of run in phase who were evaluable on day 56

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | SD patients entering randomized phase |
|----------------------------|---------------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

patients with SD at the end of run-in phase entering randomized phase

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | blinded placebo |
|----------------------------|-----------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

patients in blinded phase randomized to placebo

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | blinded sorafenib |
| Subject analysis set type  | Full analysis     |

Subject analysis set description:

patients in blinded phase randomized to sorafenib

| <b>Reporting group values</b>                                                                   | treated in run-in phase | not evaluable at day 56 | evaluable on day 56 |
|-------------------------------------------------------------------------------------------------|-------------------------|-------------------------|---------------------|
| Number of subjects                                                                              | 147                     | 30                      | 117                 |
| Age categorical<br>Units: Subjects                                                              |                         |                         |                     |
| Adults (18-64 years)                                                                            |                         |                         |                     |
| From 65-84 years                                                                                |                         |                         |                     |
| 85 years and over                                                                               |                         |                         |                     |
| Gender categorical<br>Units: Subjects                                                           |                         |                         |                     |
| Female                                                                                          |                         |                         |                     |
| Male                                                                                            |                         |                         |                     |
| patients enrolled                                                                               |                         |                         |                     |
| patients fulfilling the inclusion criteria versus patients who could not enter the run-in phase |                         |                         |                     |
| Units: Subjects                                                                                 |                         |                         |                     |
| patients enrolled                                                                               | 147                     | 147                     | 117                 |
| not recorded                                                                                    | 0                       | 30                      | 30                  |
| Age                                                                                             |                         |                         |                     |
| age of patients                                                                                 |                         |                         |                     |
| Units: years                                                                                    |                         |                         |                     |
| median                                                                                          | 62                      |                         |                     |
| full range (min-max)                                                                            | 23 to 88                |                         |                     |

| <b>Reporting group values</b>                                                                   | SD patients entering randomized phase | blinded placebo | blinded sorafenib |
|-------------------------------------------------------------------------------------------------|---------------------------------------|-----------------|-------------------|
| Number of subjects                                                                              | 78                                    | 39              | 39                |
| Age categorical<br>Units: Subjects                                                              |                                       |                 |                   |
| Adults (18-64 years)                                                                            |                                       |                 |                   |
| From 65-84 years                                                                                |                                       |                 |                   |
| 85 years and over                                                                               |                                       |                 |                   |
| Gender categorical<br>Units: Subjects                                                           |                                       |                 |                   |
| Female                                                                                          |                                       |                 |                   |
| Male                                                                                            |                                       |                 |                   |
| patients enrolled                                                                               |                                       |                 |                   |
| patients fulfilling the inclusion criteria versus patients who could not enter the run-in phase |                                       |                 |                   |
| Units: Subjects                                                                                 |                                       |                 |                   |
| patients enrolled                                                                               |                                       |                 |                   |
| not recorded                                                                                    |                                       |                 |                   |
| Age                                                                                             |                                       |                 |                   |
| age of patients                                                                                 |                                       |                 |                   |
| Units: years                                                                                    |                                       |                 |                   |
| median                                                                                          |                                       | 66              | 58                |
| full range (min-max)                                                                            |                                       | 47 to 88        | 23 to 79          |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                       |                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                 | run-in phase                          |
| Reporting group description: -                                                                                                                                                                                                                                                                                                                                                                                        |                                       |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                 | Sorafenib Arm                         |
| Reporting group description:<br>In patients who completed the run-in period, tumor response was classified according to RECIST. Patients with partial response (PR) were continued on sorafenib, patients with progression (PD) were taken off study and patients with stable disease (SD) were randomly assigned to sorafenib (2 x 200 mg bid) or matching placebo in a double-blind fashion without stratification. |                                       |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                 | Placebo                               |
| Reporting group description:<br>control arm with placebo                                                                                                                                                                                                                                                                                                                                                              |                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                            | treated in run-in phase               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                             | Full analysis                         |
| Subject analysis set description:<br>patients entering run in phase and receiving study medication in not blinded phase                                                                                                                                                                                                                                                                                               |                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                            | not evaluable at day 56               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                             | Full analysis                         |
| Subject analysis set description:<br>patient that entered run-in phase but not being evaluable at the end of this phase                                                                                                                                                                                                                                                                                               |                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                            | evaluable on day 56                   |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                             | Full analysis                         |
| Subject analysis set description:<br>patients of run in phase who were evaluable on day 56                                                                                                                                                                                                                                                                                                                            |                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                            | SD patients entering randomized phase |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                             | Full analysis                         |
| Subject analysis set description:<br>patients with SD at the end of run-in phase entering randomized phase                                                                                                                                                                                                                                                                                                            |                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                            | blinded placebo                       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                             | Full analysis                         |
| Subject analysis set description:<br>patients in blinded phase randomized to placebo                                                                                                                                                                                                                                                                                                                                  |                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                            | blinded sorafenib                     |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                             | Full analysis                         |
| Subject analysis set description:<br>patients in blinded phase randomized to sorafenib                                                                                                                                                                                                                                                                                                                                |                                       |

### Primary: PFS

|                                                                                                                    |         |
|--------------------------------------------------------------------------------------------------------------------|---------|
| End point title                                                                                                    | PFS     |
| End point description:<br>PFS measured by ct-scan: after 56days run in, then every 8 weeks within randomized phase |         |
| End point type                                                                                                     | Primary |
| End point timeframe:<br>PFS measured by ct-scan: after 56days run in, then every 8 weeks within randomized phase   |         |

| <b>End point values</b>     | Sorafenib Arm   | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 39              | 39              |  |  |
| Units: months               | 6               | 2               |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | PFS of Sorafenib versus Placebo |
|-----------------------------------|---------------------------------|
|-----------------------------------|---------------------------------|

Statistical analysis description:

According to the Study Protocol, the primary objective of the study was to determine progression-free survival (PFS) of Sorafenib versus Placebo after random assignment to blinded study medication in the randomised subset (tumour assessment according to RECIST 1.1 criteria)

|                                         |                         |
|-----------------------------------------|-------------------------|
| Comparison groups                       | Sorafenib Arm v Placebo |
| Number of subjects included in analysis | 78                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0079 <sup>[1]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |

Notes:

[1] - A statistical significant difference between the treatment arms was found with a p-value of the log-rank test of 0.0079. The hazard ratio was 0.527

## Secondary: OS

|                 |    |
|-----------------|----|
| End point title | OS |
|-----------------|----|

End point description:

measured by ct-scan after 56days after run-in phase and every 8 weeks thereafter within randomization phase

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

End point timeframe:

measured by ct-scan after 56days after run-in phase and every 8 weeks thereafter within randomization phase

| <b>End point values</b>     | Sorafenib Arm   | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 39              | 39              |  |  |
| Units: months               | 15              | 14              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

One year after LPLV: December 2016

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

### Reporting groups

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

Reporting group description: -

|                       |           |
|-----------------------|-----------|
| Reporting group title | Sorafenib |
|-----------------------|-----------|

Reporting group description: -

| <b>Serious adverse events</b>                        | Placebo         | Sorafenib       |  |
|------------------------------------------------------|-----------------|-----------------|--|
| Total subjects affected by serious adverse events    |                 |                 |  |
| subjects affected / exposed                          | 8 / 39 (20.51%) | 8 / 39 (20.51%) |  |
| number of deaths (all causes)                        | 39              | 39              |  |
| number of deaths resulting from adverse events       | 0               | 1               |  |
| General disorders and administration site conditions |                 |                 |  |
| general disorders and administration site conditions |                 |                 |  |
| subjects affected / exposed                          | 2 / 39 (5.13%)  | 2 / 39 (5.13%)  |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 1 / 1           |  |
| Gastrointestinal disorders                           |                 |                 |  |
| gastrointestinal disorders                           |                 |                 |  |
| subjects affected / exposed                          | 2 / 39 (5.13%)  | 4 / 39 (10.26%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 4 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Placebo          | Sorafenib        |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 38 / 39 (97.44%) | 36 / 39 (92.31%) |  |

|                                                                                                                                                                        |                        |                        |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| Investigations<br>Investigations<br>subjects affected / exposed<br>occurrences (all)                                                                                   | 12 / 39 (30.77%)<br>31 | 8 / 39 (20.51%)<br>21  |  |
| Vascular disorders<br>Vascular disorders<br>subjects affected / exposed<br>occurrences (all)                                                                           | 6 / 39 (15.38%)<br>6   | 7 / 39 (17.95%)<br>7   |  |
| Nervous system disorders<br>Nervous system disorders<br>subjects affected / exposed<br>occurrences (all)                                                               | 3 / 39 (7.69%)<br>3    | 6 / 39 (15.38%)<br>6   |  |
| General disorders and administration<br>site conditions<br>General disorders and administration<br>site conditions<br>subjects affected / exposed<br>occurrences (all) | 14 / 39 (35.90%)<br>36 | 14 / 39 (35.90%)<br>36 |  |
| Gastrointestinal disorders<br>gastrointestinal disorder<br>subjects affected / exposed<br>occurrences (all)                                                            | 18 / 39 (46.15%)<br>46 | 23 / 39 (58.97%)<br>59 |  |
| Hepatobiliary disorders<br>Hepatobiliary disorder<br>subjects affected / exposed<br>occurrences (all)                                                                  | 10 / 39 (25.64%)<br>26 | 6 / 39 (15.38%)<br>15  |  |
| Skin and subcutaneous tissue disorders<br>Skin and subcutaneous tissue<br>disorders<br>subjects affected / exposed<br>occurrences (all)                                | 10 / 39 (25.64%)<br>26 | 26 / 39 (66.67%)<br>67 |  |
| Metabolism and nutrition disorders<br>Metabolism and nutrition disorders<br>subjects affected / exposed<br>occurrences (all)                                           | 6 / 39 (15.38%)<br>15  | 8 / 39 (20.51%)<br>21  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13 August 2013 | <p>the treatment allocation of patients will be unblinded if they experience progression during the randomized phase. Until 19th July 2013 31 patients have been unblinded as they experienced progression during the randomized phase. 19 of these patients had received placebo and only 12 patients had received sorafenib.</p> <p>As patients are randomized equally to both treatment arms (sorafenib or placebo), the suspicion arises that with regard to the primary endpoint progression-free survival after random assignment to blinded study medication treatment with sorafenib is more effective.</p> <p>Therefore, in order to prevent patient's unnecessary exposure to placebo an interim analysis will be performed to verify or exclude this suspicion.</p> <p>Further on, due to the retirement of Prof. Dr. Max Scheulen on 1st September 2013, the coordinating investigator will change to Frau Dr. Heike Richly.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported