Clinical trial results:
A 96-week, prospective, multicenter, randomised, double-blind, placebo-controlled, 2-parallel groups, Phase 3 study to compare efficacy and safety of masitinib 4.5 mg/kg/day versus placebo in the treatment of patients with primary progressive or relapse-free secondary progressive multiple sclerosis

Summary

EudraCT number	2010-021219-17
Trial protocol	ES DE SK GR BG
Global end of trial date	11 February 2019
Results information	
Result version number	v1 (current)
This version publication date	26 May 2022
First version publication date	26 May 2022
Summary attachment (see zip file)	Vermersch P, et al. Efficacy and Safety of Masitinib in Progressive Forms of Multiple Sclerosis: A Randomized, Phase 3, Clinical Trial. Neurol Neuroimmunol Neuroinflamm. 2022;9(3):e1148. (Vermersch 2022 - Neurol Neuroimmunol Neuroinflamm (Article&Suppl).pdf)

Trial information

Trial identification	
Sponsor protocol code	AB07002
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01433497
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	AB Science
Sponsor organisation address	3 avenue George V, Paris, France, 75008
Public contact	Clinical Study Coordinator, AB Science, 33 0147200014, clinical@ab-science.com
Scientific contact	Clinical Study Coordinator, AB Science, 33 0147200014, clinical@ab-science.com

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2019
Global end of trial reached?	Yes
Global end of trial date	11 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether masitinib can decrease progression of disability, measured by the Expanded Disability Status Scale (EDSS), in adults with primary progressive MS (PPMS) or patients with nonactive secondary progressive MS (nSPMS) (with no exacerbations in the last 2 years).

Protection of trial subjects:

The study protocol and amendments were approved by the institutional review board or ethics committee at each participating clinical site and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. An independent Data Safety Monitoring Committee monitored safety throughout the study protocol period. Dose reduction or treatment interruption was allowed for moderate or severe toxicity according to predefined criteria.

Background therapy:

Multiple sclerosis (MS) is an inflammatory, demyelinating, and degenerative disease of the CNS. The clinical course of MS is heterogeneous with patients falling into 2 core categories from a pharmacotherapy perspective. The first category, relapsing disease, is associated with processes of inflammatory demyelination, resulting in relapses followed by remissions. The second category, progressive disease, is associated with processes of progressive neurodegeneration resulting in a gradual accrual of neurologic disability. Additional MS phenotype descriptors are based on disease activity (determined by clinical relapses and/or MRI activity) and disease progression (measured by clinical evaluation). Hence, progressive MS can be described as active and with/without progression or not active and with/without progression. The vast majority of MS drugs primarily benefit active/relapsing forms of MS with limited efficacy in the progressive forms. This therapeutic divide is consistent with the growing opinion that active/relapsing MS and progressive MS are primarily driven by different disease mechanisms; the former characterized by activity of the peripheral adaptive immune system and the latter by an additional, predominant activity of the innate immune system, compartmentalized within the CNS.

Masitinib is a selective oral tyrosine kinase inhibitor, targeting innate immune cells (mast cells and microglia) that are involved in the pathophysiology of progressive MS. Clinical proof of concept that masitinib slows disability progression in patients with progressive MS was previously demonstrated in a small phase 2 trial [Vermersch P, et al. BMC Neurol. 2012;12:36]. Masitinib has also demonstrated neuroprotective action in amyotrophic lateral sclerosis (ALS) and Alzheimer disease, via inhibition of microglia, macrophage, and mast cell activity. These are types of innate immune cells that are present in the CNS and are involved in the pathophysiology of progressive MS.

Evidence for comparator:

Study AB07002 was a placebo-controlled trial, therefore, no active comparator drug was used.

Actual start date of recruitment	25 August 2011
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	France: 12
Country: Number of subjects enrolled	Algeria: 1
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Greece: 27
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Poland: 188
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Tunisia: 32
Country: Number of subjects enrolled	Ukraine: 91
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	656
EEA total number of subjects	467

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)	627
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first randomization: 25 August 2011
Date of last randomization: 10 March 2017
Date of completion: 11 February 2019 (last patient last visit)
The study was conducted at 108 sites from 20 countries

Pre-assignment

Screening details:

Eligibility criteria were an age of 18–75 years, MS diagnosis according to the revised McDonald criteria of PPMS or nSPMS without relapse for at least 2 years prior to inclusion, and a baseline score on the EDSS of 2.0–6.0 inclusive. Clinical evidence of disability progression over the preceding 2 years (increase in EDSS score of at least 1.0).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Patients were centrally randomized using a computerized central randomization system and minimization method according to the covariates of MS phenotype (PPMS or nSPMS), baseline EDSS score, baseline MSFC subscale scores, and geographical region.

Arms

Are arms mutually exclusive?	Yes
Arm title	Masitinib arm from the 4.5 mg/kg/d parallel group

Arm description:

Masitinib treatment-arm from the masitinib 4.5 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Arm type	Experimental
Investigational medicinal product name	Masitinib mesylate
Investigational medicinal product code	AB1010
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily doses of masitinib at the dose of 4.5 mg/kg/day, taken twice daily (morning, evening) with a meal (breakfast, dinner). Tablets of masitinib contained either 100 mg or 200 mg of masitinib base (respectively corresponding to 119.3 mg and 238.5 mg of the mesylate salt AB1010) and were to be given as per the weight of the patient.

Arm title	Masitinib arm from the fixed 6.0 mg/kg/d parallel group

Arm description:

Masitinib treatment-arm from the fixed masitinib 6.0 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Arm type	Experimental

Investigational medicinal product name	Masitinib mesylate
Investigational medicinal product code	AB1010
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily doses of masitinib at the dose of 4.5 mg/kg/day, taken twice daily (morning, evening) with a meal (breakfast, dinner). Tablets of masitinib contained either 100 mg or 200 mg of masitinib base (respectively corresponding to 119.3 mg and 238.5 mg of the mesylate salt AB1010) and were to be given as per the weight of the patient.

Arm title	Masitinib arm from the titrated 6.0 mg/kg/d parallel group

Arm description:

Masitinib treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group, wherein patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks which was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Arm type	Experimental
Investigational medicinal product name	Masitinib mesylate
Investigational medicinal product code	AB1010
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily doses of masitinib (taken twice daily (morning, evening) with a meal (breakfast, dinner).at an initial dose of 4.5 mg/kg/d for 12 weeks that was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Tablets of masitinib contained either 100 mg or 200 mg of masitinib base (respectively corresponding to 119.3 mg and 238.5 mg of the mesylate salt AB1010) and were to be given as per the weight of the patient.

Arm title	Placebo arm from the 4.5 mg/kg/d parallel group

Arm description:

Placebo treatment-arm from the masitinib 4.5 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily doses of matched placebo, taken twice daily (morning, evening) with a meal (breakfast, dinner).

Arm title	Placebo arm from the fixed 6.0 mg/kg/d parallel group

Arm description:

Placebo treatment-arm from the fixed masitinib 6.0 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily doses of matched placebo, taken twice daily (morning, evening) with a meal (breakfast, dinner).

Arm title	Placebo arm from the titrated 6.0 mg/kg/d parallel group

Arm description:

Matched placebo treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group, wherein patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks which was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily doses of matched placebo, taken twice daily (morning, evening) with a meal (breakfast, dinner).

Number of subjects in period 1	Masitinib arm from the 4.5 mg/kg/d parallel group	Masitinib arm from the fixed 6.0 mg/kg/d parallel group	Masitinib arm from the titrated 6.0 mg/kg/d parallel group
Started	200	27	203
Completed	99	3	127
Not completed	101	24	76
Adverse event, serious fatal	-	-	1
Cancer	2	-	1
IMP non compliance	-	-	-
Travel	-	-	-
Consent withdrawn by subject	12	-	2
Adverse event, non-fatal	33	10	40
Prohibited treatment	-	-	-
Regulatory suspension	8	11	-
Not related Adverse Event	3	1	3
Unknown	5	-	4
Eligibility criteria not respected	-	-	-
Lost to follow-up	1	-	1
Protocol deviation	12	2	8
Lack of efficacy	25	-	16

Number of subjects in period 1	Placebo arm from the 4.5 mg/kg/d parallel group	Placebo arm from the fixed 6.0 mg/kg/d parallel group	Placebo arm from the titrated 6.0 mg/kg/d parallel group
Started	101	18	107
Completed	67	5	74
Not completed	34	13	33
Adverse event, serious fatal	1	-	-

Cancer	-	-	-
IMP non compliance	-	-	2
Travel	4	-	1
Consent withdrawn by subject	6	-	3
Adverse event, non-fatal	2	-	4
Prohibited treatment	-	-	1
Regulatory suspension	3	7	-
Not related Adverse Event	-	1	2
Unknown	4	-	2
Eligibility criteria not respected	-	1	3
Lost to follow-up	1	1	-
Protocol deviation	1	-	-
Lack of efficacy	12	3	15

Baseline characteristics

Reporting groups	
Reporting group title	Masitinib arm from the 4.5 mg/kg/d parallel group
Reporting group description:	
Masitinib treatment-arm from the masitinib 4.5 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.	
Reporting group title	Masitinib arm from the fixed 6.0 mg/kg/d parallel group
Reporting group description:	
Masitinib treatment-arm from the fixed masitinib 6.0 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.	
Reporting group title	Masitinib arm from the titrated 6.0 mg/kg/d parallel group
Reporting group description:	
Masitinib treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group, wherein patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks which was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.	
Reporting group title	Placebo arm from the 4.5 mg/kg/d parallel group
Reporting group description:	
Placebo treatment-arm from the masitinib 4.5 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.	
Reporting group title	Placebo arm from the fixed 6.0 mg/kg/d parallel group
Reporting group description:	
Placebo treatment-arm from the fixed masitinib 6.0 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.	
Reporting group title	Placebo arm from the titrated 6.0 mg/kg/d parallel group
Reporting group description:	
Matched placebo treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group, wherein patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks which was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.	

Reporting group values	Masitinib arm from the 4.5 mg/kg/d parallel group	Masitinib arm from the fixed 6.0 mg/kg/d parallel group	Masitinib arm from the titrated 6.0 mg/kg/d parallel group
Number of subjects	200	27	203
Age categorical			
Units: Subjects			
Adults (18-64 years)	189	25	197
From 65-84 years	11	2	6
Age continuous			
Units: years			
arithmetic mean	49.8	53.0	48.6
standard deviation	± 9.63	± 9.67	± 10.10
Gender categorical			
Units: Subjects			
Female	111	17	122
Male	89	10	81

EDSS Category			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: Subjects			
At least 6	98	9	100
5 and 5.5	41	6	49
Less than 5	61	12	54
MS phenotype			
Patients with primary progressive MS (PPMS) or patients with nonactive secondary progressive MS (nSPMS) (with no exacerbations in the last 2 years). MS phenotype descriptors are based on disease activity (determined by clinical relapses and/or MRI activity) and disease progression (measured by clinical evaluation). Hence, progressive MS can be described as primary progressive MS (PPMS) or nonactive secondary progressive MS (nSPMS).			
Units: Subjects			
PPMS	79	17	81
nSPMS	121	10	122
EDSS Score			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: point			
arithmetic mean	5.2	4.8	5.5
standard deviation	± 1.07	± 1.14	± 0.95
Disease Duration from Onset			
Disease duration from onset of MS symptom at the time of randomization			
Units: Years			
arithmetic mean	14.0	13.7	14.2
standard deviation	± 9.14	± 9.56	± 9.96
Disease Duration from MS Diagnosis			
Disease Duration from MS diagnosis at the time of randomization			
Units: Years			
arithmetic mean	9.1	10.4	10.0
standard deviation	± 7.77	± 8.84	± 8.62
MSFC Timed 25-Foot Walk Test			
Multiple Sclerosis Functional Composite (MSFC) raw score for its component measurement of timed 25-foot walk test (T25FW, averaged time from 2 tests). MSFC is a composite instrument of disability.			
Units: seconds			
arithmetic mean	22.8	11.2	19.2
standard deviation	± 31.52	± 13.34	± 24.18
MSFC 9-HPT			
MSFC 9-hole peg test (9-HPT), averaged time from 2 tests on each hand (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: seconds			
arithmetic mean	34.0	31.4	32.9
standard deviation	± 18.63	± 18.02	± 14.3
MSFC PASAT-3			
Paced Auditory Serial Addition Test–3 (PASAT-3) (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: points			
arithmetic mean	41.6	46.4	41.9
standard deviation	± 13.36	± 11.02	± 13.29

Reporting group values	Placebo arm from the 4.5 mg/kg/d parallel group	Placebo arm from the fixed 6.0 mg/kg/d parallel	Placebo arm from the titrated 6.0 mg/kg/d parallel

		group	group
Number of subjects	101	18	107
Age categorical Units: Subjects			
Adults (18-64 years)	94	18	104
From 65-84 years	7	0	3
Age continuous Units: years			
arithmetic mean	49.7	51.6	48.8
standard deviation	± 10.19	± 7.43	± 9.68
Gender categorical Units: Subjects			
Female	54	8	65
Male	47	10	42
EDSS Category			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: Subjects			
At least 6	48	6	51
5 and 5.5	21	6	21
Less than 5	32	6	35
MS phenotype			
Patients with primary progressive MS (PPMS) or patients with nonactive secondary progressive MS (nSPMS) (with no exacerbations in the last 2 years). MS phenotype descriptors are based on disease activity (determined by clinical relapses and/or MRI activity) and disease progression (measured by clinical evaluation). Hence, progressive MS can be described as primary progressive MS (PPMS) or nonactive secondary progressive MS (nSPMS).			
Units: Subjects			
PPMS	45	9	46
nSPMS	56	9	61
EDSS Score			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: point			
arithmetic mean	5.1	5.0	5.5
standard deviation	± 1.06	± 1.02	± 1.01
Disease Duration from Onset			
Disease duration from onset of MS symptom at the time of randomization			
Units: Years			
arithmetic mean	12.6	12.2	12.5
standard deviation	± 7.96	± 7.06	± 8.81
Disease Duration from MS Diagnosis			
Disease Duration from MS diagnosis at the time of randomization			
Units: Years			
arithmetic mean	9.0	8.8	8.3
standard deviation	± 8.17	± 7.78	± 8.26
MSFC Timed 25-Foot Walk Test			
Multiple Sclerosis Functional Composite (MSFC) raw score for its component measurement of timed 25-foot walk test (T25FW, averaged time from 2 tests). MSFC is a composite instrument of disability.			
Units: seconds			
arithmetic mean	22.7	11.9	18.8
standard deviation	± 37.91	± 13.36	± 24.07

MSFC 9-HPT			
MSFC 9-hole peg test (9-HPT), averaged time from 2 tests on each hand (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: seconds			
arithmetic mean	34.2	29.5	35.1
standard deviation	± 20.55	± 6.96	± 25.53
MSFC PASAT-3			
Paced Auditory Serial Addition Test–3 (PASAT-3) (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: points			
arithmetic mean	40.1	42.9	42.2
standard deviation	± 14.47	± 13.71	± 12.36

Reporting group values	Total		
Number of subjects	656		
Age categorical			
Units: Subjects			
Adults (18-64 years)	627		
From 65-84 years	29		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	377		
Male	279		
EDSS Category			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: Subjects			
At least 6	312		
5 and 5.5	144		
Less than 5	200		
MS phenotype			
Patients with primary progressive MS (PPMS) or patients with nonactive secondary progressive MS (nSPMS) (with no exacerbations in the last 2 years). MS phenotype descriptors are based on disease activity (determined by clinical relapses and/or MRI activity) and disease progression (measured by clinical evaluation). Hence, progressive MS can be described as primary progressive MS (PPMS) or nonactive secondary progressive MS (nSPMS).			
Units: Subjects			
PPMS	277		
nSPMS	379		
EDSS Score			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: point			
arithmetic mean			
standard deviation	-		
Disease Duration from Onset			
Disease duration from onset of MS symptom at the time of randomization			
Units: Years			
arithmetic mean			

standard deviation	-		
Disease Duration from MS Diagnosis			
Disease Duration from MS diagnosis at the time of randomization			
Units: Years arithmetic mean standard deviation	- 		
MSFC Timed 25-Foot Walk Test			
Multiple Sclerosis Functional Composite (MSFC) raw score for its component measurement of timed 25-foot walk test (T25FW, averaged time from 2 tests). MSFC is a composite instrument of disability.			
Units: seconds arithmetic mean standard deviation	- 		
MSFC 9-HPT			
MSFC 9-hole peg test (9-HPT), averaged time from 2 tests on each hand (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: seconds arithmetic mean standard deviation	- 		
MSFC PASAT-3			
Paced Auditory Serial Addition Test–3 (PASAT-3) (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: points arithmetic mean standard deviation	- 		

Subject analysis sets

Subject analysis set title	Masitinib arm from the 4.5 mg/kg/d parallel group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Masitinib treatment-arm from the masitinib 4.5 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.
1 patient was excluded from the ITT data set because of no study drug intake,

Subject analysis set title	Placebo arm from the 4.5 mg/kg/d parallel group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo treatment-arm from the masitinib 4.5 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Subject analysis set title	Masitinib arm from titrated 6.0 mg/kg/d parallel group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Masitinib treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group.

Subject analysis set title	Placebo arm from titrated 6.0 mg/kg/d parallel group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Reporting group values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group	Masitinib arm from titrated 6.0 mg/kg/d parallel group
Number of subjects	199	101	203
Age categorical Units: Subjects			
Adults (18-64 years)	188	188	197
From 65-84 years	11	11	6
Age continuous Units: years			
arithmetic mean	49.8	49.7	48.6
standard deviation	± 9.63	± 10.19	± 10.10
Gender categorical Units: Subjects			
Female	111	54	122
Male	88	47	81
EDSS Category			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: Subjects			
At least 6	98	48	100
5 and 5.5	41	21	49
Less than 5	60	32	54
MS phenotype			
Patients with primary progressive MS (PPMS) or patients with nonactive secondary progressive MS (nSPMS) (with no exacerbations in the last 2 years). MS phenotype descriptors are based on disease activity (determined by clinical relapses and/or MRI activity) and disease progression (measured by clinical evaluation). Hence, progressive MS can be described as primary progressive MS (PPMS) or nonactive secondary progressive MS (nSPMS).			
Units: Subjects			
PPMS	79	45	81
nSPMS	120	56	122
EDSS Score			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: point			
arithmetic mean	5.2	5.1	5.5
standard deviation	± 1.1	± 1.06	± 0.95
Disease Duration from Onset			
Disease duration from onset of MS symptom at the time of randomization			
Units: Years			
arithmetic mean	14.0	12.6	14.2
standard deviation	± 9.1	± 7.96	± 9.96
Disease Duration from MS Diagnosis			
Disease Duration from MS diagnosis at the time of randomization			
Units: Years			
arithmetic mean	9.2	9.0	10.0
standard deviation	± 7.8	± 8.17	± 8.62
MSFC Timed 25-Foot Walk Test			
Multiple Sclerosis Functional Composite (MSFC) raw score for its component measurement of timed 25-foot walk test (T25FW, averaged time from 2 tests). MSFC is a composite instrument of disability.			
Units: seconds			
arithmetic mean	22.9	22.7	19.2

standard deviation	± 31.6	± 37.91	± 24.18
MSFC 9-HPT			
MSFC 9-hole peg test (9-HPT), averaged time from 2 tests on each hand (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: seconds			
arithmetic mean	34.2	34.2	32.9
standard deviation	± 18.6	± 20.55	± 14.3
MSFC PASAT-3			
Paced Auditory Serial Addition Test–3 (PASAT-3) (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: points			
arithmetic mean	41.5	40.1	41.9
standard deviation	± 13.4	± 14.47	± 13.29

Reporting group values	Placebo arm from titrated 6.0 mg/kg/d parallel group		
Number of subjects	107		
Age categorical Units: Subjects			
Adults (18-64 years)	104		
From 65-84 years	3		
Age continuous Units: years			
arithmetic mean	48.8		
standard deviation	± 9.68		
Gender categorical Units: Subjects			
Female	65		
Male	42		
EDSS Category			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: Subjects			
At least 6	51		
5 and 5.5	21		
Less than 5	35		
MS phenotype			
Patients with primary progressive MS (PPMS) or patients with nonactive secondary progressive MS (nSPMS) (with no exacerbations in the last 2 years). MS phenotype descriptors are based on disease activity (determined by clinical relapses and/or MRI activity) and disease progression (measured by clinical evaluation). Hence, progressive MS can be described as primary progressive MS (PPMS) or nonactive secondary progressive MS (nSPMS).			
Units: Subjects			
PPMS	46		
nSPMS	61		
EDSS Score			
Expanded Disability Status Scale (EDSS), range, 0 to 10.0 in 0.5-point increments, with higher scores indicating greater disability			
Units: point			
arithmetic mean	5.5		
standard deviation	± 1.01		
Disease Duration from Onset			
Disease duration from onset of MS symptom at the time of randomization			

Units: Years			
arithmetic mean	12.5		
standard deviation	± 8.81		
Disease Duration from MS Diagnosis			
Disease Duration from MS diagnosis at the time of randomization			
Units: Years			
arithmetic mean	8.3		
standard deviation	± 8.26		
MSFC Timed 25-Foot Walk Test			
Multiple Sclerosis Functional Composite (MSFC) raw score for its component measurement of timed 25-foot walk test (T25FW, averaged time from 2 tests). MSFC is a composite instrument of disability.			
Units: seconds			
arithmetic mean	18.8		
standard deviation	± 24.07		
MSFC 9-HPT			
MSFC 9-hole peg test (9-HPT), averaged time from 2 tests on each hand (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: seconds			
arithmetic mean	35.1		
standard deviation	± 25.53		
MSFC PASAT-3			
Paced Auditory Serial Addition Test–3 (PASAT-3) (raw score). Multiple Sclerosis Functional Composite (MSFC) is a composite instrument of disability.			
Units: points			
arithmetic mean	42.2		
standard deviation	± 12.36		

End points

End points reporting groups

Reporting group title	Masitinib arm from the 4.5 mg/kg/d parallel group

Reporting group description:

Masitinib treatment-arm from the masitinib 4.5 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Reporting group title	Masitinib arm from the fixed 6.0 mg/kg/d parallel group

Reporting group description:

Masitinib treatment-arm from the fixed masitinib 6.0 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Reporting group title	Masitinib arm from the titrated 6.0 mg/kg/d parallel group

Reporting group description:

Masitinib treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group, wherein patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks which was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Reporting group title	Placebo arm from the 4.5 mg/kg/d parallel group

Reporting group description:

Placebo treatment-arm from the masitinib 4.5 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Reporting group title	Placebo arm from the fixed 6.0 mg/kg/d parallel group

Reporting group description:

Placebo treatment-arm from the fixed masitinib 6.0 mg/kg/d parallel group. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Reporting group title	Placebo arm from the titrated 6.0 mg/kg/d parallel group

Reporting group description:

Matched placebo treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group, wherein patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks which was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Subject analysis set title	Masitinib arm from the 4.5 mg/kg/d parallel group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Masitinib treatment-arm from the masitinib 4.5 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.
1 patient was excluded from the ITT data set because of no study drug intake,

Subject analysis set title	Placebo arm from the 4.5 mg/kg/d parallel group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo treatment-arm from the masitinib 4.5 mg/kg/d parallel group.
Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Subject analysis set title	Masitinib arm from titrated 6.0 mg/kg/d parallel group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Masitinib treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group.

Subject analysis set title	Placebo arm from titrated 6.0 mg/kg/d parallel group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo treatment-arm from the titrated masitinib 6.0 mg/kg/d parallel group.

Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Primary: δEDSS (repeated-measures EDSS change)

End point title	δEDSS (repeated-measures EDSS change)

End point description:

Change from baseline on the EDSS, calculated using repeated measures methodology (i.e., generalized estimating equation [GEE]) based on all time points measured every 12 weeks over 96 weeks (δEDSS); i.e., a population-averaged score comprising 8 consecutive data points from each patient.

Results were expressed as least-squares mean (LSM) change on the EDSS from baseline (δEDSS, wherein a positive value indicates disability progression), with treatment effect (masitinib vs placebo) reported as the between treatment-arm difference (LSM difference, wherein a negative value favors masitinib). The change on the EDSS from baseline was calculated using a GEE model with normal distribution and identity link function, 97.04% CIs, and 2-sided comparison at an overall alpha level of 0.030 (adjusted for a single interim analysis). Missing data imputed via last observation carried forward methodology for those patients discontinuing before week 96 because of a safety event or lack of efficacy

End point type	Primary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group	Masitinib arm from titrated 6.0 mg/kg/d parallel group	Placebo arm from titrated 6.0 mg/kg/d parallel group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	101	203	107
Units: points				
least squares mean (standard error)	0.001 (± 0.034)	0.098 (± 0.041)	0.009 (± 0.0352)	-0.005 (± 0.009)

Statistical analyses

Statistical analysis title	LSM difference (4.5 mg/kg/d Parallel Group)

Statistical analysis description:

Between treatment-arm difference in dEDSS, wherein a negative value favors masitinib (i.e., masitinib arm minus its related placebo arm).
NOTE that each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0257
Method	ANCOVA GEE model
Parameter estimate	Mean difference (net)
Point estimate	-0.097

Confidence interval	
level	Other: 97 %
sides	2-sided
lower limit	-0.192
upper limit	-0.002
Variability estimate	Standard error of the mean
Dispersion value	0.0435

Statistical analysis title	LSM difference (titrated 6 mg/kg/d Parallel Group)

Statistical analysis description:

Between treatment-arm difference in dEDSS, wherein a negative value favors masitinib (i.e., masitinib arm minus its related placebo arm).
NOTE that each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Comparison groups	Masitinib arm from titrated 6.0 mg/kg/d parallel group v Placebo arm from titrated 6.0 mg/kg/d parallel group
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8019
Method	ANCOVA GEE model
Parameter estimate	Mean difference (net)
Point estimate	0.014
Confidence interval	
level	Other: 97 %
sides	2-sided
lower limit	-0.111
upper limit	0.1399
Variability estimate	Standard error of the mean
Dispersion value	0.0577

Secondary: Ordinal EDSS Analysis

End point title	Ordinal EDSS Analysis

End point description:

Consistency of the primary analysis was tested using predefined sensitivity analyses (EDSS-related secondary endpoints), including change from baseline in ordinal EDSS score averaged for all time points over 96 weeks; a 3-level ordinal EDSS model (GEE [W12–W96]) wherein values of +1, 0, or −1 were assigned for improved, stable, or worsening condition, respectively. This approach simultaneously measures intrasubject and intragroup incidence of positive and negative outcomes over duration of treatment. A worsening condition was defined as an increase from baseline in the EDSS of ≥1.0 point for a baseline score of ≤5.5 or of ≥0.5 points for a baseline score of >5.5 points. Likewise, an improving condition was defined by a decrease from baseline in the EDSS of the aforementioned values.
NOTE

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group	Masitinib arm from titrated 6.0 mg/kg/d parallel group	Placebo arm from titrated 6.0 mg/kg/d parallel group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	101	203	107
Units: points				
number (not applicable)	199	101	203	107

Statistical analyses

Statistical analysis title	Ordinal EDSS (4.5 mg/kg/d Parallel Group)

Statistical analysis description:

Change from baseline in ordinal EDSS score averaged for all time points over 96 weeks; a 3-level ordinal EDSS model (GEE [W12–W96]) wherein values of +1, 0, or −1 were assigned for improved, stable, or worsening condition, respectively.

NOTE that each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0444
Method	ANCOVA GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.376
upper limit	0.988
Variability estimate	Standard error of the mean
Dispersion value	0.1501

Statistical analysis title	Ordinal EDSS (titrated 6 mg/kg/d Parallel Group)

Statistical analysis description:

Change from baseline in ordinal EDSS score averaged for all time points over 96 weeks; a 3-level ordinal EDSS model (GEE [W12–W96]) wherein values of +1, 0, or −1 were assigned for improved, stable, or worsening condition, respectively.

NOTE that each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

Comparison groups	Masitinib arm from titrated 6.0 mg/kg/d parallel group v Placebo arm from titrated 6.0 mg/kg/d parallel group

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6756
Method	ANCOVA GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	1.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.629
upper limit	2.044
Variability estimate	Standard error of the mean
Dispersion value	0.3408

Secondary: Time-to-Confirmed (12 weeks) EDSS progression

End point title	Time-to-Confirmed (12 weeks) EDSS progression

End point description:

Time-to-confirmed (TTC) EDSS progression. Predefined time-to-event analysis of risk of EDSS progression confirmed at week 12, wherein a worsening condition was defined as an increase from baseline in the EDSS of .1.0 point for a baseline score of .5.5 or of .0.5 points for a baseline score of >5.5 points.

NOTE that each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control arm.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group	Masitinib arm from titrated 6.0 mg/kg/d parallel group	Placebo arm from titrated 6.0 mg/kg/d parallel group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	101	203	107
Units: events	22	18	25	17

Statistical analyses

Statistical analysis title	TTC EDSS progression (4.5 mg/kg/d parallel group)

Statistical analysis description:

Time-to-confirmed (TTC) EDSS progression in the 4.5 mg/kg/d parallel arm.
Kaplan-Meier analysis

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.327

Notes:

[1] - Log-rank p-value is adjusted for baseline MSFC components, baseline EDSS and Region

Statistical analysis title	TTC EDSS progression (titrated parallel group)

Statistical analysis description:

Time-to-confirmed (TTC) EDSS progression in the titrated 6.0 mg/kg/d parallel arm.
Kaplan-Meier analysis

Comparison groups	Masitinib arm from titrated 6.0 mg/kg/d parallel group v Placebo arm from titrated 6.0 mg/kg/d parallel group
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2935 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[2] - Log-rank p-value is adjusted for baseline MSFC components, baseline EDSS and Region

Secondary: Time-to-first EDSS progression

End point title	Time-to-first EDSS progression

End point description:

Time-to-first EDSS progression. Predefined time-to-event analysis of risk of EDSS progression (unconfirmed), wherein a worsening condition was defined as an increase from baseline in the EDSS of .1.0 point for a baseline score of .5.5 or of .0.5 points for a baseline score of >5.5 points.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group	Masitinib arm from titrated 6.0 mg/kg/d parallel group	Placebo arm from titrated 6.0 mg/kg/d parallel group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	101	203	107
Units: events	34	31	42	25

Statistical analyses

Statistical analysis title	TTF EDSS progression (4.5 mg/kg/d parallel group)

Statistical analysis description:

Time-to-first (TTF) EDSS progression in the 4.5 mg/kg/d parallel arm.
Kaplan-Meier analysis

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0342 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.96
Variability estimate	Standard error of the mean
Dispersion value	0.254

Notes:

[3] - Log-rank p-value is adjusted for baseline MSFC components, baseline EDSS and Region

Statistical analysis title	TTF EDSS progression (titrated parallel group)

Statistical analysis description:

Time-to-first (TTF) EDSS progression in the titrated 6.0 mg/kg/d parallel arm.
Kaplan-Meier analysis

Comparison groups	Placebo arm from titrated 6.0 mg/kg/d parallel group v Masitinib arm from titrated 6.0 mg/kg/d parallel group
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7153 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.52
Variability estimate	Standard error of the mean
Dispersion value	0.264

Notes:

[4] - Log-rank p-value is adjusted for baseline MSFC components, baseline EDSS and Region

Secondary: Multiple Sclerosis Functional Composite (MSFC) Score

End point title	Multiple Sclerosis Functional Composite (MSFC) Score

End point description:

Change from baseline on the MSFC raw scores averaged for all time points over 96 weeks, calculated using repeated measures methodology (mixed-effect model repeated measure, timeframe [W12–W96]).

The Multiple Sclerosis Functional Composite (MSFC) is a standardized, three-part tool used to assess the degree of disability in patients with MS. The MSFC was created for use in clinical studies and measures three key areas of MS disability—leg function/walking, arm and hand function, and cognitive function.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: points				
least squares mean (standard error)	0.031 (± 0.0221)	0.042 (± 0.0271)		

Statistical analyses

Statistical analysis title	MSFC Difference (4.5 mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in MSFC (i.e., masitinib arm minus its related placebo arm).

Comparison groups	Placebo arm from the 4.5 mg/kg/d parallel group v Masitinib arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.729
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	-0.011

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.052
Variability estimate	Standard error of the mean
Dispersion value	0.0318

Secondary: MSFC T25FW

End point title	MSFC T25FW

End point description:

Change from baseline on the MSFC component measure of timed 25-foot walk test (T25FW, averaged time from 2 tests)
The T25-FW is a quantitative mobility and leg function performance test based on a timed 25-walk

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: seconds				
least squares mean (standard error)	1.345 (± 1.3582)	3.042 (± 1.6661)		

Statistical analyses

Statistical analysis title	MSFC T25FW Difference (4.5 mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in MSFC T25FW (i.e., masitinib arm minus its related placebo arm).

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3848
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	-1.697

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.534
upper limit	2.14
Variability estimate	Standard error of the mean
Dispersion value	1.9498

Secondary: MSFC 9-HPT

End point title	MSFC 9-HPT

End point description:

Change from baseline on the MSFC component measure of 9-hole peg test (9-HPT, averaged time from 2 tests on each hand)
The 9-HPT is a brief, standardized, quantitative test of upper extremity function.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: seconds				
least squares mean (standard error)	-1.027 (± 1.4455)	3.256 (± 1.7704)		

Statistical analyses

Statistical analysis title	MSFC 9-HPT Difference (4.5 mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in MSFC 9-HPT (i.e., masitinib arm minus its related placebo arm).

Comparison groups	Placebo arm from the 4.5 mg/kg/d parallel group v Masitinib arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0388
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	-4.283

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.344
upper limit	-0.221
Variability estimate	Standard error of the mean
Dispersion value	2.0644

Secondary: MSFC PASAT-3

End point title	MSFC PASAT-3

End point description:

Change from baseline on the MSFC component measure of Paced Auditory Serial Addition Test–3 (PASAT-3)
The PASAT is a measure of cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: points				
least squares mean (standard error)	2.209 (± 0.4758)	2.806 (± 0.5826)		

Statistical analyses

Statistical analysis title	MSFC PASAT Difference (4.5 mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in MSFC PASAT-3 (i.e., masitinib arm minus its related placebo arm).

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3807
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	-0.597

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.935
upper limit	0.741
Variability estimate	Standard error of the mean
Dispersion value	0.68

Secondary: MSQOL-54 Physical Health

End point title	MSQOL-54 Physical Health

End point description:

Change from baseline in the MS quality of life (MSQOL-54) subscale of Physical Health, calculated using repeated measures methodology (mixed-effect model repeated measure, timeframe [W12–W96]).
The MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument. This 54-item instrument generates 12 subscales along with two summary scores (Physical Health and Mental Health) and two additional single-item measures.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: points				
least squares mean (standard error)	-0.976 (± 0.7663)	-1.221 (± 0.9411)		

Statistical analyses

Statistical analysis title	MSQOL-54 PH Difference (4.5mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in MSQOL-54 Physical Health (PH)
(masitinib arm minus its related placebo arm)

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8234
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	0.246

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.918
upper limit	2.409
Variability estimate	Standard error of the mean
Dispersion value	1.0996

Secondary: MSQOL-54 Mental Health

End point title	MSQOL-54 Mental Health

End point description:

Change from baseline in the MS quality of life (MSQOL-54) subscale of Mental Health, calculated using repeated measures methodology (mixed-effect model repeated measure, timeframe [W12–W96]).
The MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument. This 54-item instrument generates 12 subscales along with two summary scores (Physical Health and Mental Health) and two additional single-item measures.

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: points				
least squares mean (standard error)	-1.863 (± 0.9436)	-1.107 (± 1.1580)		

Statistical analyses

Statistical analysis title	MSQOL-54 MH Difference (4.5mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in MSQOL-54 Mental Health (MH)
(masitinib arm minus its related placebo arm)

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5776
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	-0.755

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.421
upper limit	1.91
Variability estimate	Standard error of the mean
Dispersion value	1.3555

Secondary: Health State Visual Analogue Scale (EQ-VAS)

End point title	Health State Visual Analogue Scale (EQ-VAS)

End point description:

Change from baseline in the Health State Visual Analogue Scale (EQ-VAS)
(Quality of life instrument consisting of a vertical visual analog scale wherein a score of 0 indicates worst imaginable health and 100 indicates best imaginable health).

End point type	Secondary

End point timeframe:

96 weeks

End point values	Masitinib arm from the 4.5 mg/kg/d parallel group	Placebo arm from the 4.5 mg/kg/d parallel group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	101		
Units: points				
least squares mean (standard error)	0.877 (± 0.9329)	-1.495 (± 1.1148)		

Statistical analyses

Statistical analysis title	EQ-VAS Difference (4.5 mg/kg/d parallel group)

Statistical analysis description:

Between treatment-arm difference in EQ-VAS
(masitinib arm minus its related placebo arm)

Comparison groups	Masitinib arm from the 4.5 mg/kg/d parallel group v Placebo arm from the 4.5 mg/kg/d parallel group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0753
Method	Logrank
Parameter estimate	Mean difference (net)
Point estimate	2.372

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.243
upper limit	4.987
Variability estimate	Standard error of the mean
Dispersion value	1.3294

Adverse events

Adverse events information

Timeframe for reporting adverse events:

96 weeks

Adverse event reporting additional description:

Treatment Emergent Adverse Events (TEAEs) is defined as Adverse Events (AEs) begin after the administration of study drug and/or within 28 days after the last dose and/or worsening after the date of the first study drug.
Safety dataset excluded 1 patient from ITT because of no intake of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Pooled Placebo

Reporting group description:

Safety for each masitinib dose level was compared against a pooled placebo population

Reporting group title	Masitinib 4.5 mg/kg/d

Reporting group description:

Patients were randomly assigned to receive masitinib at 4.5 mg/kg/d (administered orally as 2 daily intakes) or equivalent placebo.

Reporting group title	Masitinib 6.0 mg/kg/d (fixed dose)

Reporting group description:

Patients were randomly assigned to receive masitinib at a fixed dose of 6.0 mg/kg/d (administered orally as 2 daily intakes) or equivalent placebo.

Reporting group title	Titrated masitinib 6.0 mg/kg/d

Reporting group description:

An independent parallel group was introduced as an amendment in which patients were randomly assigned to receive masitinib (administered orally as 2 daily intakes) at an initial dose of 4.5 mg/kg/d for 12 weeks that was then up-titrated (escalated) to a planned dose of 6.0 mg/kg/d or equivalent placebo.

Serious adverse events	Pooled Placebo	Masitinib 4.5 mg/kg/d	Masitinib 6.0 mg/kg/d (fixed dose)
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 226 (11.95%)	42 / 199 (21.11%)	6 / 27 (22.22%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Bladder Papilloma			

subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Neuroendocrine Tumour Of The Lung			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Prostate Cancer			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Uterine Leiomyoma			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	2 / 226 (0.88%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Interstitial Lung Disease			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Nasal Mucosal Ulcer			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal Ulceration			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Granuloma			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 226 (0.44%)	1 / 199 (0.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar I Disorder			

subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Depressed Mood			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Mental Disorder			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Psychiatric Symptom			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Investigations			
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 226 (0.00%)	2 / 199 (1.01%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Cytology Abnormal			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Eosinophil Count Increased			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			

subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Head Injury			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Forearm Fracture			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Meniscus Injury			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Pelvic Fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Radius Fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Spinal Column Injury			

subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Spinal Compression Fracture			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Cord Injury			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Sternal Fracture			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Ulna Fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Upper Limb Fracture			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Myocardial Infarction			

subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Failure			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Nervous system disorders			
Multiple Sclerosis Relapse			
subjects affected / exposed	5 / 226 (2.21%)	4 / 199 (2.01%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 7	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis			
subjects affected / exposed	2 / 226 (0.88%)	2 / 199 (1.01%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplegia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Ischaemic Stroke			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Paraparesis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Primary Progressive Multiple Sclerosis			
subjects affected / exposed	0 / 226 (0.00%)	2 / 199 (1.01%)	0 / 27 (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
Sciatica			

subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Brain Stem Stroke			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Loss Of Consciousness			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Radicular Syndrome			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Speech Disorder			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 226 (0.00%)	2 / 199 (1.01%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Thrombocytopenic Purpura			

subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Gastrointestinal disorders			
Mouth Ulceration			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Diarrhoea			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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

Pancreatic Disorder			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Pancreatitis Acute			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Tongue Ulceration			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face Oedema			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental Death			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Generalised Oedema			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Pyrexia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholangitis Acute			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Cholecystitis Acute			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Cholestatic			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed Liver Injury			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash Maculo-Papular			
subjects affected / exposed	0 / 226 (0.00%)	3 / 199 (1.51%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema Multiforme			
subjects affected / exposed	0 / 226 (0.00%)	2 / 199 (1.01%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-Plantar Erythrodysaesthesia			

Syndrome			
subjects affected / exposed	0 / 226 (0.00%)	2 / 199 (1.01%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash Generalised			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cutaneous Vasculitis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus Ulcer			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Eruption			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus Generalised			

subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash Macular			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Exfoliation			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Necrosis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Stevens-Johnson Syndrome			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swelling Face			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Toxic Epidermal Necrolysis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic Skin Eruption			

subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Urethral Stenosis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Incontinence			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbar Spinal Stenosis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Osteoarthritis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Spondylolisthesis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	2 / 226 (0.88%)	2 / 199 (1.01%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Sepsis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Arthritis Bacterial			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal Skin Infection			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis Aseptic			
subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Oral Viral Infection			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	0 / 27 (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
Pneumonia Bacterial			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 226 (0.00%)	1 / 199 (0.50%)	0 / 27 (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
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Titrated masitinib 6.0 mg/kg/d		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 203 (24.14%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder Papilloma			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine Tumour Of The Lung			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate Cancer			

subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial Lung Disease			

subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal Mucosal Ulcer				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngeal Ulceration				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Granuloma				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	2 / 203 (0.99%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bipolar I Disorder				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed Mood				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental Disorder				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric Symptom				

subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood Bilirubin Increased			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cytology Abnormal			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eosinophil Count Increased			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases Increased			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight Decreased			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Head Injury				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Forearm Fracture				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meniscus Injury				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic Fracture				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius Fracture				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Column Injury				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Compression Fracture				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Injury				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sternal Fracture				

subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia Fracture				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna Fracture				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Limb Fracture				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial Infarction				
subjects affected / exposed	2 / 203 (0.99%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Left Ventricular Failure				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Multiple Sclerosis Relapse				
subjects affected / exposed	6 / 203 (2.96%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Multiple Sclerosis				

subjects affected / exposed	3 / 203 (1.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Diplegia				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic Stroke				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Paraparesis				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Primary Progressive Multiple Sclerosis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain Stem Stroke				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss Of Consciousness				

subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radicular Syndrome			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Speech Disorder			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 203 (1.97%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenic Purpura			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Mouth Ulceration			
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Odynophagia			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic Disorder			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Acute			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue Ulceration			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Face Oedema				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Accidental Death				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised Oedema				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis Acute				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis Acute				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug-Induced Liver Injury				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis Cholestatic				

subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mixed Liver Injury				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash Maculo-Papular				
subjects affected / exposed	4 / 203 (1.97%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Erythema Multiforme				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-Plantar Erythrodysaesthesia Syndrome				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash Generalised				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cutaneous Vasculitis				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Decubitus Ulcer				

subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug Eruption				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eczema				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pruritus				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pruritus Generalised				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash Macular				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin Exfoliation				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin Necrosis				

subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin Ulcer				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson Syndrome				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Swelling Face				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic Epidermal Necrolysis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic Skin Eruption				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Hydronephrosis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urethral Stenosis				

subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Incontinence				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Goitre				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Back Pain				
subjects affected / exposed	1 / 203 (0.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar Spinal Stenosis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	0 / 203 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal Sepsis			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal Abscess			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis Bacterial			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cystitis			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fungal Skin Infection			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung Infection			

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis Aseptic			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oral Viral Infection			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia Bacterial			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pooled Placebo	Masitinib 4.5 mg/kg/d	Masitinib 6.0 mg/kg/d (fixed dose)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 226 (81.86%)	188 / 199 (94.47%)	26 / 27 (96.30%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 226 (5.31%)	3 / 199 (1.51%)	1 / 27 (3.70%)
occurrences (all)	13	4	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 226 (5.75%)	14 / 199 (7.04%)	2 / 27 (7.41%)
occurrences (all)	13	14	2
Oedema Peripheral			
subjects affected / exposed	1 / 226 (0.44%)	14 / 199 (7.04%)	4 / 27 (14.81%)
occurrences (all)	1	15	4
Gait Disturbance			
subjects affected / exposed	13 / 226 (5.75%)	10 / 199 (5.03%)	1 / 27 (3.70%)
occurrences (all)	14	10	1
Pyrexia			
subjects affected / exposed	2 / 226 (0.88%)	7 / 199 (3.52%)	3 / 27 (11.11%)
occurrences (all)	2	8	3
Peripheral Swelling			
subjects affected / exposed	0 / 226 (0.00%)	5 / 199 (2.51%)	0 / 27 (0.00%)
occurrences (all)	0	7	0
Asthenia			
subjects affected / exposed	4 / 226 (1.77%)	6 / 199 (3.02%)	2 / 27 (7.41%)
occurrences (all)	4	6	2
Face Oedema			
subjects affected / exposed	0 / 226 (0.00%)	0 / 199 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	3
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 226 (2.21%)	11 / 199 (5.53%)	0 / 27 (0.00%)
occurrences (all)	5	12	0
Investigations			
Blood Triglycerides Increased			

subjects affected / exposed	24 / 226 (10.62%)	18 / 199 (9.05%)	1 / 27 (3.70%)
occurrences (all)	39	25	1
Lymphocyte Count Decreased			
subjects affected / exposed	11 / 226 (4.87%)	22 / 199 (11.06%)	3 / 27 (11.11%)
occurrences (all)	12	25	3
Alanine Aminotransferase Decreased			
subjects affected / exposed	15 / 226 (6.64%)	14 / 199 (7.04%)	0 / 27 (0.00%)
occurrences (all)	27	19	0
Haemoglobin Decreased			
subjects affected / exposed	7 / 226 (3.10%)	21 / 199 (10.55%)	1 / 27 (3.70%)
occurrences (all)	11	29	1
Aspartate Aminotransferase Increased			
subjects affected / exposed	10 / 226 (4.42%)	18 / 199 (9.05%)	1 / 27 (3.70%)
occurrences (all)	11	21	1
Protein Total Decreased			
subjects affected / exposed	9 / 226 (3.98%)	18 / 199 (9.05%)	0 / 27 (0.00%)
occurrences (all)	10	24	0
White Blood Cell Count Decreased			
subjects affected / exposed	5 / 226 (2.21%)	19 / 199 (9.55%)	0 / 27 (0.00%)
occurrences (all)	7	25	0
Blood Phosphorus Decreased			
subjects affected / exposed	5 / 226 (2.21%)	24 / 199 (12.06%)	0 / 27 (0.00%)
occurrences (all)	5	32	0
Haematocrit Decreased			
subjects affected / exposed	4 / 226 (1.77%)	15 / 199 (7.54%)	1 / 27 (3.70%)
occurrences (all)	6	22	2
Blood Bilirubin Decreased			
subjects affected / exposed	13 / 226 (5.75%)	4 / 199 (2.01%)	0 / 27 (0.00%)
occurrences (all)	20	6	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	13 / 226 (5.75%)	9 / 199 (4.52%)	1 / 27 (3.70%)
occurrences (all)	14	10	1
Haematocrit Increased			

subjects affected / exposed	14 / 226 (6.19%)	3 / 199 (1.51%)	0 / 27 (0.00%)
occurrences (all)	20	9	0
Red Blood Cell Count Decreased			
subjects affected / exposed	1 / 226 (0.44%)	16 / 199 (8.04%)	1 / 27 (3.70%)
occurrences (all)	3	18	2
Alanine Aminotransferase Increased			
subjects affected / exposed	7 / 226 (3.10%)	8 / 199 (4.02%)	1 / 27 (3.70%)
occurrences (all)	7	9	1
Blood Cholesterol Increased			
subjects affected / exposed	13 / 226 (5.75%)	9 / 199 (4.52%)	0 / 27 (0.00%)
occurrences (all)	16	14	0
Blood Creatinine Decreased			
subjects affected / exposed	12 / 226 (5.31%)	10 / 199 (5.03%)	0 / 27 (0.00%)
occurrences (all)	13	10	0
Weight Decreased			
subjects affected / exposed	2 / 226 (0.88%)	9 / 199 (4.52%)	4 / 27 (14.81%)
occurrences (all)	3	9	4
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	4 / 226 (1.77%)	13 / 199 (6.53%)	1 / 27 (3.70%)
occurrences (all)	4	15	1
Blood Sodium Increased			
subjects affected / exposed	3 / 226 (1.33%)	11 / 199 (5.53%)	0 / 27 (0.00%)
occurrences (all)	3	12	0
Monocyte Count Increased			
subjects affected / exposed	10 / 226 (4.42%)	16 / 199 (8.04%)	0 / 27 (0.00%)
occurrences (all)	11	19	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	16 / 226 (7.08%)	13 / 199 (6.53%)	1 / 27 (3.70%)
occurrences (all)	25	26	1
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 226 (5.31%)	14 / 199 (7.04%)	2 / 27 (7.41%)
occurrences (all)	21	18	3
Multiple Sclerosis Relapse			

subjects affected / exposed	11 / 226 (4.87%)	15 / 199 (7.54%)	0 / 27 (0.00%)
occurrences (all)	18	16	0
Muscle Spasticity			
subjects affected / exposed	12 / 226 (5.31%)	4 / 199 (2.01%)	0 / 27 (0.00%)
occurrences (all)	13	4	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 226 (1.33%)	11 / 199 (5.53%)	1 / 27 (3.70%)
occurrences (all)	3	15	2
Eosinophilia			
subjects affected / exposed	4 / 226 (1.77%)	5 / 199 (2.51%)	3 / 27 (11.11%)
occurrences (all)	4	7	3
Eye disorders			
Eyelid Oedema			
subjects affected / exposed	1 / 226 (0.44%)	10 / 199 (5.03%)	5 / 27 (18.52%)
occurrences (all)	1	12	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 226 (3.98%)	29 / 199 (14.57%)	5 / 27 (18.52%)
occurrences (all)	12	36	8
Nausea			
subjects affected / exposed	9 / 226 (3.98%)	21 / 199 (10.55%)	7 / 27 (25.93%)
occurrences (all)	11	24	9
Vomiting			
subjects affected / exposed	3 / 226 (1.33%)	11 / 199 (5.53%)	4 / 27 (14.81%)
occurrences (all)	3	14	6
Dry Mouth			
subjects affected / exposed	3 / 226 (1.33%)	5 / 199 (2.51%)	2 / 27 (7.41%)
occurrences (all)	3	5	3
Upper Respiratory Tract Infection			
subjects affected / exposed	11 / 226 (4.87%)	7 / 199 (3.52%)	0 / 27 (0.00%)
occurrences (all)	11	7	0
Skin and subcutaneous tissue disorders			
Rash Maculo-Papular			
subjects affected / exposed	2 / 226 (0.88%)	15 / 199 (7.54%)	3 / 27 (11.11%)
occurrences (all)	5	18	5
Erythema			

subjects affected / exposed	8 / 226 (3.54%)	12 / 199 (6.03%)	3 / 27 (11.11%)
occurrences (all)	13	17	3
Rash			
subjects affected / exposed	8 / 226 (3.54%)	3 / 199 (1.51%)	5 / 27 (18.52%)
occurrences (all)	13	16	7
Pruritus			
subjects affected / exposed	3 / 226 (1.33%)	14 / 199 (7.04%)	2 / 27 (7.41%)
occurrences (all)	4	17	2
Skin Exfoliation			
subjects affected / exposed	2 / 226 (0.88%)	3 / 199 (1.51%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Rash Generalised			
subjects affected / exposed	0 / 226 (0.00%)	5 / 199 (2.51%)	4 / 27 (14.81%)
occurrences (all)	0	7	4
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 226 (0.44%)	0 / 199 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	14 / 226 (6.19%)	13 / 199 (6.53%)	1 / 27 (3.70%)
occurrences (all)	15	13	1
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 226 (8.41%)	28 / 199 (14.07%)	0 / 27 (0.00%)
occurrences (all)	22	41	0
Urinary Tract Infection			
subjects affected / exposed	19 / 226 (8.41%)	28 / 199 (14.07%)	0 / 27 (0.00%)
occurrences (all)	22	41	0

Non-serious adverse events	Titrated masitinib 6.0 mg/kg/d		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 203 (90.64%)		
Vascular disorders			
Hypertension			

subjects affected / exposed	3 / 203 (1.48%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 203 (4.43%)		
occurrences (all)	10		
Oedema Peripheral			
subjects affected / exposed	9 / 203 (4.43%)		
occurrences (all)	10		
Gait Disturbance			
subjects affected / exposed	2 / 203 (0.99%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	9 / 203 (4.43%)		
occurrences (all)	11		
Peripheral Swelling			
subjects affected / exposed	12 / 203 (5.91%)		
occurrences (all)	14		
Asthenia			
subjects affected / exposed	8 / 203 (3.94%)		
occurrences (all)	8		
Face Oedema			
subjects affected / exposed	3 / 203 (1.48%)		
occurrences (all)	3		
Psychiatric disorders			
Depression			
subjects affected / exposed	9 / 203 (4.43%)		
occurrences (all)	9		
Investigations			
Blood Triglycerides Increased			
subjects affected / exposed	16 / 203 (7.88%)		
occurrences (all)	19		
Lymphocyte Count Decreased			
subjects affected / exposed	17 / 203 (8.37%)		
occurrences (all)	21		
Alanine Aminotransferase Decreased			

subjects affected / exposed	9 / 203 (4.43%)			
occurrences (all)	14			
Haemoglobin Decreased				
subjects affected / exposed	15 / 203 (7.39%)			
occurrences (all)	18			
Aspartate Aminotransferase Increased				
subjects affected / exposed	19 / 203 (9.36%)			
occurrences (all)	22			
Protein Total Decreased				
subjects affected / exposed	11 / 203 (5.42%)			
occurrences (all)	17			
White Blood Cell Count Decreased				
subjects affected / exposed	14 / 203 (6.90%)			
occurrences (all)	18			
Blood Phosphorus Decreased				
subjects affected / exposed	7 / 203 (3.45%)			
occurrences (all)	8			
Haematocrit Decreased				
subjects affected / exposed	9 / 203 (4.43%)			
occurrences (all)	13			
Blood Bilirubin Decreased				
subjects affected / exposed	8 / 203 (3.94%)			
occurrences (all)	11			
Gamma-Glutamyltransferase Increased				
subjects affected / exposed	9 / 203 (4.43%)			
occurrences (all)	10			
Haematocrit Increased				
subjects affected / exposed	5 / 203 (2.46%)			
occurrences (all)	8			
Red Blood Cell Count Decreased				
subjects affected / exposed	11 / 203 (5.42%)			
occurrences (all)	13			
Alanine Aminotransferase Increased				

subjects affected / exposed	16 / 203 (7.88%)		
occurrences (all)	17		
Blood Cholesterol Increased			
subjects affected / exposed	2 / 203 (0.99%)		
occurrences (all)	2		
Blood Creatinine Decreased			
subjects affected / exposed	6 / 203 (2.96%)		
occurrences (all)	7		
Weight Decreased			
subjects affected / exposed	10 / 203 (4.93%)		
occurrences (all)	11		
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	5 / 203 (2.46%)		
occurrences (all)	6		
Blood Sodium Increased			
subjects affected / exposed	4 / 203 (1.97%)		
occurrences (all)	4		
Monocyte Count Increased			
subjects affected / exposed	12 / 203 (5.91%)		
occurrences (all)	13		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 203 (2.96%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 203 (5.42%)		
occurrences (all)	13		
Multiple Sclerosis Relapse			
subjects affected / exposed	14 / 203 (6.90%)		
occurrences (all)	17		
Muscle Spasticity			
subjects affected / exposed	5 / 203 (2.46%)		
occurrences (all)	5		
Blood and lymphatic system disorders			

Lymphopenia subjects affected / exposed occurrences (all) Eosinophilia subjects affected / exposed occurrences (all)	13 / 203 (6.40%) 17 5 / 203 (2.46%) 5		
Eye disorders Eyelid Oedema subjects affected / exposed occurrences (all)	12 / 203 (5.91%) 15		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Dry Mouth subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	17 / 203 (8.37%) 27 23 / 203 (11.33%) 29 7 / 203 (3.45%) 8 5 / 203 (2.46%) 6 15 / 203 (7.39%) 17		
Skin and subcutaneous tissue disorders Rash Maculo-Papular subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus	15 / 203 (7.39%) 18 9 / 203 (4.43%) 10 15 / 203 (7.39%) 18		

subjects affected / exposed occurrences (all) Skin Exfoliation subjects affected / exposed occurrences (all) Rash Generalised subjects affected / exposed occurrences (all)	8 / 203 (3.94%) 15 15 / 203 (7.39%) 22 4 / 203 (1.97%) 4		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 0 / 203 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	 13 / 203 (6.40%) 14		
Infections and infestations Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all)	 19 / 203 (9.36%) 21 19 / 203 (9.36%) 21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2012	Protocol amendments were implemented during the study with data remaining blinded throughout, i.e. no changes were data-driven. Study AB07002 initially planned to enrol patients into a 6 mg/kg/day (fixed dose) treatment-arm. However, following analysis of severe adverse event (AE) and discontinuation rates for all non-oncology clinical trials (not including the current AB07002 study), it was shown that single agent masitinib starting at a dose of 3 or 4.5 mg/kg/day had an incidence similar to placebo, whereas single agent masitinib starting at a dose of 6 mg/kg/day showed increased frequency of certain events (for example, neutropenia and skin toxicity) with respect to placebo (unpublished data). A related analysis also revealed that up-titrated (escalated) doses from 3 or 4.5 mg/kg/day to 6 mg/kg/day improved tolerability and minimized discontinuations during the first 3 months of treatment when compared with a stable starting dose of 6 mg/kg/day. Indeed, this titrated dose regimen showed a similar discontinuation rate as when maintaining a stable dose of 3 or 4.5 mg/kg/day during and after the first 3 months. An amendment to the protocol of study AB07002 was therefore an unavoidable consequence of these developments and was made with an objective to improve the benefit/risk balance. Change was implemented over two protocol versions. First, it was decided to terminate the 6 mg/kg/day (starting dose) treatment-arm (as per protocol version 5.0; May, 2012). Second, there was the addition of an independent parallel group in which patients were randomly assigned (1:2) to receive placebo or masitinib as a titrated treatment regimen, i.e. an initial dose of 4.5 mg/kg/day for 12 weeks that was then titrated to a planned dose of 6.0 mg/kg/day (as per protocol version 6.0; August, 2013).
15 September 2016	Protocol amendments were implemented during the study with data remaining blinded throughout, i.e. no changes were data-driven. Study AB07002 initially planned to use the endpoint of Multiple Sclerosis Functional Composite (MSFC) for its primary analysis. However, during the study, the European Medicines Agency (EMA) 'Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis'* was issued in which use of the Kurtzke's Expanded Disability Status Scale (EDSS) as primary endpoint was clearly recommended. It was also stated that MSFC should be used as secondary measurement of disability. This guideline was adopted by Committee for Medicinal Products for Human Use (CHMP) in March 2015. Following this development, it was decided to change the primary analysis from an endpoint based on Multiple Sclerosis Functional Composite (MSFC) to an endpoint based on Expanded Disability Status Scale (EDSS). Analysis based on MSFC was consequently reassigned as a secondary endpoint. This change was implemented in the last protocol amendment (version 9; Sept 2016). * European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/771815/2011, Rev. 2. https://www.ema.europa.eu/en/clinical-investigation-medicinalproducts-treatment-multiple-sclerosis (accessed 09 September 2020).

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.

Validation of these positive findings via a confirmatory phase 3 study will be necessary, in part because neuroimaging data were not collected during the during the current study and also due to an absence of signal on secondary end points

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35190477

http://www.ncbi.nlm.nih.gov/pubmed/22691628