



## Clinical trial results:

**DOVIGIST: Phase II trial to evaluate the efficacy and safety of Dovitinib (TKI258) in patients with gastrointestinal stromal tumors refractory and/or intolerant to imatinib.**

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.**

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-001725-24 |
| Trial protocol           | BE ES FI IT DE |
| Global end of trial date | 31 July 2014   |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 07 July 2018 |
| First version publication date | 07 July 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CTKI258AIC02 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01478373 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                            |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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                       | 31 July 2014 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 31 July 2014 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To assess the antitumor activity of dovitinib in terms of disease control rate (DCR): Complete Response (CR) + Partial Response (PR) + Stable Disease (SD), at 12 weeks in patients with documented disease progression while on therapy with imatinib for unresectable and/or metastatic gastrointestinal stromal tumors (GIST), recurrent GIST on adjuvant imatinib or within the first 3 months after discontinuation of adjuvant imatinib and/ or, unresectable and/or metastatic GIST intolerant to imatinib.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 31 January 2012 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Spain: 11  |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Italy: 11  |
| Country: Number of subjects enrolled | Germany: 1 |
| Worldwide total number of subjects   | 39         |
| EEA total number of subjects         | 39         |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|                                          |    |
|------------------------------------------|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 26 |
| From 65 to 84 years                      | 13 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

39 Patients enrolled. One patient was a protocol deviation which excluded the patient from the Full Analysis Set.

### Period 1

|                              |                 |
|------------------------------|-----------------|
| Period 1 title               | Treatment Phase |
| Is this the baseline period? | Yes             |
| Allocation method            | Not applicable  |
| Blinding used                | Not blinded     |

### Arms

|           |           |
|-----------|-----------|
| Arm title | Dovitinib |
|-----------|-----------|

Arm description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Dovitinib    |
| Investigational medicinal product code | TKI258       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

| Number of subjects in period 1 | Dovitinib |
|--------------------------------|-----------|
| Started                        | 39        |
| Completed                      | 38        |
| Not completed                  | 1         |
| Protocol deviation             | 1         |

### Period 2

|                              |                |
|------------------------------|----------------|
| Period 2 title               | Survival Phase |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

## Arms

|           |           |
|-----------|-----------|
| Arm title | Dovitinib |
|-----------|-----------|

### Arm description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Dovitinib    |
| Investigational medicinal product code | TKI258       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

### Dosage and administration details:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

| Number of subjects in period 2 | Dovitinib |
|--------------------------------|-----------|
| Started                        | 38        |
| Completed                      | 0         |
| Not completed                  | 38        |
| Adverse event, non-fatal       | 8         |
| Progressive Disease            | 27        |
| crossover to another study     | 2         |
| Protocol deviation             | 1         |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Dovitinib |
|-----------------------|-----------|

Reporting group description:

Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal.

| Reporting group values                                | Dovitinib | Total |  |
|-------------------------------------------------------|-----------|-------|--|
| Number of subjects                                    | 39        | 39    |  |
| Age categorical<br>Units: Subjects                    |           |       |  |
| In utero                                              | 0         | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0         | 0     |  |
| Newborns (0-27 days)                                  | 0         | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0         | 0     |  |
| Children (2-11 years)                                 | 0         | 0     |  |
| Adolescents (12-17 years)                             | 0         | 0     |  |
| Adults (18-64 years)                                  | 26        | 26    |  |
| From 65-84 years                                      | 13        | 13    |  |
| 85 years and over                                     | 0         | 0     |  |
| Age Continuous  <br>Units: Years                      |           |       |  |
| arithmetic mean                                       | 59.2      |       |  |
| standard deviation                                    | ± 10.14   | -     |  |
| Gender, Male/Female<br>Units: Participants            |           |       |  |
| Female                                                | 17        | 17    |  |
| Male                                                  | 22        | 22    |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                        |           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Reporting group title                                                                                                                                                                                                                                                  | Dovitinib |
| Reporting group description:<br>Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal. |           |
| Reporting group title                                                                                                                                                                                                                                                  | Dovitinib |
| Reporting group description:<br>Patients received Dovitinib (TKI258) on an outpatient basis at the dose of 500 mg qd for 5 days followed by 2 days off, every week for cycle of 4 weeks (28d) until disease progression, unacceptable toxicity, or consent withdrawal. |           |

### Primary: Antitumor activity of Dovitinib in terms of disease control rate (DCR): Complete Response+Partial Response +Stable Disease

|                                                                                                                                                                                                                              |                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                              | Antitumor activity of Dovitinib in terms of disease control rate (DCR): Complete Response+Partial Response +Stable Disease <sup>[1]</sup> |
| End point description:<br>DCR is defined as the proportion of patients with a best overall response of Complete Responses (CR), Partial Response (PR) and Stable Disease (SD) at 12 weeks according to RECIST (version 1.1). |                                                                                                                                           |
| End point type                                                                                                                                                                                                               | Primary                                                                                                                                   |
| End point timeframe:<br>12 Weeks                                                                                                                                                                                             |                                                                                                                                           |

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: Statistical analysis between treatment groups does not apply as this is a single arm exact binomial single-stage Phase II study.

| End point values                  | Dovitinib           |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 38                  |  |  |  |
| Units: Percentage of Participants |                     |  |  |  |
| number (confidence interval)      | 52.6 (38.2 to 66.7) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS) of patients treated with Dovitinib

|                                                                                                                                                                                                         |                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| End point title                                                                                                                                                                                         | Progression-free survival (PFS) of patients treated with Dovitinib |
| End point description:<br>The PFS duration: time from entry into the study to the date of the first documented progression (assessed using conventional RECIST (version 1.1) or death due to any cause. |                                                                    |
| End point type                                                                                                                                                                                          | Secondary                                                          |

End point timeframe:

9 months

|                              |                 |  |  |  |
|------------------------------|-----------------|--|--|--|
| <b>End point values</b>      | Dovitinib       |  |  |  |
| Subject group type           | Reporting group |  |  |  |
| Number of subjects analysed  | 38              |  |  |  |
| Units: Days                  |                 |  |  |  |
| median (confidence interval) | 141 (86 to 225) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to treatment failure (TTF) of patients treated with Dovitinib

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Time to treatment failure (TTF) of patients treated with Dovitinib |
|-----------------|--------------------------------------------------------------------|

End point description:

TTF: the date of entry into the study to the earliest date of the first objective tumor progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol deviation' or 'Administrative problems'.

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

End point timeframe:

9 months

|                              |                 |  |  |  |
|------------------------------|-----------------|--|--|--|
| <b>End point values</b>      | Dovitinib       |  |  |  |
| Subject group type           | Reporting group |  |  |  |
| Number of subjects analysed  | 38              |  |  |  |
| Units: Days                  |                 |  |  |  |
| median (confidence interval) | 122 (81 to 223) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response or stable disease (SD)

|                 |                                             |
|-----------------|---------------------------------------------|
| End point title | Duration of response or stable disease (SD) |
|-----------------|---------------------------------------------|

End point description:

Duration of response or stable disease: time from the date of entry into the study to the earliest date of the first objective tumor progression or death.

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



End point timeframe:

9 months

|                                      |                  |  |  |  |
|--------------------------------------|------------------|--|--|--|
| <b>End point values</b>              | Dovitinib        |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 38               |  |  |  |
| Units: Days                          |                  |  |  |  |
| arithmetic mean (standard deviation) | 193.2 (± 117.78) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to tumor progression (TTP) of patients treated with Dovitinib

|                                                                                                                                                              |                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| End point title                                                                                                                                              | Time to tumor progression (TTP) of patients treated with Dovitinib |
| End point description:<br>TTP: time from the date of entry into the study to first documentation of tumor progression or death due to the underlying cancer. |                                                                    |
| End point type                                                                                                                                               | Secondary                                                          |
| End point timeframe:<br>9 months                                                                                                                             |                                                                    |

|                              |                 |  |  |  |
|------------------------------|-----------------|--|--|--|
| <b>End point values</b>      | Dovitinib       |  |  |  |
| Subject group type           | Reporting group |  |  |  |
| Number of subjects analysed  | 38              |  |  |  |
| Units: Days                  |                 |  |  |  |
| median (confidence interval) | 141 (85 to 229) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall response rate (ORR) of patients treated with Dovitinib

|                                                                                                                                                                                                             |                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| End point title                                                                                                                                                                                             | Overall response rate (ORR) of patients treated with Dovitinib |
| End point description:<br>Outcome Measure Description: ORR: proportion of patients whose best overall response is either complete response (CR) or partial response (PR) according to RECIST (version 1.1). |                                                                |
| End point type                                                                                                                                                                                              | Secondary                                                      |

End point timeframe:

Baseline, 12 weeks

| End point values                  | Dovitinib         |  |  |  |
|-----------------------------------|-------------------|--|--|--|
| Subject group type                | Reporting group   |  |  |  |
| Number of subjects analysed       | 38                |  |  |  |
| Units: Percentage of Participants |                   |  |  |  |
| number (confidence interval)      | 2.6 (0.1 to 11.9) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS) of patients treated with Dovitinib

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Overall survival (OS) of patients treated with Dovitinib |
|-----------------|----------------------------------------------------------|

End point description:

Outcome Measure Description: OS: time from the date of entry into the study to the date of death due to any cause. A patient who has not died by the date of the analysis cut-off would have the OS censored at the time of the last contact before the cut-off date.

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

End point timeframe:

21 months (9 months of estimated treatment plus 12 months of survival follow up)

| End point values             | Dovitinib                      |  |  |  |
|------------------------------|--------------------------------|--|--|--|
| Subject group type           | Reporting group                |  |  |  |
| Number of subjects analysed  | 38                             |  |  |  |
| Units: Months                |                                |  |  |  |
| median (confidence interval) | 9999.9 (-99999.99 to 99999.99) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DCR (CR+PR+SD) at the end of treatment

|                 |                                        |
|-----------------|----------------------------------------|
| End point title | DCR (CR+PR+SD) at the end of treatment |
|-----------------|----------------------------------------|

End point description:

DCR is defined as the proportion of patients with a best overall response of CR, PR and SD at the end of dovitinib treatment according to RECIST (version 1.1).

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

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End point timeframe:

End of Treatment

---

|                                   |                     |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| <b>End point values</b>           | Dovitinib           |  |  |  |
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 38                  |  |  |  |
| Units: Percentate of Participants |                     |  |  |  |
| number (confidence interval)      | 52.6 (38.2 to 66.7) |  |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Dovitinib |
|-----------------------|-----------|

Reporting group description:

Dovitinib

| Serious adverse events                                              | Dovitinib        |  |  |
|---------------------------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed                                         | 16 / 39 (41.03%) |  |  |
| number of deaths (all causes)                                       | 1                |  |  |
| number of deaths resulting from adverse events                      | 1                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Malignant melanoma                                                  |                  |  |  |
| subjects affected / exposed                                         | 1 / 39 (2.56%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Prostate cancer                                                     |                  |  |  |
| subjects affected / exposed                                         | 1 / 39 (2.56%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders                                                  |                  |  |  |
| Aortic thrombosis                                                   |                  |  |  |
| subjects affected / exposed                                         | 1 / 39 (2.56%)   |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Phlebitis                                                           |                  |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia                                             |                 |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Fatigue                                              |                 |  |  |
| subjects affected / exposed                          | 4 / 39 (10.26%) |  |  |
| occurrences causally related to treatment / all      | 2 / 5           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General physical health deterioration                |                 |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Inflammation                                         |                 |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Localised oedema                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Mucosal dryness                                      |                 |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Oedema peripheral                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 39 (2.56%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Systemic inflammatory response syndrome              |                 |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Chronic obstructive pulmonary disease           |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea                                        |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hiccups                                         |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lung disorder                                   |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Mania                                           |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Red blood cell count decreased                  |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Weight decreased                                |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Cardiac arrest                                  |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |
| Tachycardia                                     |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Neuropathy peripheral                           |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Paraesthesia                                    |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Anaemia                                         |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Leukopenia                                      |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Pancytopenia                                    |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain upper                            |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites                                         |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea                                          |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Peritoneal haemorrhage                          |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting                                        |                |  |  |
| subjects affected / exposed                     | 3 / 39 (7.69%) |  |  |
| occurrences causally related to treatment / all | 2 / 7          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |



|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Cholestasis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Toxic skin eruption                             |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| H1N1 influenza                                  |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tracheobronchitis                               |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased appetite                              |                |  |  |
| subjects affected / exposed                     | 2 / 39 (5.13%) |  |  |
| occurrences causally related to treatment / all | 1 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 1 / 39 (2.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|                                                       |                  |  |  |
|-------------------------------------------------------|------------------|--|--|
| <b>Non-serious adverse events</b>                     | Dovitinib        |  |  |
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 36 / 39 (92.31%) |  |  |
| Vascular disorders                                    |                  |  |  |

|                                                                          |                        |  |  |
|--------------------------------------------------------------------------|------------------------|--|--|
| Deep vein thrombosis<br>subjects affected / exposed<br>occurrences (all) | 2 / 39 (5.13%)<br>2    |  |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)         | 13 / 39 (33.33%)<br>16 |  |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)          | 2 / 39 (5.13%)<br>2    |  |  |
| General disorders and administration<br>site conditions                  |                        |  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)           | 4 / 39 (10.26%)<br>4   |  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)             | 15 / 39 (38.46%)<br>22 |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)              | 14 / 39 (35.90%)<br>22 |  |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)              | 3 / 39 (7.69%)<br>3    |  |  |
| Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all) | 4 / 39 (10.26%)<br>6   |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 7 / 39 (17.95%)<br>7   |  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)    | 3 / 39 (7.69%)<br>3    |  |  |
| Respiratory, thoracic and mediastinal<br>disorders                       |                        |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 2 / 39 (5.13%)<br>2    |  |  |
| Dysphonia                                                                |                        |  |  |

|                                                                                                               |                        |  |  |
|---------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                              | 3 / 39 (7.69%)<br>3    |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                  | 6 / 39 (15.38%)<br>9   |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                 | 4 / 39 (10.26%)<br>4   |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                          | 3 / 39 (7.69%)<br>4    |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                  | 4 / 39 (10.26%)<br>4   |  |  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                                            | 2 / 39 (5.13%)<br>2    |  |  |
| Investigations<br>Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 11 / 39 (28.21%)<br>15 |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                        | 10 / 39 (25.64%)<br>19 |  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                                 | 4 / 39 (10.26%)<br>6   |  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                      | 13 / 39 (33.33%)<br>15 |  |  |
| Blood calcium decreased<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 39 (5.13%)<br>2    |  |  |
| Blood lactate dehydrogenase<br>increased                                                                      |                        |  |  |

|                                     |                  |  |  |
|-------------------------------------|------------------|--|--|
| subjects affected / exposed         | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                   | 3                |  |  |
| Blood triglycerides increased       |                  |  |  |
| subjects affected / exposed         | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                   | 2                |  |  |
| C-reactive protein increased        |                  |  |  |
| subjects affected / exposed         | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                   | 2                |  |  |
| Gamma-glutamyltransferase increased |                  |  |  |
| subjects affected / exposed         | 14 / 39 (35.90%) |  |  |
| occurrences (all)                   | 18               |  |  |
| Lipase increased                    |                  |  |  |
| subjects affected / exposed         | 4 / 39 (10.26%)  |  |  |
| occurrences (all)                   | 8                |  |  |
| Protein total decreased             |                  |  |  |
| subjects affected / exposed         | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                   | 5                |  |  |
| Weight decreased                    |                  |  |  |
| subjects affected / exposed         | 12 / 39 (30.77%) |  |  |
| occurrences (all)                   | 13               |  |  |
| Nervous system disorders            |                  |  |  |
| Dysaesthesia                        |                  |  |  |
| subjects affected / exposed         | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                   | 3                |  |  |
| Dysgeusia                           |                  |  |  |
| subjects affected / exposed         | 6 / 39 (15.38%)  |  |  |
| occurrences (all)                   | 8                |  |  |
| Headache                            |                  |  |  |
| subjects affected / exposed         | 8 / 39 (20.51%)  |  |  |
| occurrences (all)                   | 12               |  |  |
| Neuropathy peripheral               |                  |  |  |
| subjects affected / exposed         | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                   | 2                |  |  |
| Paraesthesia                        |                  |  |  |

|                                                                           |                      |  |  |
|---------------------------------------------------------------------------|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                          | 6 / 39 (15.38%)<br>7 |  |  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)              | 4 / 39 (10.26%)<br>4 |  |  |
| Blood and lymphatic system disorders                                      |                      |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)               | 6 / 39 (15.38%)<br>9 |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)           | 3 / 39 (7.69%)<br>7  |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 3 / 39 (7.69%)<br>3  |  |  |
| Ear and labyrinth disorders                                               |                      |  |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)              | 2 / 39 (5.13%)<br>2  |  |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)               | 3 / 39 (7.69%)<br>3  |  |  |
| Eye disorders                                                             |                      |  |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)               | 2 / 39 (5.13%)<br>2  |  |  |
| Keratitis<br>subjects affected / exposed<br>occurrences (all)             | 3 / 39 (7.69%)<br>3  |  |  |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all) | 6 / 39 (15.38%)<br>7 |  |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)     | 2 / 39 (5.13%)<br>2  |  |  |
| Periorbital oedema                                                        |                      |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 2 / 39 (5.13%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Gastrointestinal disorders  |                  |  |  |
| Abdominal pain              |                  |  |  |
| subjects affected / exposed | 10 / 39 (25.64%) |  |  |
| occurrences (all)           | 12               |  |  |
| Abdominal pain upper        |                  |  |  |
| subjects affected / exposed | 7 / 39 (17.95%)  |  |  |
| occurrences (all)           | 12               |  |  |
| Constipation                |                  |  |  |
| subjects affected / exposed | 7 / 39 (17.95%)  |  |  |
| occurrences (all)           | 8                |  |  |
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 28 / 39 (71.79%) |  |  |
| occurrences (all)           | 48               |  |  |
| Dry mouth                   |                  |  |  |
| subjects affected / exposed | 6 / 39 (15.38%)  |  |  |
| occurrences (all)           | 8                |  |  |
| Dyspepsia                   |                  |  |  |
| subjects affected / exposed | 3 / 39 (7.69%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Gastric disorder            |                  |  |  |
| subjects affected / exposed | 3 / 39 (7.69%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Haemorrhoids                |                  |  |  |
| subjects affected / exposed | 3 / 39 (7.69%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Stomatitis                  |                  |  |  |
| subjects affected / exposed | 2 / 39 (5.13%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Nausea                      |                  |  |  |
| subjects affected / exposed | 17 / 39 (43.59%) |  |  |
| occurrences (all)           | 26               |  |  |
| Toothache                   |                  |  |  |
| subjects affected / exposed | 2 / 39 (5.13%)   |  |  |
| occurrences (all)           | 2                |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                   |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--|--|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                              | 21 / 39 (53.85%)<br>33                                                                                                            |  |  |
| Hepatobiliary disorders<br>Hepatocellular injury<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                      | 2 / 39 (5.13%)<br>2                                                                                                               |  |  |
| Skin and subcutaneous tissue disorders<br>Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)<br><br>Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all) | 2 / 39 (5.13%)<br>2<br><br>2 / 39 (5.13%)<br>2<br><br>8 / 39 (20.51%)<br>8<br><br>2 / 39 (5.13%)<br>2<br><br>6 / 39 (15.38%)<br>6 |  |  |
| Renal and urinary disorders<br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Proteinuria<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                     | 4 / 39 (10.26%)<br>4<br><br>4 / 39 (10.26%)<br>7                                                                                  |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle spasms                                                                                                                                                                                                                                                                     | 5 / 39 (12.82%)<br>6                                                                                                              |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Musculoskeletal pain               |                  |  |  |
| subjects affected / exposed        | 4 / 39 (10.26%)  |  |  |
| occurrences (all)                  | 5                |  |  |
| Musculoskeletal stiffness          |                  |  |  |
| subjects affected / exposed        | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Myalgia                            |                  |  |  |
| subjects affected / exposed        | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Pain in extremity                  |                  |  |  |
| subjects affected / exposed        | 7 / 39 (17.95%)  |  |  |
| occurrences (all)                  | 13               |  |  |
| Infections and infestations        |                  |  |  |
| Nasopharyngitis                    |                  |  |  |
| subjects affected / exposed        | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                  | 2                |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Decreased appetite                 |                  |  |  |
| subjects affected / exposed        | 14 / 39 (35.90%) |  |  |
| occurrences (all)                  | 17               |  |  |
| Dyslipidaemia                      |                  |  |  |
| subjects affected / exposed        | 3 / 39 (7.69%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Hypercholesterolaemia              |                  |  |  |
| subjects affected / exposed        | 4 / 39 (10.26%)  |  |  |
| occurrences (all)                  | 5                |  |  |
| Hyperkalaemia                      |                  |  |  |
| subjects affected / exposed        | 2 / 39 (5.13%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Hypertriglyceridaemia              |                  |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 13 / 39 (33.33%) |  |  |
| occurrences (all)           | 25               |  |  |
| Hypoalbuminaemia            |                  |  |  |
| subjects affected / exposed | 7 / 39 (17.95%)  |  |  |
| occurrences (all)           | 7                |  |  |
| Hypocalcaemia               |                  |  |  |
| subjects affected / exposed | 4 / 39 (10.26%)  |  |  |
| occurrences (all)           | 4                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28 October 2011 | This amendment included modifications to the original protocol in order to modify the exclusion criteria and also modifications to parts of the protocol in order to correct some wording mistakes and update some clinical parts.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 11 January 2012 | This amendment included modifications to the protocol to revise the exclusion criterion pertaining to left ventricular ejection fraction based on the recommendation of ESMO regarding monitoring of cardio toxicity of chemotherapeutic and radiotherapy-related agents.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 19 July 2012    | This amendment included modifications to the protocol with the main aim to comply with request from German Health Authorities (BfArM) raised on 27-Feb-2012. Inclusion and exclusion criteria were modified and other minor changes were implemented. The inclusion criterion was modified to specify that patients with documented disease progression on prior therapy with imatinib at a dose of at least 400 mg/day or patients with unresectable and/or metastatic GIST intolerant to imatinib were eligible for the study. The exclusion criteria were amended to include QT-related medical conditions, usage of effective contraception and two highly effective birth-control methods for women of child-bearing age and to specify that the treatment with acetylsalicylic at the dialy dose of 100 mg or lower was allowed. |
| 09 July 2013    | This amendment included updates to the safety information (based on Investigator's Brochure v10.0, safety cut-off 10-Sep-2012) and to revise the concomitant medication section in order to align it with the preliminary drug-drug interaction data from the CTI258A2119 study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

### 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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> for complete trial results.

Notes: