



Clinical trial results:

The TEAM trial (Tasigna efficacy in advanced melanoma): A phase II, open label, multi-center, single-arm study to assess the efficacy of Tasigna® in the treatment of patients with metastatic and/or inoperable melanoma harboring a c-Kit mutation

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results

Summary

EudraCT number	2009-015514-21
Trial protocol	BE SE DE NL IT ES
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	CAMN107B2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01028222
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 December 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the clinical efficacy of nilotinib, based on overall response rate (ORR), in the treatment of c-Kit mutated melanoma in patients who have not received prior therapy with TKIs (tyrosine kinase inhibitors).

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	11 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Brazil: 5
Worldwide total number of subjects	55
EEA total number of subjects	20

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)	24
From 65 to 84 years	28
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The randomization ratio for the two treatment groups was 1:1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nilotinib

Arm description:

400 mg twice daily

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was provided as 200 mg hard gelatin capsules for oral use.

Arm title	DTIC
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Arm description:

850 mg/m² IV every 3 weeks

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DTIC was supplied locally as sterile powder for i.v. infusion

Number of subjects in period 1	Nilotinib	DTIC
Started	42	13
Cross over from DTIC to Nilotinib	0 ^[1]	10
Completed	4	0
Not completed	38	13
Consent withdrawn by subject	1	-
Disease progression	33	9

Adverse event, non-fatal	2	-
Protocol deviation	1	-
Crossover to nilotinib w/out progression	-	2
Administrative problems	1	1
Lost to follow-up	-	1

Notes:

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

Justification: The number of subjects in this period represents the number of patients who crossed over from DTIC to Nilotinib.

Baseline characteristics

Reporting groups

Reporting group title	Nilotinib
Reporting group description: 400 mg twice daily	
Reporting group title	DTIC
Reporting group description: 850 mg/m ² IV every 3 weeks	

Reporting group values	Nilotinib	DTIC	Total
Number of subjects	42	13	55
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	4	24
From 65-84 years	21	7	28
85 years and over	1	2	3
Age Continuous Units: Years			
arithmetic mean	64.7	68.8	
standard deviation	± 12.39	± 12.99	-
Gender, Male/Female Units: Participants			
Female	23	8	31
Male	19	5	24

End points

End points reporting groups

Reporting group title	Nilotinib
Reporting group description:	
400 mg twice daily	
Reporting group title	DTIC
Reporting group description:	
850 mg/m ² IV every 3 weeks	

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR) ^[1]
End point description:	
ORR was defined as the proportion of participants with a best overall response (BOR) of a confirmed complete response or partial response (CR+PR) determined by Response Evaluation Criteria in Solid Tumors (RECIST v1.0) based on local investigators' assessment (CT/MRI/photography). Per RECIST, CR: disappearance of all target lesions, all non-target lesions, and no new lesion; PR: a $\geq 30\%$ decrease in the sum of the longest dimensions of the target lesions (TLs) taking as a reference the baseline sum, no unequivocal progression of non-TLs, and no new lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments at least 4 weeks apart.	
End point type	Primary
End point timeframe:	
End of study (up to 39 months)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a single arm study, no statistical analysis was performed.

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Participants	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable overall response rate (DORR)

End point title	Durable overall response rate (DORR)
End point description:	
DORR was defined as the rate of best overall response (CR+PR) lasting at least 12 weeks determined by RECIST v1.0 based on local investigators' assessment (CT/MRI/photography). The duration of ORR responders is computed from the date of first documented response (CR/PR) to the date of first documented progression or death due to underlying disease. Per RECIST, CR: disappearance of all target lesions, all non-target lesions, and no new lesion; PR: a $\geq 30\%$ decrease in the sum of the longest dimensions of the target lesions (TLs) taking as a reference the baseline sum, no worsening of non-TLs, and no new lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments at least 4 weeks apart.	
End point type	Secondary

End point timeframe:
End of study (up to 39 months)

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Participants	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
End point description:	PFS was defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. Progression is defined using RECIST v1.0, as a $\geq 20\%$ increase in the sum of longest diameter of all target lesions, from smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or unequivocal progression of non-target lesions.
End point type	Secondary
End point timeframe:	
End of study (up to 39 months)	

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Months				
median (confidence interval 95%)	4.2 (2.1 to 5.8)	4.2 (0.8 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	OS was defined as the time from the date of the start of treatment to the date of death due to any cause.
End point type	Secondary
End point timeframe:	
End of study (up to 39 months)	

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Months				
median (confidence interval 95%)	18 (10.9 to 20.3)	22.8 (4.9 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to objective response (TOR)

End point title	Time to objective response (TOR)
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End point description:

TOR was defined as the time between the start date of treatment until first documented confirmed response of CR or PR determined by RECIST v1.0 based on local investigators' assessment (CT/MRI/photography). Per RECIST, CR: disappearance of all target lesions, all non-target lesions, and no new lesion; PR: a $\geq 30\%$ decrease in the sum of the longest dimensions of the target lesions (TLs) taking as a reference the baseline sum, no unequivocal progression of non-TLs, and no new lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments at least 4 weeks apart.

End point type	Secondary
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End point timeframe:

End of study (up to 39 months)

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: months				
median (confidence interval 95%)	999 (-999 to 999)	999 (-999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)
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End point description:

DCR was defined as the proportion of participants with an overall response of CR of any duration, PR of any duration, or stable disease (SD) for a minimum of 12 weeks from start of treatment. Per RECIST, CR: disappearance of all target lesions, all non-target lesions, and no new lesion; PR: a $\geq 30\%$ decrease in the sum of the longest dimensions of the target lesions (TLs) taking as a reference the

baseline sum, no unequivocal progression of non-TLs, and no new lesions; PD, a $\geq 20\%$ increase in TLs, clearly worsening of non-TLs, or emergence of new lesions; SD: no change or small changes that do not meet previously given criteria for CR, PR or PD.

End point type	Secondary
End point timeframe:	
End of study (up to 39 months)	

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Participants	20	7		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS rate

End point title	PFS rate
End point description:	
PFS was defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. Progression is defined using RECIST v1.0, as a $\geq 20\%$ increase in the sum of longest diameter of all target lesions, from smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or unequivocal progression of non-target lesions.	
End point type	Secondary
End point timeframe:	
End of study (up to 39 months)	

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Percentage of participants				
number (not applicable)	34.6	23.1		

Statistical analyses

No statistical analyses for this end point

Secondary: OS rate

End point title	OS rate
End point description:	
OS was defined as the time from the date of the start of treatment to the date of death due to any cause.	

End point type	Secondary
End point timeframe:	
End of study (up to 39 months)	

End point values	Nilotinib	DTIC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: Percentage of participants				
number (not applicable)	63.6	66.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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	Nilotinib
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Reporting group description:

Nilotinib

Reporting group title	Crossover nilotinib
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Reporting group description:

Crossover nilotinib

Reporting group title	DTIC
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Reporting group description:

DTIC

Serious adverse events	Nilotinib	Crossover nilotinib	DTIC
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 42 (28.57%)	4 / 10 (40.00%)	1 / 13 (7.69%)
number of deaths (all causes)	1	8	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lipase increased			
subjects affected / exposed	2 / 42 (4.76%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 42 (7.14%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 42 (7.14%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Herpes zoster cutaneous disseminated			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Nilotinib	Crossover nilotinib	DTIC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 42 (95.24%)	10 / 10 (100.00%)	9 / 13 (69.23%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tumour pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 42 (7.14%)	2 / 10 (20.00%)	0 / 13 (0.00%)
occurrences (all)	3	2	0
Lymphoedema			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Vein disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 42 (4.76%)	3 / 10 (30.00%)	1 / 13 (7.69%)
occurrences (all)	2	4	4
Chills			
subjects affected / exposed	3 / 42 (7.14%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	3	0	0
Fatigue			

subjects affected / exposed occurrences (all)	13 / 42 (30.95%) 25	4 / 10 (40.00%) 6	5 / 13 (38.46%) 6
Feeling cold subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
General physical health deterioration subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	2 / 10 (20.00%) 3	1 / 13 (7.69%) 1
Pain subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	2 / 10 (20.00%) 3	3 / 13 (23.08%) 4
Suprapubic pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Temperature intolerance subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Ulcer haemorrhage subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 10 (10.00%) 2	1 / 13 (7.69%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	9 / 42 (21.43%) 13	3 / 10 (30.00%) 3	2 / 13 (15.38%) 3
Dyspnoea			

subjects affected / exposed	5 / 42 (11.90%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	9	1	1
Epistaxis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lung infiltration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Throat irritation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 42 (4.76%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	1
Confusional state			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	5 / 42 (11.90%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	6	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 42 (23.81%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	18	1	1
Amylase increased			

subjects affected / exposed	8 / 42 (19.05%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	10	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 42 (19.05%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	13	0	3
Bilirubin conjugated increased			
subjects affected / exposed	11 / 42 (26.19%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	27	4	0
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 42 (11.90%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	5	0	0
Blood bilirubin increased			
subjects affected / exposed	19 / 42 (45.24%)	3 / 10 (30.00%)	1 / 13 (7.69%)
occurrences (all)	45	8	1
Blood bilirubin unconjugated increased			
subjects affected / exposed	9 / 42 (21.43%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	26	2	0
Blood cholesterol increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	2 / 42 (4.76%)	2 / 10 (20.00%)	0 / 13 (0.00%)
occurrences (all)	3	3	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 42 (9.52%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	7	2	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Blood pressure decreased			
subjects affected / exposed	4 / 42 (9.52%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	4	0	0
Blood pressure increased			

subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 42 (26.19%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	14	3	1
Haemoglobin decreased			
subjects affected / exposed	2 / 42 (4.76%)	2 / 10 (20.00%)	0 / 13 (0.00%)
occurrences (all)	5	6	0
Lipase increased			
subjects affected / exposed	8 / 42 (19.05%)	2 / 10 (20.00%)	1 / 13 (7.69%)
occurrences (all)	12	2	1
Low density lipoprotein increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Platelet count decreased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Total bile acids increased			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	2	4	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Wound			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Amnesia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Diabetic neuropathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	3 / 42 (7.14%)	2 / 10 (20.00%)	2 / 13 (15.38%)
occurrences (all)	3	2	2
Epilepsy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	6 / 42 (14.29%)	3 / 10 (30.00%)	5 / 13 (38.46%)
occurrences (all)	7	3	7
Hypoaesthesia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Monoplegia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Speech disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 42 (11.90%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	6	0	0
Leukopenia			
subjects affected / exposed	3 / 42 (7.14%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	8	0	0
Lymphopenia			

subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	1 / 10 (10.00%) 2	0 / 13 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 4	0 / 10 (0.00%) 0	1 / 13 (7.69%) 2
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 3	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Lacrimation increased subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	9 / 42 (21.43%) 12	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Diarrhoea			

subjects affected / exposed	7 / 42 (16.67%)	3 / 10 (30.00%)	1 / 13 (7.69%)
occurrences (all)	9	4	1
Dyspepsia			
subjects affected / exposed	3 / 42 (7.14%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	4	0	2
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	18 / 42 (42.86%)	2 / 10 (20.00%)	5 / 13 (38.46%)
occurrences (all)	24	2	11
Odynophagia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Oral discomfort			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tongue ulceration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	11 / 42 (26.19%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	19	1	1
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	5 / 42 (11.90%)	2 / 10 (20.00%)	1 / 13 (7.69%)
occurrences (all)	5	4	1

Dry skin			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Night sweats			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Photosensitivity reaction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	3 / 42 (7.14%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	4	1	1
Rash			
subjects affected / exposed	20 / 42 (47.62%)	3 / 10 (30.00%)	2 / 13 (15.38%)
occurrences (all)	24	4	2
Skin burning sensation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Skin hypopigmentation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 42 (0.00%)	2 / 10 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 42 (9.52%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	9	1	0
Back pain			

subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Bone pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 10 (0.00%) 0	2 / 13 (15.38%) 2
Muscular weakness subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 3	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Pain in extremity subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 7	2 / 10 (20.00%) 3	2 / 13 (15.38%) 2
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Ear infection subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Erysipelas subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	1 / 13 (7.69%) 1
Gingivitis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Herpes zoster subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0

Influenza			
subjects affected / exposed	2 / 42 (4.76%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	3	2	0
Nasopharyngitis			
subjects affected / exposed	3 / 42 (7.14%)	2 / 10 (20.00%)	2 / 13 (15.38%)
occurrences (all)	3	3	3
Oral fungal infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 42 (2.38%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Sinusitis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Staphylococcal infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 42 (30.95%)	3 / 10 (30.00%)	2 / 13 (15.38%)
occurrences (all)	15	3	2
Dehydration			

subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Hypercholesterolaemia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 7	1 / 10 (10.00%) 9	1 / 13 (7.69%) 2
Hyperglycaemia subjects affected / exposed occurrences (all)	9 / 42 (21.43%) 9	3 / 10 (30.00%) 9	1 / 13 (7.69%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 5	2 / 10 (20.00%) 8	1 / 13 (7.69%) 2
Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 5	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 9	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 12	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2010	This amendment introduced the following key changes: To implement minor changes to the inclusion and exclusion criteria based on improved knowledge on the patient population and following input from the Steering Committee for the trial: •To clarify procedural and operational aspects of the protocol • To ensure greater consistency with the Imaging Charter developed and with the procedures of the Central Imaging Review committee working on the trial. Additionally, to ensure consistency between the protocol and Post Text Supplement 1 (RECIST 1.0) •As the population had been limited to patients receiving no more than one prior systemic anticancer therapy for advanced disease and to ensure balance between the two treatment arms (nilotinib and DTIC), randomization was stratified by whether or not the patient received prior systemic anticancer therapy for melanoma • To address other administrative and typographical corrections noted in the original protocol •To include updated safety information related to the use of nilotinib and the need to collect pregnancy information from partners of males taking nilotinib.
27 July 2011	This amendment introduced the following key changes: Due to substantial difficulties identifying and recruiting eligible patients, the trial design was altered from a randomized, two-arm, Phase III study to a single-arm, Simon two-stage Phase II study. While the original protocol required the recruitment of 120 patients, this amendment required the study to recruit only 41 patients (patients randomized to nilotinib prior to Amendment 2 were to be counted in this total, but those randomized to DTIC were not). There was scope within this amendment for patients randomized to DTIC under Amendment 1 or earlier to cross-over to nilotinib, either immediately or at the time of progression. Primary and secondary objectives and endpoints were updated. By implementing this amendment, the clinical study was to be concluded at an earlier date and important clinical information was thus to be disseminated to the medical community in a more rapid fashion.
20 December 2012	This amendment introduced the following key changes: The primary analysis was to be performed once all patients enrolled into the study had reached the Week 24 visit or had discontinued study treatment. This amendment was implemented to clarify: • The treatment of patients regardless if the primary endpoint was met or not • The extension of the follow-up to 24 months after last patient first visit to obtain longer term outcome data •The possibility for patients benefiting from the study treatment at the end of study in the opinion of the investigator to transition to a rollover 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, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results

