



## Clinical trial results:

**A prospective, single-arm, multicenter, uncontrolled, open-label Phase II trial of refametinib (BAY 86-9766) in combination with sorafenib as first line treatment in patients with RAS mutant Hepatocellular Carcinoma (HCC)**

### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2013-000241-39          |
| Trial protocol           | AT CZ GB DE BE IT HU ES |
| Global end of trial date | 08 February 2017        |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 10 February 2018 |
| First version publication date | 10 February 2018 |

### Trial information

#### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | BAY86-9766 / 16728 |
|-----------------------|--------------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bayer AG  |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,                |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trialscontact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trialscontact@bayer.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 08 February 2017 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 08 February 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of refametinib in combination with sorafenib in subjects with Kirsten rat sarcoma viral oncogene homolog (KRAS/GTPase KRas) or Neuroblastoma RAS viral oncogene homolog (NRAS) mutant unresectable or metastatic Hepatocellular carcinoma (HCC).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council of Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 27 September 2013 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Efficacy, Safety  |
| Long term follow-up duration                              | 19 Months         |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 1        |
| Country: Number of subjects enrolled | France: 4         |
| Country: Number of subjects enrolled | Germany: 2        |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Hong Kong: 1      |
| Country: Number of subjects enrolled | Japan: 2          |
| Country: Number of subjects enrolled | Spain: 1          |
| Country: Number of subjects enrolled | Switzerland: 1    |
| Country: Number of subjects enrolled | Taiwan: 2         |
| Country: Number of subjects enrolled | Thailand: 1       |
| Worldwide total number of subjects   | 16                |
| EEA total number of subjects         | 9                 |

Notes:

| <b>Subjects enrolled per age group</b>    |   |
|---|---|
| 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)                      | 8 |
| From 65 to 84 years                       | 8 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study conducted in 21 countries (Austria, Belgium, China, Czech Republic, France, Germany, United Kingdom, Hong Kong, Hungary, Israel, Italy, Japan, New Zealand, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United States) between 27 September 2013 (first subject first visit) and 08 February 2017 (last subject last visit).

### Pre-assignment

Screening details:

In Stage 1 of the study, 820 subjects were included in screening phase 1 for KRAS or NRAS mutations, of them 24 completed screening phase 1 and enrolled for screening phase 2 (for study treatment eligibility). In phase 2 screening, 7 were screening failures and 1 died. Finally, 16 subjects were assigned to treatment. Stage 2 was not performed.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |  |
|-----------|--|
| Arm title | Refametinib 50 mg BID + Sorafenib 400 mg BID |
|-----------|--|

Arm description:

Subjects received refametinib 50 milligram (mg) as tablets (50 mg tablets or 20 mg + 30 mg tablets), orally, twice daily (bid) in combination with sorafenib 400 mg as tablets (2 \* 200 mg tablets), orally bid without food in a 3-week treatment cycle until disease progression as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no hand-foot skin reaction (HFSR), fatigue, or gastrointestinal (GI) toxicities of grade 2 or higher occurred.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Sorafenib     |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Coated tablet |
| Routes of administration               | Oral use      |

Dosage and administration details:

Subjects received sorafenib 400 mg as tablets (2 \* 200 mg tablets), orally bid without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

|  |               |
|--|---------------|
| Investigational medicinal product name | Refametinib   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Coated tablet |
| Routes of administration               | Oral use      |

Dosage and administration details:

Subjects received refametinib 50 mg as tablets (50 mg tablets or 20 mg + 30 mg tablets), orally bid, without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met.

| <b>Number of subjects in period 1</b>                 | Refametinib 50 mg<br>BID + Sorafenib 400<br>mg BID |
|---|--|
| Started   | 16   |
| Completed   | 12   |
| Not completed   | 4  |
| Consent withdrawn by subject                          | 2  |
| AE Not Associated With<br>ClinicalDisease Progression | 2  |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 16            | 16    |  |
| Age Categorical        |               |       |  |
| Units: Subjects        |               |       |  |

|   |       |    |  |
|---|-------|----|--|
| Age Continuous  |       |    |  |
| Units: years  |       |    |  |
| arithmetic mean   | 67.2  |    |  |
| standard deviation  | ± 8.3 | -  |  |
| Gender Categorical  |       |    |  |
| Units: Subjects   |       |    |  |
| Female  | 4     | 4  |  |
| Male  | 12    | 12 |  |
| Eastern cooperative oncology group (ECOG) Performance Status (PS)   |       |    |  |
| ECOG PS was measured in a scale from 0 (best) to grade 4 (worst), where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours (h), 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, and 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair. |       |    |  |
| Units: Subjects   |       |    |  |
| Fully Active  | 10    | 10 |  |
| Restricted Active   | 6     | 6  |  |
| Macrovascular Invasion  |       |    |  |
| Macrovascular invasion was defined as presence or absence of invasion of portal or hepatic vasculature by tumor.  |       |    |  |
| Units: Subjects   |       |    |  |
| No  | 9     | 9  |  |
| Yes   | 7     | 7  |  |
| Barcelona Clinic Liver Cancer (BCLC) stage  |       |    |  |
| BCLC classification divides HCC subjects in 5 stages (0=very early stage, A=early stage, B=intermediate stage, C=advanced stage and D=terminal stage) according to pre-established prognostic variables, and allocates therapies according to treatment-related status. Thus, it provides information on both prognostic prediction and treatment allocation.   |       |    |  |
| Units: Subjects   |       |    |  |
| A (Early Stage)   | 2     | 2  |  |
| B (Intermediate Stage)  | 2     | 2  |  |
| C (Advanced Stage)  | 12    | 12 |  |

## End points

### End points reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Refametinib 50 mg BID + Sorafenib 400 mg BID |
|-----------------------|--|

Reporting group description:

Subjects received refametinib 50 milligram (mg) as tablets (50 mg tablets or 20 mg + 30 mg tablets), orally, twice daily (bid) in combination with sorafenib 400 mg as tablets (2 \* 200 mg tablets), orally bid without food in a 3-week treatment cycle until disease progression as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no hand-foot skin reaction (HFSR), fatigue, or gastrointestinal (GI) toxicities of grade 2 or higher occurred.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full analysis set (FAS) |
|----------------------------|-------------------------|

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

Subject analysis set description:

FAS (N=16) included all subjects assigned to the study treatment.

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Asia population |
|----------------------------|-----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Asia population (N=6) included all Asian subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | RoW population |
|----------------------------|----------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

RoW population (N=10) included all RoW subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

### Primary: Objective Tumor Response Rate (ORR) According to mRECIST Assessed by Central Radiological Review

|                 |   |
|-----------------|---|
| End point title | Objective Tumor Response Rate (ORR) According to mRECIST Assessed by Central Radiological Review <sup>[1]</sup> |
|-----------------|---|

End point description:

ORR was defined as the proportion of subjects who had a best response rating over the whole duration of the study of complete response (CR) or partial response (PR) according to mRECIST. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of less than (<) 10 millimeter (mm). PR was defined as at least a 30 percent (%) decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Subjects with no PR or CR, as well as subjects who prematurely discontinued without an evaluable assessment or subjects with an observed CR or PR that was not confirmed were considered non-responders for the analysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

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: As Stage 1 of the study was exploratory, there was no statistical testing at the end of Stage 1; all analyses were descriptive only.

| End point values            | Asia population      | RoW population       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 6 <sup>[2]</sup>     | 10 <sup>[3]</sup>    |  |  |
| Units: Subjects             |                      |                      |  |  |
| Responder                   | 0                    | 0                    |  |  |
| Non-Responder               | 6                    | 10                   |  |  |

Notes:

[2] - FAS

[3] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: ORR According to RECIST v.1.1 Assessed by Central Radiological Review

|                 |   |
|-----------------|---|
| End point title | ORR According to RECIST v.1.1 Assessed by Central Radiological Review |
|-----------------|---|

End point description:

ORR was defined as the proportion of subjects who had a best response rating over the whole duration of the study of CR or PR according to RECIST v.1.1. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Subjects with no PR or CR, as well as subjects who prematurely discontinued without an evaluable assessment or subjects with an observed CR or PR that was not confirmed were considered non-responders for the analysis.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values            | Asia population      | RoW population       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 6 <sup>[4]</sup>     | 10 <sup>[5]</sup>    |  |  |
| Units: Count of subjects    |                      |                      |  |  |
| Responder                   | 0                    | 0                    |  |  |
| Non-Responder               | 6                    | 10                   |  |  |

Notes:

[4] - FAS

[5] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: ORR According to mRECIST and RECIST v.1.1 Assessed by Investigator

|                 |  |
|-----------------|--|
| End point title | ORR According to mRECIST and RECIST v.1.1 Assessed by Investigator |
|-----------------|--|

End point description:

The investigator's assessment of ORR according to mRECIST and RECIST 1.1 was defined as the proportion of subjects who have a best response rating over the whole duration of the study of CR or



PR. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Subjects with no PR or CR, as well as subjects who prematurely discontinued without an evaluable assessment or subjects with an observed CR or PR that was not confirmed were considered non-responders for the analysis.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values             | Asia population      | RoW population       |  |  |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed  | 6 <sup>[6]</sup>     | 10 <sup>[7]</sup>    |  |  |
| Units: Count of subjects     |                      |                      |  |  |
| Responder (mRECIST)          | 0                    | 1                    |  |  |
| Non-Responder (mRECIST)      | 6                    | 9                    |  |  |
| Responder (RECIST v.1.1)     | 0                    | 1                    |  |  |
| Non-Responder (RECIST v.1.1) | 6                    | 9                    |  |  |

Notes:

[6] - FAS

[7] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Control Rate (DCR) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

|                 |  |
|-----------------|--|
| End point title | Disease Control Rate (DCR) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review |
|-----------------|--|

End point description:

DCR was defined as the proportion of subjects who have a best response rating over the whole duration of the study of CR, PR or stable disease (SD) according to mRECIST and RECIST 1.1 criteria. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Subjects prematurely discontinuing without an assessment was considered non-responders for the analysis.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values             | Asia population      | RoW population       |  |  |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed  | 6 <sup>[8]</sup>     | 10 <sup>[9]</sup>    |  |  |
| Units: Count of subjects     |                      |                      |  |  |
| Responder (mRECIST)          | 2                    | 5                    |  |  |
| Non-Responder (mRECIST)      | 4                    | 5                    |  |  |
| Responder (RECIST v.1.1)     | 2                    | 5                    |  |  |
| Non-Responder (RECIST v.1.1) | 4                    | 5                    |  |  |

Notes:

[8] - FAS

[9] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: DCR According to mRECIST and RECIST v.1.1 Assessed by Investigator

|                 |  |
|-----------------|--|
| End point title | DCR According to mRECIST and RECIST v.1.1 Assessed by Investigator |
|-----------------|--|

End point description:

DCR was defined as the proportion of subjects who have a best response rating over the whole duration of the study of CR, PR or stable disease (SD) according to mRECIST and RECIST 1.1 criteria. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Subjects prematurely discontinuing without an assessment was considered non-responders for the analysis.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values             | Asia population      | RoW population       |  |  |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed  | 6 <sup>[10]</sup>    | 10 <sup>[11]</sup>   |  |  |
| Units: Count of subjects     |                      |                      |  |  |
| Responder (mRECIST)          | 3                    | 4                    |  |  |
| Non-Responder (mRECIST)      | 3                    | 6                    |  |  |
| Responder (RECIST v.1.1)     | 3                    | 4                    |  |  |
| Non-Responder (RECIST v.1.1) | 3                    | 6                    |  |  |

Notes:

[10] - FAS

[11] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:  |                       |
| OS was defined as the time from the first day with study drug intake until death from any cause or until the last date the subject was known to be alive. In the below table, "99999" indicates that data was not estimable due to censored data. |                       |
| End point type  | Secondary             |
| End point timeframe:  |                       |
| From start of study treatment until death from any cause or until the last date the subject was known to be alive (evaluated in every 6 weeks) (total 41 months approximately)  |                       |

| End point values                 | Asia population      | RoW population       |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 6 <sup>[12]</sup>    | 10 <sup>[13]</sup>   |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) | 99 (39 to 99999)     | 427 (36 to 99999)    |  |  |

Notes:

[12] - FAS

[13] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Radiographic Tumor Progression (TTRP) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

|  |   |
|--|---|
| End point title  | Time to Radiographic Tumor Progression (TTRP) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review |
| End point description:   |   |
| TTRP was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of the first observed radiographic disease progression. In the below table, "99999" indicates that data was not estimable due to censored data. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)   |   |

| End point values                 | Asia population      | RoW population       |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 6 <sup>[14]</sup>    | 10 <sup>[15]</sup>   |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) |                      |                      |  |  |
| mRECIST                          | 42 (39 to 99999)     | 167 (42 to 99999)    |  |  |
| RECIST v.1.1                     | 42 (39 to 99999)     | 126 (42 to 132)      |  |  |

Notes:

[14] - FAS

[15] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: TTRP According to mRECIST and RECIST v.1.1 Assessed by Investigator

|                 |   |
|-----------------|---|
| End point title | TTRP According to mRECIST and RECIST v.1.1 Assessed by Investigator |
|-----------------|---|

End point description:

TTRP was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of the first observed radiographic disease progression.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values                 | Asia population      | RoW population       |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 6 <sup>[16]</sup>    | 10 <sup>[17]</sup>   |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) |                      |                      |  |  |
| mRECIST                          | 56 (28 to 84)        | 84 (42 to 167)       |  |  |
| RECIST v.1.1                     | 56 (28 to 84)        | 84 (42 to 167)       |  |  |

Notes:

[16] - FAS

[17] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR) According to mRECIST and RECIST v.1.1 Assessed by Investigator

|                 |   |
|-----------------|---|
| End point title | Duration of Response (DOR) According to mRECIST and RECIST v.1.1 Assessed by Investigator |
|-----------------|---|

End point description:

DOR was defined as the time from the date of first objective radiological response to the date where PD was first documented radiologically or death (if death occurred first).

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values            | Asia population      | RoW population       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 6                    | 10                   |  |  |
| Units: Days                 |                      |                      |  |  |
| mRECIST                     | 0                    | 83                   |  |  |
| RECIST v.1.1                | 0                    | 83                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Objective Response Assessed by Central Radiological Review and Investigator

|                 |   |
|-----------------|---|
| End point title | Time to Objective Response Assessed by Central Radiological Review and Investigator |
|-----------------|---|

End point description:

Time to objective response was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) until the date when an objective tumor response (CR or PR) was first documented. CR was defined as disappearance of all target lesions, disappearance of all non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values                 | Asia population      | RoW population       |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 0 <sup>[18]</sup>    | 0 <sup>[19]</sup>    |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) | ( to )               | ( to )               |  |  |

Notes:

[18] - No objective tumor responses were observed in this study.

[19] - No objective tumor responses were observed in this study.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Tumor Size Assessed by Central Radiological Review and Investigator

|                 |   |
|-----------------|---|
| End point title | Change in Tumor Size Assessed by Central Radiological Review and Investigator |
|-----------------|---|

End point description:

Number of participants with a determined best change in tumor size. Due to database constraints, best percent change in target lesions from baseline by mRECIST independent assessments (Reader 1 and Reader 2) and investigator assessments are displayed in the charts uploaded as attachment.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Refametinib 50 mg BID + Sorafenib 400 mg BID |  |  |  |
| Subject group type          | Reporting group                              |  |  |  |
| Number of subjects analysed | 16   |  |  |  |
| Units: Participants         |  |  |  |  |
| Reader 1                    | 13   |  |  |  |
| Reader 2                    | 12   |  |  |  |
| Investigator                | 10   |  |  |  |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Best percent change in target lesions by mRECIST/Best |
|-----------------------------------|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

|                 |   |
|-----------------|---|
| End point title | Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review |
|-----------------|---|

End point description:

The overall best response was defined as the best response recorded from date of the first dose of study treatment (refametinib or sorafenib) until the end of treatment. In the below table, "99999" indicates that no overall response were observed.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

|                                  |                      |                      |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>          | Asia population      | RoW population       |  |  |
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 6 <sup>[20]</sup>    | 10 <sup>[21]</sup>   |  |  |
| Units: Percentage of subjectes   |                      |                      |  |  |
| number (confidence interval 95%) |                      |                      |  |  |
| mRECIST - Unconfirmed PR         | 16.7 (0.42 to 64.12) | 20.0 (2.52 to 55.61) |  |  |

|                               |                        |                        |  |  |
|-------------------------------|------------------------|------------------------|--|--|
| mRECIST - SD                  | 16.7 (0.42 to 64.12)   | 30.0 (6.67 to 65.25)   |  |  |
| mRECIST - PD                  | 50.0 (11.81 to 88.19)  | 20.0 (2.52 to 55.61)   |  |  |
| mRECIST - Not Evaluable       | 16.7 (0.42 to 64.12)   | 99999 (99999 to 99999) |  |  |
| mRECIST - Missing             | 99999 (99999 to 99999) | 30.0 (6.67 to 65.25)   |  |  |
| RECIST v.1.1 - Unconfirmed PR | 16.7 (0.42 to 64.12)   | 99999 (99999 to 99999) |  |  |
| RECIST v.1.1 - SD             | 16.7 (0.42 to 64.12)   | 50.0 (18.71 to 81.29)  |  |  |
| RECIST v.1.1 - PD             | 50.0 (11.81 to 88.19)  | 20.0 (2.52 to 55.61)   |  |  |
| RECIST v.1.1 - Not Evaluable  | 16.7 (0.42 to 64.12)   | 99999 (99999 to 99999) |  |  |
| RECIST v.1.1 - Missing        | 99999 (99999 to 99999) | 30.0 (6.67 to 65.25)   |  |  |

Notes:

[20] - FAS

[21] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Investigator

|                 |  |
|-----------------|--|
| End point title | Best Overall Response According to mRECIST and RECIST v.1.1 Assessed by Investigator |
|-----------------|--|

End point description:

The overall best response was defined as the best response recorded from date of the first dose of study treatment (refametinib or sorafenib) until the end of treatment. In the below table, "99999" indicates that no overall response were observed.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values                 | Asia population        | RoW population         |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed      | 6 <sup>[22]</sup>      | 10 <sup>[23]</sup>     |  |  |
| Units: Percentage of subjects    |                        |                        |  |  |
| number (confidence interval 95%) |                        |                        |  |  |
| mRECIST - PR                     | 99999 (99999 to 99999) | 10.0 (0.25 to 44.50)   |  |  |
| mRECIST - Unconfirmed PR         | 16.7 (0.42 to 64.12)   | 99999 (99999 to 99999) |  |  |
| mRECIST - SD                     | 33.3 (4.33 to 77.72)   | 30.0 (6.67 to 65.25)   |  |  |
| mRECIST - PD                     | 50.0 (11.81 to 88.19)  | 30.0 (6.67 to 65.25)   |  |  |
| mRECIST - Missing                | 99999 (99999 to 99999) | 30.0 (6.67 to 65.25)   |  |  |

|                               |                        |                        |  |  |
|-------------------------------|------------------------|------------------------|--|--|
| RECIST v.1.1 - PR             | 99999 (99999 to 99999) | 10.0 (0.25 to 44.50)   |  |  |
| RECIST v.1.1 - Unconfirmed PR | 16.7 (0.42 to 64.12)   | 99999 (99999 to 99999) |  |  |
| RECIST v.1.1 - SD             | 33.3 (4.33 to 77.72)   | 30.0 (6.67 to 65.25)   |  |  |
| RECIST v.1.1 - PD             | 50.0 (11.81 to 88.19)  | 30.0 (6.67 to 65.25)   |  |  |
| RECIST v.1.1 - Missing        | 99999 (99999 to 99999) | 30.0 (6.67 to 65.25)   |  |  |

Notes:

[22] - FAS

[23] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival (PFS) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review

|                 |   |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) According to mRECIST and RECIST v.1.1 Assessed by Central Radiological Review |
|-----------------|---|

End point description:

PFS was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of first observed disease progression (radiological or clinical, whichever was first) or death due to any cause, if death occurs before progression was documented. In the below table, "99999" indicates that data was not estimable due to censored data.

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

End point timeframe:

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

| End point values                 | Asia population      | RoW population       |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 6 <sup>[24]</sup>    | 10 <sup>[25]</sup>   |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) |                      |                      |  |  |
| mRECIST                          | 42 (39 to 99)        | 84 (36 to 99999)     |  |  |
| RECIST v.1.1                     | 42 (39 to 99999)     | 126 (36 to 132)      |  |  |

Notes:

[24] - FAS

[25] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS According to mRECIST and RECIST v.1.1 Assessed by Investigator

|                 |  |
|-----------------|--|
| End point title | PFS According to mRECIST and RECIST v.1.1 Assessed by Investigator |
|-----------------|--|



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**End point description:**

PFS was defined as the time from the date of the first dose of study treatment (refametinib or sorafenib) to the date of first observed disease progression (radiological or clinical, whichever was first) or death due to any cause, if death occurs before progression was documented. In the below table, "99999" indicates that data was not estimable due to censored data.

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

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**End point timeframe:**

From start of study treatment until disease progression (evaluated in every 6 weeks) (total 41 months approximately)

---

| End point values                 | Asia population      | RoW population       |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 6 <sup>[26]</sup>    | 10 <sup>[27]</sup>   |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) |                      |                      |  |  |
| mRECIST                          | 53 (14 to 84)        | 65 (36 to 167)       |  |  |
| RECIST v.1.1                     | 53 (14 to 84)        | 65 (36 to 167)       |  |  |

**Notes:**

[26] - FAS

[27] - FAS

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)**

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|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) |
|-----------------|--|

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**End point description:**

An adverse event (AE) was any untoward medical occurrence in subject after providing written informed consent for participation in the study. AE may or may not be temporally or causally associated with the use of a medicinal product. A serious adverse event (SAE) was an AE resulting in any of following outcomes or deemed significant for any other reason: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly / birth defect; and another medical important serious event as judged by investigator.

Treatment-emergent adverse events (TEAEs) were defined as adverse events that started or worsened after the start of study drug administration up to 30 (+5) days after last administration of the study medication.

---

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

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**End point timeframe:**

From start of study treatment up 30 (+5) days after the last administration of study treatment; Subjects were contacted every 3 months to determine survival status, if applicable (approximately 3.5 years)

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| End point values            | Asia population      | RoW population       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 6 <sup>[28]</sup>    | 10 <sup>[29]</sup>   |  |  |
| Units: Count of subjects    |                      |                      |  |  |
| TEAE                        | 6                    | 10                   |  |  |
| TESAE                       | 6                    | 7                    |  |  |

Notes:

[28] - SAF

[29] - SAF

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) at Stage 2

|                 |   |
|-----------------|---|
| End point title | Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) at Stage 2 |
|-----------------|---|

End point description:

The FACT-Hep (version 4) was a 45 item, self-administered, multi-dimensional, psychometrically sound questionnaire developed to measure the quality of life (QoL) in subjects with hepatobiliary cancers, including metastatic colorectal cancer, hepatocellular carcinoma (HCC), and pancreatic, gallbladder and bile duct cancer. The FACT-Generic (FACT-G) contains 27 core questionnaires designed to measure general aspects of HRQoL of subjects with any form of cancer. Hepatobiliary Cancer Subscale (HCS) contains 18 questionnaires, designed to measure specific concerns/problems related to QoL in subjects with hepatobiliary cancers. It contains 5 domains: Physical Well-Being (PWB), Social Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and HCS. The FACT-Hep total score was the sum of PWB, SWB, EWB, FWB and HCS domain scores ranging from 0 to 180. Higher score means better HRQoL.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Stage On Day 1 of Cycle 1, 2, 3 and EOT (within 7 days after last drug administration)

| End point values            | Asia population      | RoW population       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 0 <sup>[30]</sup>    | 0 <sup>[31]</sup>    |  |  |
| Units: Score on a scale     |                      |                      |  |  |

Notes:

[30] - Data was not reported for this endpoint, since stage 2 analysis of the study was not performed.

[31] - Data was not reported for this endpoint, since stage 2 analysis of the study was not performed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs occurring from start of study treatment up 30 (+5) days after the last administration of study treatment. Subjects were contacted every 3 months to determine survival status, if applicable (approximately 3.5 years)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Rest of world (RoW) population |
|-----------------------|--------------------------------|

Reporting group description:

Rest of world (RoW) population: RoW subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Asia population |
|-----------------------|-----------------|

Reporting group description:

Asia population: Asian subjects who received refametinib 50 mg bid orally in combination with sorafenib 400 mg bid orally without food in a 3-week treatment cycle until disease progression as defined by mRECIST, clinical progression, or any other criteria for discontinuation from study treatment were met. In Cycle 1 reduced sorafenib dose (600 mg daily; 200 mg in the morning + 400 mg in the evening) was administered, which was escalated to the standard dose in Cycle 2, if no HFSR, fatigue, or GI toxicities of grade 2 or higher occurred.

| Serious adverse events                            | Rest of world (RoW) population | Asia population |  |
|---|--------------------------------|-----------------|--|
| Total subjects affected by serious adverse events |                                |                 |  |
| subjects affected / exposed                       | 7 / 10 (70.00%)                | 6 / 6 (100.00%) |  |
| number of deaths (all causes)                     | 6                              | 3               |  |
| number of deaths resulting from adverse events    | 2                              | 1               |  |
| Investigations                                    |                                |                 |  |
| Blood creatine phosphokinase increased            |                                |                 |  |
| subjects affected / exposed                       | 2 / 10 (20.00%)                | 4 / 6 (66.67%)  |  |
| occurrences causally related to treatment / all   | 2 / 6                          | 5 / 6           |  |
| deaths causally related to treatment / all        | 0 / 0                          | 0 / 0           |  |
| Injury, poisoning and procedural complications    |                                |                 |  |
| Subarachnoid haemorrhage                          |                                |                 |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)                 | 1 / 6 (16.67%)  |  |
| occurrences causally related to treatment / all   | 0 / 0                          | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0                          | 0 / 0           |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| Vascular disorders                                   |                 |                |  |
| Hypertensive emergency                               |                 |                |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 8          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Nervous system disorders                             |                 |                |  |
| Epilepsy   |                 |                |  |
| subjects affected / exposed                          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Loss of consciousness                                |                 |                |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Syncope  |                 |                |  |
| subjects affected / exposed                          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| General disorders and administration site conditions |                 |                |  |
| Pyrexia  |                 |                |  |
| subjects affected / exposed                          | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| General physical health deterioration                |                 |                |  |
| subjects affected / exposed                          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all      | 4 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all           | 1 / 1           | 0 / 0          |  |
| Eye disorders  |                 |                |  |
| Glaucoma   |                 |                |  |
| subjects affected / exposed                          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Retinal detachment                                   |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Retinal vein occlusion                          |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                      |                 |                |  |
| Diarrhoea                                       |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatobiliary disorders                         |                 |                |  |
| Hepatic failure                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Hepatitis acute                                 |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Dyspnoea  |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| Skin and subcutaneous tissue disorders          |                 |                |  |
| Dermatitis acneiform                            |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infections and infestations                     |                 |                |  |
| Pneumonia                                       |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 6 (16.67%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| Upper respiratory tract infection               |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Metabolism and nutrition disorders              |                 |                |  |
| Dehydration                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hyperglycaemia                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| 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>                     | Rest of world (RoW) population | Asia population |  |
|---|--------------------------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                                |                 |  |
| subjects affected / exposed                           | 10 / 10 (100.00%)              | 6 / 6 (100.00%) |  |
| Vascular disorders                                    |                                |                 |  |
| Haematoma   |                                |                 |  |
| subjects affected / exposed                           | 1 / 10 (10.00%)                | 0 / 6 (0.00%)   |  |
| occurrences (all)                                     | 1                              | 0               |  |
| Hypertension  |                                |                 |  |
| subjects affected / exposed                           | 7 / 10 (70.00%)                | 6 / 6 (100.00%) |  |
| occurrences (all)                                     | 18                             | 13              |  |
| Diabetic macroangiopathy                              |                                |                 |  |
| subjects affected / exposed                           | 1 / 10 (10.00%)                | 0 / 6 (0.00%)   |  |
| occurrences (all)                                     | 1                              | 0               |  |
| General disorders and administration site conditions  |                                |                 |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Asthenia  |                 |                |  |
| subjects affected / exposed                     | 3 / 10 (30.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 5               | 0              |  |
| Chills  |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 1               | 0              |  |
| Fatigue   |                 |                |  |
| subjects affected / exposed                     | 6 / 10 (60.00%) | 4 / 6 (66.67%) |  |
| occurrences (all)                               | 11              | 4              |  |
| Gait disturbance                                |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Malaise   |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Mucosal inflammation                            |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Pyrexia   |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 2              |  |
| Oedema peripheral                               |                 |                |  |
| subjects affected / exposed                     | 4 / 10 (40.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 7               | 1              |  |
| General physical health deterioration           |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 2               | 0              |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Dyspnoea  |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 1               | 1              |  |
| Epistaxis                                       |                 |                |  |
| subjects affected / exposed                     | 2 / 10 (20.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 3               | 0              |  |
| Pleural effusion                                |                 |                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | 1 / 6 (16.67%)<br>2 |  |
| Psychiatric disorders                            |                     |                     |  |
| Anxiety  |                     |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)     | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 2                   | 0                   |  |
| Confusional state                                |                     |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)     | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Delirium   |                     |                     |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Insomnia   |                     |                     |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Organic brain syndrome                           |                     |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)     | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Investigations                                   |                     |                     |  |
| Alanine aminotransferase increased               |                     |                     |  |
| subjects affected / exposed                      | 2 / 10 (20.00%)     | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 5                   | 2                   |  |
| Aspartate aminotransferase increased             |                     |                     |  |
| subjects affected / exposed                      | 4 / 10 (40.00%)     | 4 / 6 (66.67%)      |  |
| occurrences (all)                                | 13                  | 6                   |  |
| Bilirubin conjugated increased                   |                     |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)     | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 3                   | 0                   |  |
| Blood creatine phosphokinase increased           |                     |                     |  |
| subjects affected / exposed                      | 2 / 10 (20.00%)     | 3 / 6 (50.00%)      |  |
| occurrences (all)                                | 2                   | 9                   |  |
| Blood bilirubin increased                        |                     |                     |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Blood creatinine increased                       |                     |                     |  |



|                                       |                 |                |
|---------------------------------------|-----------------|----------------|
| subjects affected / exposed           | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 1               | 0              |
| Blood lactate dehydrogenase increased |                 |                |
| subjects affected / exposed           | 1 / 10 (10.00%) | 1 / 6 (16.67%) |
| occurrences (all)                     | 1               | 2              |
| C-reactive protein increased          |                 |                |
| subjects affected / exposed           | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 1               | 0              |
| Electrocardiogram QT prolonged        |                 |                |
| subjects affected / exposed           | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 1               | 0              |
| Gamma-glutamyltransferase increased   |                 |                |
| subjects affected / exposed           | 2 / 10 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all)                     | 5               | 1              |
| Haemoglobin decreased                 |                 |                |
| subjects affected / exposed           | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                     | 1               | 0              |
| Lipase increased                      |                 |                |
| subjects affected / exposed           | 0 / 10 (0.00%)  | 3 / 6 (50.00%) |
| occurrences (all)                     | 0               | 3              |
| Lymphocyte count decreased            |                 |                |
| subjects affected / exposed           | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                     | 0               | 2              |
| Neutrophil count decreased            |                 |                |
| subjects affected / exposed           | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                     | 0               | 1              |
| Platelet count decreased              |                 |                |
| subjects affected / exposed           | 0 / 10 (0.00%)  | 3 / 6 (50.00%) |
| occurrences (all)                     | 0               | 7              |
| Weight decreased                      |                 |                |
| subjects affected / exposed           | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                     | 0               | 4              |
| Weight increased                      |                 |                |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 1               | 0              |  |
| Eastern Cooperative Oncology Group<br>performance status worsened |                 |                |  |
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 2               | 0              |  |
| Child-Pugh-Turcotte score increased                               |                 |                |  |
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 2               | 0              |  |
| Injury, poisoning and procedural<br>complications                 |                 |                |  |
| Subarachnoid haemorrhage  |                 |                |  |
| subjects affected / exposed                                       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)   | 0               | 1              |  |
| Limb injury   |                 |                |  |
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 1               | 0              |  |
| Cardiac disorders   |                 |                |  |
| Atrioventricular block first degree                               |                 |                |  |
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 1               | 0              |  |
| Nervous system disorders  |                 |                |  |
| Dizziness   |                 |                |  |
| subjects affected / exposed                                       | 3 / 10 (30.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)   | 3               | 1              |  |
| Disturbance in attention  |                 |                |  |
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 1               | 0              |  |
| Dysarthria  |                 |                |  |
| subjects affected / exposed                                       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)   | 0               | 1              |  |
| Headache  |                 |                |  |
| subjects affected / exposed                                       | 2 / 10 (20.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)   | 2               | 1              |  |
| Hepatic encephalopathy  |                 |                |  |
| subjects affected / exposed                                       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)   | 1               | 0              |  |
| Sciatica  |                 |                |  |

|                                      |                 |                |  |
|--------------------------------------|-----------------|----------------|--|
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 1               | 0              |  |
| Syncope                              |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 1               | 0              |  |
| Blood and lymphatic system disorders |                 |                |  |
| Anaemia                              |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 2 / 6 (33.33%) |  |
| occurrences (all)                    | 1               | 3              |  |
| Thrombocytopenia                     |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 3               | 0              |  |
| Eye disorders                        |                 |                |  |
| Glaucoma                             |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 1               | 0              |  |
| Vision blurred                       |                 |                |  |
| subjects affected / exposed          | 2 / 10 (20.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 2               | 0              |  |
| Visual acuity reduced                |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 1               | 0              |  |
| Visual impairment                    |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                    | 1               | 0              |  |
| Chorioretinopathy                    |                 |                |  |
| subjects affected / exposed          | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                    | 0               | 1              |  |
| Gastrointestinal disorders           |                 |                |  |
| Abdominal distension                 |                 |                |  |
| subjects affected / exposed          | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                    | 0               | 2              |  |
| Abdominal pain                       |                 |                |  |
| subjects affected / exposed          | 1 / 10 (10.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)                    | 1               | 2              |  |
| Abdominal pain upper                 |                 |                |  |

|                                  |                 |                |
|----------------------------------|-----------------|----------------|
| subjects affected / exposed      | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                | 0               | 1              |
| Anal ulcer                       |                 |                |
| subjects affected / exposed      | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                | 1               | 0              |
| Ascites                          |                 |                |
| subjects affected / exposed      | 2 / 10 (20.00%) | 2 / 6 (33.33%) |
| occurrences (all)                | 3               | 2              |
| Constipation                     |                 |                |
| subjects affected / exposed      | 2 / 10 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all)                | 2               | 1              |
| Diarrhoea                        |                 |                |
| subjects affected / exposed      | 7 / 10 (70.00%) | 3 / 6 (50.00%) |
| occurrences (all)                | 15              | 16             |
| Dry mouth                        |                 |                |
| subjects affected / exposed      | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                | 0               | 1              |
| Dyspepsia                        |                 |                |
| subjects affected / exposed      | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                | 1               | 0              |
| Gastrooesophageal reflux disease |                 |                |
| subjects affected / exposed      | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                | 1               | 0              |
| Mallory-Weiss syndrome           |                 |                |
| subjects affected / exposed      | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                | 1               | 0              |
| Nausea                           |                 |                |
| subjects affected / exposed      | 2 / 10 (20.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                | 2               | 0              |
| Stomatitis                       |                 |                |
| subjects affected / exposed      | 1 / 10 (10.00%) | 2 / 6 (33.33%) |
| occurrences (all)                | 2               | 2              |
| Toothache                        |                 |                |
| subjects affected / exposed      | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                | 1               | 0              |
| Vomiting                         |                 |                |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 4 / 10 (40.00%)<br>6 | 1 / 6 (16.67%)<br>1 |  |
| Hepatobiliary disorders                          |                      |                     |  |
| Hepatic pain                                     |                      |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)      | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 1                    | 0                   |  |
| Skin and subcutaneous tissue disorders           |                      |                     |  |
| Alopecia   |                      |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 1                    | 1                   |  |
| Dermatitis acneiform                             |                      |                     |  |
| subjects affected / exposed                      | 2 / 10 (20.00%)      | 4 / 6 (66.67%)      |  |
| occurrences (all)                                | 3                    | 8                   |  |
| Dry skin   |                      |                     |  |
| subjects affected / exposed                      | 2 / 10 (20.00%)      | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 2                    | 0                   |  |
| Eczema   |                      |                     |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)       | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 0                    | 1                   |  |
| Hyperhidrosis                                    |                      |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)      | 0 / 6 (0.00%)       |  |
| occurrences (all)                                | 2                    | 0                   |  |
| Pain of skin                                     |                      |                     |  |
| subjects affected / exposed                      | 0 / 10 (0.00%)       | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 0                    | 1                   |  |
| Palmar-plantar erythrodysaesthesia<br>syndrome   |                      |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 2                    | 3                   |  |
| Pruritus   |                      |                     |  |
| subjects affected / exposed                      | 1 / 10 (10.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 1                    | 1                   |  |
| Rash   |                      |                     |  |
| subjects affected / exposed                      | 4 / 10 (40.00%)      | 1 / 6 (16.67%)      |  |
| occurrences (all)                                | 10                   | 1                   |  |
| Rash maculo-papular                              |                      |                     |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 6               | 0              |  |
| Urticaria                                       |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Nail ridging                                    |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Renal and urinary disorders                     |                 |                |  |
| Proteinuria                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 2               | 0              |  |
| Urinary incontinence                            |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 1               | 0              |  |
| Diabetic nephropathy                            |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 1               | 0              |  |
| Musculoskeletal and connective tissue disorders |                 |                |  |
| Arthralgia                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 1               | 0              |  |
| Back pain                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 3               | 0              |  |
| Flank pain                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 1               | 0              |  |
| Muscle spasms                                   |                 |                |  |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                               | 0               | 1              |  |
| Pain in extremity                               |                 |                |  |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                               | 1               | 0              |  |
| Neck pain                                       |                 |                |  |

|                                   |                 |                |  |
|-----------------------------------|-----------------|----------------|--|
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 2              |  |
| Spinal osteoarthritis             |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Infections and infestations       |                 |                |  |
| Dermatitis infected               |                 |                |  |
| subjects affected / exposed       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                 | 1               | 0              |  |
| Gastroenteritis                   |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Herpes zoster                     |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Oral candidiasis                  |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Paronychia                        |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 2              |  |
| Pneumonia                         |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Pulmonary tuberculosis            |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Upper respiratory tract infection |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |
| Candida infection                 |                 |                |  |
| subjects affected / exposed       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                 | 2               | 0              |  |
| Tinea versicolour                 |                 |                |  |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                 | 0               | 1              |  |

|                                    |                 |                |  |
|------------------------------------|-----------------|----------------|--|
| Metabolism and nutrition disorders |                 |                |  |
| Acidosis                           |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                  | 3               | 0              |  |
| Dehydration                        |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Diabetes mellitus                  |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Hyperglycaemia                     |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                  | 0               | 1              |  |
| Hyperuricaemia                     |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                  | 1               | 0              |  |
| Hypoalbuminaemia                   |                 |                |  |
| subjects affected / exposed        | 2 / 10 (20.00%) | 3 / 6 (50.00%) |  |
| occurrences (all)                  | 4               | 4              |  |
| Hypocalcaemia                      |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                  | 1               | 0              |  |
| Hypokalaemia                       |                 |                |  |
| subjects affected / exposed        | 0 / 10 (0.00%)  | 1 / 6 (16.67%) |  |
| occurrences (all)                  | 0               | 4              |  |
| Hyponatraemia                      |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)                  | 4               | 1              |  |
| Hypophosphataemia                  |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)                  | 3               | 1              |  |
| Hypoproteinaemia                   |                 |                |  |
| subjects affected / exposed        | 1 / 10 (10.00%) | 0 / 6 (0.00%)  |  |
| occurrences (all)                  | 1               | 0              |  |
| Decreased appetite                 |                 |                |  |



|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 4 / 10 (40.00%) | 1 / 6 (16.67%) |  |
| occurrences (all)           | 7               | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 22 October 2013 | <ol style="list-style-type: none"><li>1. Wording regarding use of refametinib tablets was clarified;<br/>-based on final pharmacokinetic results from a clinical relative bioavailability study (15221) where tablets exhibited comparable bioavailability to capsules, refametinib tablets could be used in clinical trials as an alternative for capsules.</li><li>2. Exclusion criteria were amended;<br/>-Subjects with a QTc greater than 480 milliseconds at the time of screening were excluded from the study due to the potential for QT prolongation with sorafenib<br/>-Exclusion criterion regarding women of childbearing potential was amended to reduce the time gap between the pregnancy evaluation and the beginning of treatment.<br/>-Exclusion criterion regarding systemic anticancer therapy was clarified, as subjectswith prior systemic anticancer therapy were not eligible for this study.</li><li>3. A dose modification scheme for hepatotoxic events was included, since hepatotoxicity is an "identified risk" for the refametinib-sorafenib combination.</li><li>4. Guidance regarding reporting of contrast media was added.</li><li>5. Additional safety electrocardiograms (ECGs) were added in order to characterize the cardiovascular safety at anticipated maximum plasma concentrations of the study treatment.</li></ol> |

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.

Occurrence of "±" in relation with geometric CV is auto-generated. Decimal places were automatically truncated if last decimal equals zero. Biomarker and PK anlysis were defined as additional objectives/variables of this study.

Notes: