



## Clinical trial results:

**A single stage phase II, multi-centre, open label study of Glivec® in combination with Pioglitazone, Etoricoxib, Dexamethasone and low-dose Treosulfane for anti-inflammatory and angiostatic treatment in patients with hormone-refractory prostate cancer**

**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	2006-000218-19
Trial protocol	DE
Global end of trial date	12 August 2015

## Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

## Trial information

### Trial identification

Sponsor protocol code	CSTI571BDE59
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00427999
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, 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	12 August 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 August 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary Objective: To investigate the effect of a treatment with Imatinib mesylate (Glivec®), Pioglitazone (Actos®), Etoricoxib (Arcoxia®), and Dexamethasone (Fortecortin®) in combination with metronomic chemotherapy (Treosulfane: Ovastat®) on the PSA response rate in patients with hormone refractory prostate cancer.

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	26 February 2007
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	Germany: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	21
From 65 to 84 years	46
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In 11 centers 72 patients were screened, 67 enrolled, of which 65 were treated and 33 completed the treatment phase. Intent to Treat (ITT) population included 61 patients. For the extension follow-up phase 19 patients were included in the safety analysis.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	STI571+ pioglitazone+ etoricoxib + dexamethasone + treosulfane
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Arm description:

STI571 (imatinib) 400mg po daily + pioglitazone 60mg po daily + etoricoxib 60mg po daily + dexamethasone 1mg po daily + treosulfane 500mg po daily

Arm type	Experimental
Investigational medicinal product name	imatinib
Investigational medicinal product code	STI571
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

imatinib 400 mg tablet orally daily

Investigational medicinal product name	pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

pioglitazone 60 mg tablet orally daily

Investigational medicinal product name	dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

dexamethasone 1 mg tablet orally daily

Investigational medicinal product name	etoricoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

etoricoxib 60mg tablet orally daily

Investigational medicinal product name	Treosulfane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Treosulfane 2x 250mg capsules orally daily

<b>Number of subjects in period 1<sup>[1]</sup></b>	<b>STI571+ pioglitazone+ etoricoxib + dexamethasone + treosulfane</b>
Started	65
Intent to Treat (ITT)	61
Extension Follow-up	19 <sup>[2]</sup>
Completed	33
Not completed	32
Adverse event, serious fatal	1
Consent withdrawn by subject	9
Adverse event, non-fatal	6
Unsatisfactory therapeutic effect	13
Abnormal laboratory values	1
Protocol deviation	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 2 patients who were randomized were not treated

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

Justification: 33 patients completed the core...19 of the 33patient entered the extension portion of the trial.

## Baseline characteristics

### Reporting groups

Reporting group title	STI571+ pioglitazone+ etoricoxib + dexamethasone + treosulfane
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Reporting group description:

STI571 (imatinib) 400mg po daily + pioglitazone 60mg po daily + etoricoxib 60mg po daily + dexamethasone 1mg po daily + treosulfane 500mg po daily

Reporting group values	STI571+ pioglitazone+ etoricoxib + dexamethasone + treosulfane	Total	
Number of subjects	65	65	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	21	
From 65-84 years	44	44	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	67		
standard deviation	± 7	-	
Gender, Male/Female			
Units: participants			
Male	65	65	
Female	0	0	

## End points

### End points reporting groups

Reporting group title	STI571+ pioglitazone+ etoricoxib + dexamethasone + treosulfane
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Reporting group description:

STI571 (imatinib) 400mg po daily + pioglitazone 60mg po daily + etoricoxib 60mg po daily + dexamethasone 1mg po daily + treosulfane 500mg po daily

### Primary: To investigate the effect of a treatment with Imatinib mesylate, Pioglitazone , Etoricoxib, and Dexamethasone in combination with metronomic chemotherapy (Treosulfane) on the PSA response rate

End point title	To investigate the effect of a treatment with Imatinib mesylate, Pioglitazone , Etoricoxib, and Dexamethasone in combination with metronomic chemotherapy (Treosulfane) on the PSA response rate <sup>[1]</sup>
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End point description:

To investigate the effect of a treatment with Imatinib mesylate, Pioglitazone , Etoricoxib, and Dexamethasone in combination with metronomic chemotherapy (Treosulfane) on the PSA response rate in patients with hormone refractory prostate cancer. A patient will be defined as a responder if a PSA decline of at least 50%, which must be confirmed by a second PSA value 4 weeks later, is observed. A patient will be defined as a non-responder if PSA has not decreased during treatment. Non-response is defined as a 25% increase over the baseline on-study which is confirmed (equal or more) by a second value 4 weeks apart. The absolute increase must account for > 5 ng/ml. No statistical analysis was planned for this primary outcome.

End point type	Primary
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End point timeframe:

24 weeks in the core phase

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: since this is a single arm trial, only summary analysis were performed and are not amenable to this format of database.

End point values	STI571+ pioglitazone+ etoricoxib + dexamethasone + treosulfane			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: number of responders				
number (not applicable)				
PSA responder - No	38			
PSA responder - Yes	23			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to PSA response

End point title	Time to PSA response
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End point description:

Time to PSA response, defined as the time from first administration of study drugs to the first PSA value of a confirmed PSA response. Non-responders will be censored with date of final visit/premature discontinuation for the analysis. Median time to PSA response was not achieved

End point type	Secondary
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End point timeframe:

every 4 weeks up to 24 weeks in the core phase

<b>End point values</b>	STI571+ pioglitazone+ etoricoxib + dexamethason e + treosulfane			
Subject group type	Reporting group			
Number of subjects analysed	61 <sup>[2]</sup>			
Units: days				
median (confidence interval 95%)	999 (99 to 9999)			

Notes:

[2] - Median time to PSA response was not achieved

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to progression-free survival

End point title	Time to progression-free survival
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End point description:

Progression-free survival, defined as the time from first administration of study drugs to the first PSA value of a PSA non-responder. Responders will be censored with date of PSA response for the analysis. The median time to PSA progression free survival was not achieved

End point type	Secondary
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End point timeframe:

every 4 week upto 24 weeks in the core phase

<b>End point values</b>	STI571+ pioglitazone+ etoricoxib + dexamethason e + treosulfane			
Subject group type	Reporting group			
Number of subjects analysed	61 <sup>[3]</sup>			
Units: days				
median (confidence interval 95%)	999 (99 to 9999)			

Notes:

[3] - The median time to PSA progression free survival was not achieved



## Statistical analyses

No statistical analyses for this end point

### Secondary: overall survival rate

End point title	overall survival rate
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End point description:

Overall survival (OS) is defined as time from randomization to death from any cause or last date known alive. The median time to overall survival rate was not achieved

End point type	Secondary
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End point timeframe:

every 4 weeks up to 24 weeks in the core phase

<b>End point values</b>	STI571+ pioglitazone+ etoricoxib + dexamethason e + treosulfane			
Subject group type	Reporting group			
Number of subjects analysed	61 <sup>[4]</sup>			
Units: days				
median (confidence interval 95%)	999 (99 to 9999)			

Notes:

[4] - The median time to overall survival rate was not achieved

## Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of life assessed with EORTC-30

End point title	Quality of life assessed with EORTC-30
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End point description:

Health-related quality of life was assessed with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-30) questionnaire and was presented descriptively. The EORTC QLQ-C30 is a questionnaire including following sub-scales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain) and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Scores are averaged for each scale and transformed to 0-100 scale; higher score indicates better quality of life on global health status and functional scales and worse quality of life on symptom scales and financial difficulty scale.

End point type	Secondary
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End point timeframe:

baseline and Final Visit

<b>End point values</b>	STI571+ pioglitazone+ etoricoxib + dexamethason e + treosulfane			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline: financial difficulties (n=49)	11.6 (± 16.03)			
Baseline: appetite loss (n=50)	16 (± 29.54)			
Baseline: dyspnea (n=49)	20.4 (± 27.06)			
Baseline: constipation (n=50)	14 (± 28.64)			
Baseline: role functioning (n=50)	74 (± 28.8)			
Baseline: insomnia (n=49)	34 (± 34.35)			
Baseline: cognitive functioning (n=49)	87.1 (± 16.41)			
Baseline: diarrhea (n=50)	9.3 (± 21.34)			
Baseline: physical functioning (n=50)	81.7 (± 17.19)			
Baseline: pain (n=50)	32.3 (± 32.89)			
Baseline: emotional functioning (n=49)	64.6 (± 21.89)			
Baseline: social functioning (n=49)	72.4 (± 26.69)			
Baseline: fatigue (n=50)	32.9 (± 26.08)			
Baseline: global health status (n=49)	60 (± 18.24)			
Baseline: nausea & vomiting (n=50)	26 (± 28.8)			
Final Visit: financial difficulties (n=42)	19 (± 28.65)			
Final Visit: appetite loss (n=43)	24 (± 33.59)			
Final Visit: dyspnea (n=43)	38.8 (± 29.03)			
Final Visit: constipation (n=43)	6.2 (± 15.01)			
Final Visit: role functioning (n=43)	55.4 (± 31.01)			
Final Visit: insomnia (n=42)	31.7 (± 32.05)			
Final Visit: cognitive functioning (n=43)	81.8 (± 20.51)			
Final Visit: diarrhea (n=43)	13.2 (± 23.16)			
Final Visit: physical functioning (n=43)	66.7 (± 25.32)			
Final Visit: pain (n=43)	26 (± 30.06)			
Final Visit: emotional functioning (n=43)	61.8 (± 28.42)			
Final Visit: social functioning (n=43)	64 (± 32.52)			
Final Visit: fatigue (n=43)	46 (± 29.05)			
Final Visit: global health status (n=43)	51 (± 21.76)			
Final Visit: nausea & vomiting (n=43)	44.6 (± 31.01)			

## Statistical analyses

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 LPLV.

Adverse event reporting additional description:

Consistent with EudraCT 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. Only deaths occurring within 28 days of final dose are included.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Glivec + study combination -Core
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Reporting group description:

Glivec + study combination -Core

Reporting group title	Glivec + study combination -Extension
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Reporting group description:

Glivec + study combination -Extension

Serious adverse events	Glivec + study combination -Core	Glivec + study combination -Extension	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 65 (33.85%)	7 / 19 (36.84%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			

subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Diabetic vascular disorder			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (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			
Asthenia			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug ineffective			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 65 (3.08%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			

Alcohol withdrawal syndrome subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Thoracic vertebral fracture subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			



subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 65 (4.62%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Eyelid oedema			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder obstruction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder tamponade			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Postrenal failure			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematoma infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 65 (4.62%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 65 (3.08%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Glivec + study combination -Core	Glivec + study combination - Extension	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 65 (100.00%)	19 / 19 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Metastases to bone			
subjects affected / exposed	3 / 65 (4.62%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Metastases to central nervous system			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Vascular disorders			
Extravasation blood			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	3 / 65 (4.62%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Hypotension			
subjects affected / exposed	5 / 65 (7.69%)	0 / 19 (0.00%)	
occurrences (all)	7	0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Lymphoedema			
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)	
occurrences (all)	2	1	

Peripheral venous disease subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 8	1 / 19 (5.26%) 1	
Face oedema subjects affected / exposed occurrences (all)	15 / 65 (23.08%) 16	4 / 19 (21.05%) 4	
Fatigue subjects affected / exposed occurrences (all)	21 / 65 (32.31%) 24	9 / 19 (47.37%) 11	
General physical health deterioration subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	3 / 19 (15.79%) 3	
Generalised oedema subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 2	2 / 19 (10.53%) 2	
Inflammation subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Influenza like illness subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Malaise subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Mucosal inflammation subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Necrosis subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	
Oedema			

subjects affected / exposed occurrences (all)	24 / 65 (36.92%) 35	6 / 19 (31.58%) 8	
Oedema peripheral subjects affected / exposed occurrences (all)	35 / 65 (53.85%) 41	12 / 19 (63.16%) 16	
Pain subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5	0 / 19 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	2 / 19 (10.53%) 2	
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	23 / 65 (35.38%) 27	8 / 19 (42.11%) 8	
Cough subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	1 / 19 (5.26%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	0 / 19 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 6	0 / 19 (0.00%) 0	
Sleep disorder subjects affected / exposed occurrences (all)	6 / 65 (9.23%) 6	3 / 19 (15.79%) 3	
Investigations			



Aspartate aminotransferase increased		
subjects affected / exposed	5 / 65 (7.69%)	0 / 19 (0.00%)
occurrences (all)	5	0
Alanine aminotransferase increased		
subjects affected / exposed	4 / 65 (6.15%)	0 / 19 (0.00%)
occurrences (all)	4	0
Activated partial thromboplastin time prolonged		
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Blood albumin decreased		
subjects affected / exposed	3 / 65 (4.62%)	2 / 19 (10.53%)
occurrences (all)	5	2
Blood alkaline phosphatase increased		
subjects affected / exposed	7 / 65 (10.77%)	1 / 19 (5.26%)
occurrences (all)	8	1
Blood creatinine increased		
subjects affected / exposed	9 / 65 (13.85%)	5 / 19 (26.32%)
occurrences (all)	12	7
Blood fibrinogen increased		
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)
occurrences (all)	1	1
Blood potassium decreased		
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)
occurrences (all)	3	1
Blood lactate dehydrogenase increased		
subjects affected / exposed	10 / 65 (15.38%)	4 / 19 (21.05%)
occurrences (all)	11	5
C-reactive protein increased		
subjects affected / exposed	4 / 65 (6.15%)	3 / 19 (15.79%)
occurrences (all)	5	4
Haematocrit decreased		
subjects affected / exposed	2 / 65 (3.08%)	2 / 19 (10.53%)
occurrences (all)	2	2
Lymphocyte count decreased		

subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Monocyte count decreased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Monocyte count increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Occult blood			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Prostatic specific antigen increased			
subjects affected / exposed	2 / 65 (3.08%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Protein total decreased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Red blood cell count decreased			
subjects affected / exposed	1 / 65 (1.54%)	2 / 19 (10.53%)	
occurrences (all)	1	3	
Reticulocyte count increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	13 / 65 (20.00%)	3 / 19 (15.79%)	
occurrences (all)	13	4	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Muscle rupture			

subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Head injury			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 65 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Tachyarrhythmia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	3 / 65 (4.62%)	1 / 19 (5.26%)	
occurrences (all)	4	1	
Dizziness			
subjects affected / exposed	6 / 65 (9.23%)	0 / 19 (0.00%)	
occurrences (all)	9	0	
Headache			
subjects affected / exposed	11 / 65 (16.92%)	1 / 19 (5.26%)	
occurrences (all)	17	1	
Dysgeusia			
subjects affected / exposed	7 / 65 (10.77%)	1 / 19 (5.26%)	
occurrences (all)	7	1	
Memory impairment			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	2 / 65 (3.08%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Polyneuropathy			

subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 8	6 / 19 (31.58%) 6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 65 (32.31%)	7 / 19 (36.84%)	
occurrences (all)	25	9	
Anaemia macrocytic			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	19 / 65 (29.23%)	7 / 19 (36.84%)	
occurrences (all)	23	8	
Thrombocytopenia			
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	4 / 65 (6.15%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Vertigo			
subjects affected / exposed	7 / 65 (10.77%)	3 / 19 (15.79%)	
occurrences (all)	8	3	
Vertigo positional			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	5 / 65 (7.69%)	2 / 19 (10.53%)	
occurrences (all)	6	2	
Lacrimation increased			
subjects affected / exposed	8 / 65 (12.31%)	0 / 19 (0.00%)	
occurrences (all)	8	0	
Visual acuity reduced			
subjects affected / exposed	3 / 65 (4.62%)	1 / 19 (5.26%)	
occurrences (all)	4	1	
Gastrointestinal disorders			

Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 8	2 / 19 (10.53%) 2
Abdominal wall haematoma subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1
Constipation subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 5	2 / 19 (10.53%) 5
Diarrhoea subjects affected / exposed occurrences (all)	27 / 65 (41.54%) 40	6 / 19 (31.58%) 12
Gastric polyps subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1
Gastric ulcer subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	2 / 19 (10.53%) 2
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1
Hiatus hernia subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1
Nausea subjects affected / exposed occurrences (all)	28 / 65 (43.08%) 37	5 / 19 (26.32%) 9
Toothache subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	1 / 19 (5.26%) 1
Vomiting subjects affected / exposed occurrences (all)	16 / 65 (24.62%) 19	3 / 19 (15.79%) 3

Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Ecchymosis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
Petechiae			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	8 / 65 (12.31%)	2 / 19 (10.53%)	
occurrences (all)	8	2	
Hyperhidrosis			
subjects affected / exposed	5 / 65 (7.69%)	0 / 19 (0.00%)	
occurrences (all)	5	0	
Skin dystrophy			
subjects affected / exposed	1 / 65 (1.54%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Skin atrophy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	7 / 65 (10.77%)	0 / 19 (0.00%)	
occurrences (all)	8	0	
Skin ulcer			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	2	
Renal and urinary disorders			

Kidney fibrosis subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Renal pain subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Pollakiuria subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences (all)	11 / 65 (16.92%) 13	1 / 19 (5.26%) 1	
Cushingoid subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4	3 / 19 (15.79%) 3	
Hypogonadism male subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5	1 / 19 (5.26%) 1	
Back pain subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 8	4 / 19 (21.05%) 5	
Bone pain subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 8	2 / 19 (10.53%) 2	
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	
Joint swelling subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Muscle spasms			

subjects affected / exposed	16 / 65 (24.62%)	5 / 19 (26.32%)	
occurrences (all)	23	6	
Muscular weakness			
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 65 (1.54%)	2 / 19 (10.53%)	
occurrences (all)	1	3	
Musculoskeletal pain			
subjects affected / exposed	4 / 65 (6.15%)	0 / 19 (0.00%)	
occurrences (all)	5	0	
Myalgia			
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Myopathy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Osteonecrosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	3 / 65 (4.62%)	5 / 19 (26.32%)	
occurrences (all)	3	6	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Gingivitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	2 / 65 (3.08%)	2 / 19 (10.53%)	
occurrences (all)	2	5	
Influenza			
subjects affected / exposed	2 / 65 (3.08%)	1 / 19 (5.26%)	
occurrences (all)	3	1	



Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 10	3 / 19 (15.79%) 4	
Otitis media subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	
Sinusitis subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5	0 / 19 (0.00%) 0	
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	8 / 65 (12.31%) 8	5 / 19 (26.32%) 5	
Decreased appetite subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	2 / 19 (10.53%) 2	
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	
Obesity subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Increased appetite subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 19 (5.26%) 1	
Zinc deficiency subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 19 (5.26%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2006	Amendment 1: specifies an extension study to the existing final CSTI571BDE59-protocol and the follow up for patients entering the extension study.
29 May 2008	Amendment 2: a)Adjusting inclusion criterion for extension phase: after enrollment of 30 patients PSA responders were reported by the investigators. Inclusion criteria of extension phase should be adapted in that way, which allows offering study continuation to patients showing at least 30% PSA decrease and no signs for disease progression b)Clarification of efficacy assessment of the extension study c)Clarification of exclusion criteria of the core study-patients with symptomatic CHF according to NYHA classes II-IV are not allowed to enter the trial.Prior therapy with isotopes is not allowed. This includes each radiopharmaceutical licensed for palliation in prostate cancer or painful osseous metastatic disease, like phosphorus (32P),strontium (89SrCl), rhenium (186Re)or samarium (153Sm).Use of any oral anticoagulant is not allowed in this trial d)Clarification of study population, inclusion and exclusion criteria regarding status of hormone refractory prostate cancer-patients with a histologically proven prostate cancer which have entered the hormone refractory state are enrolled into the trial. e)Clarification of Glivec® dosing for dose escalation-dose is increased if PSA increases by at least 5% and this increase is confirmed 4 weeks later. The dose will be increased to 400mg twice daily f)Correction of dosing description for Arcoxia® (etoricoxib) and Fortecortin®(dexamethasone)-Arcoxia is provided as 30 mg tablet; 60 mg daily in the evening. In case of dose reduction 30 mg daily or 60 mg every other day are accepted. Fortecortin is provided as a tablet of 0.5 mg dose strength 1 mg daily is taken at noon g)Clarification of dose adjustments of Arcoxia® (etoricoxib) and Actos® (pioglitazon)- dose adjustment of Arcoxia and Actos coding according to "cardiac general- other" or weight gain what ever comes first should be used g)Timelines were adjusted to the enrollment rate.
28 October 2008	Amendment 3: a)Adjusting inclusion and exclusion criteria-According to the cited guidelines of EAU some intervals given in the protocol have to be aligned.First, during initial fixing of nadir and reference values regarding PSA level the period between PSA measurements will be adapted to accordant guidelines. Second, the time frame concerning change of androgen deprivation therapy in exclusion criteria will be adequately modified.In compliance with the definition of HRPC inclusion criteria are adjusted. b)Rephrasing the definition of PSA progression-definition of PSA progression was adapted to published PSA response criteria for HRPC (Bubley, J Clin Oncol 1999, 17:3461-67) and the already existing section describing the study variable. C)Changes in drug formulation-Since the indicated dose of 30mg Arcoxia is not available, the dose of 60mg is provided within the study. Given that patients had to take two tablets of 30mg Arcoxia once a day no changes in dose occur. d)Changes of statistical methods (sample size calculation, definition ofresponder/ non-responder)Classification of responder and non-responder was adapted to published recommendations on reporting trial outcomes. e)Correction of minor inconsistencies.

27 November 2009	Amendment 3: a)Adjusting inclusion and exclusion criteria-According to the cited guidelines of EAU some intervals given in the protocol have to be aligned.First, during initial fixing of nadir and reference values regarding PSA level the period between PSA measurements will be adapted to accordant guidelines. Second, the time frame concerning change of androgen deprivation therapy in exclusion criteria will be adequately modified.In compliance with the definition of HRPC inclusion criteria are adjusted. b)Rephrasing the definition of PSA progression-definition of PSA progression was adapted to published PSA response criteria for HRPC (Bubley, J Clin Oncol 1999, 17:3461-67) and the already existing section describing the study variable. C)Changes in drug formulation-Since the indicated dose of 30mg Arcoxia is not available, the dose of 60mg is provided within the study. Given that patients had to take two tablets of 30mg Arcoxia once a day no changes in dose occur. d)Changes of statistical methods (sample size calculation, definition ofresponder/ non-responder)Classification of responder and non-responder was adapted to published recommendations on reporting trial outcomes. e)Correction of minor inconsistencies.
29 July 2011	Amendment 5: New data from a retrospective cohort study carried out in France appeared to indicate a increased risk of bladder cancer with pioglitazone-containing medicines. Therefore the EMA's committee for Medicinal Products for Human Use (CHMP) started a European review of pioglitazone-containing medicines in March 2011 to investigate the signal of a possible increased risk of bladder cancer with pioglitazone. Finalizing its review on antidiabetic pioglitazone-containing medicines and the occurrence of bladder cancer July 2011, the EMA stated in a press release (21th of July) that new contra-indications and warnings for pioglitazone are recommended to reduce the small increased risk of bladder cancer. The benefit-risk balance remains positive in a limited population of type 2 diabetics. In the patient population of the study CSTI571BDE59 this risk could be reduced by including new contraindications and warnings in the protocol and periodic review of the efficacy and safety of the patient's treatment. Therefore, patients with bladder cancer or bladder cancer in their medical history, macrohematuria of unknown origin and patients with risk factors for bladder cancer (such as exposure to aromatic amines or heavy tobacco smokers) will be excluded from the trial. In light of age-related risks, the balance of benefit and risks should be carefully considered during treatment in the elderly. Furthermore, the treatment of patients on pioglitazone should be reviewed after three to six months (and regularly afterwards) to ensure that only patients who are deriving sufficient benefit continue to take it. Recruitment of this study is finished. Currently, two patients are still under treatment in the extension phase of the 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.nov>for complete trial results.

Notes: