Clinical trial results:
Multicenter, Randomised, Double-blind, Placebo-controlled, Parallel Group, Phase 2/3 Study to Compare the Efficacy and Safety of Masitinib

Summary

EudraCT number	2010-024423-24
Trial protocol	ES GR SK IT HU PT IE NL
Global end of trial date	01 November 2017

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	AB10015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02588677
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, 0033 147200014, clinical@ab-science.com
Scientific contact	Clinical Study Coordinator, AB Science, 0033 147200014, 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	05 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess masitinib as an add-on to riluzole in the treatment of ALS

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:

In the European Union a drug called riluzole is the only authorized medicinal product for Amyotrophic Lateral Sclerosis (ALS). In this study, masitinib is investigated as an add-on therapy to riluzole in patients with ALS. the Investigational Medicinal Product (IMP) consisted of masitinib and its matching placebo IMP was supplied to the study Investigators or pharmacies by the Sponsor. Riluzole was not considered as being an IMP in this study and as such was not be provided by the Sponsor. A key patient inclusion criterion was that patients should be treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening. Thus, all patients received riluzole tablet 50 mg twice a day. The product was prepared, handled, used and stored according to standard practices and the Summary of Product Characteristics (SPC).

Evidence for comparator:

In the European Union a drug called riluzole is the only authorized medicinal product for ALS. A comprehensive review by Miller and colleagues on the use of riluzole for ALS considered evidence from four randomized clinical trials involving 1477 ALS treated patients [Miller, R. G., Mitchell, J. D., Lyon, M., & Moore, D. H. (2003). Amyotrophic lateral sclerosis and other motor neuron disorders: official publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases, 4(3), 191-206]. Results from this meta-analysis indicated that riluzole 100 mg probably prolongs median survival in people with ALS by 2 to 3 months with respect to participants taking placebo and the safety of the drug is not a major concern. There are no data that directly measured quality of life from the published trials. Additionally, there was no beneficial effect of riluzole on patient function in any of the randomized trials considered separately.

Actual start date of recruitment	08 April 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 155
Country: Number of subjects enrolled	Canada: 8

Country: Number of subjects enrolled	Argentina: 119
Country: Number of subjects enrolled	Italy: 75
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Mexico: 3
Worldwide total number of subjects	394
EEA total number of subjects	264

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)	311
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were randomly assigned (1:1:1) to receive riluzole (100 mg/day) plus placebo or masitinib at 4.5 or 3.0 mg/kg/day (bis in die), with the high-dose cohort being predefined for primary analysis.

Pre-assignment

Screening details:

Eligible patients were aged 18–75 years with a laboratory-supported probable, probable, or definite diagnosis of ALS (revised El Escorial criteria), had less than 36 months duration of disease from the first ALS symptom (i.e. any progressive focal weakness or atrophy) and forced vital capacity (FVC) of at least 60% at baseline.

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	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

Patients were randomised using a computerised central randomization system and minimization method according to the covariates (i.e. prognostic factors) of: site of onset (spinal versus bulbar), ALSFRS-R score, age, geographical region, and post-onset ΔFS.

Arms

Are arms mutually exclusive?	Yes
Arm title	Masitinib 3.0 mg/kg/d

Arm description:

masitinib 3 mg/kg/d administered as an add-on to riluzole

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 3.0 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 4.5 mg/kg/d

Arm description:

masitinib 4.5 mg/kg/d administered as an add-on to riluzole

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	Placebo
Arm description: placebo administered as an add-on to riluzole	
Arm type	Active comparator
Investigational medicinal product name	Riluzole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

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

Number of subjects in period 1	Masitinib 3.0 mg/kg/d	Masitinib 4.5 mg/kg/d	Placebo
Started	131	130	133
Completed	89	83	92
Not completed	42	47	41
Adverse event, serious fatal	9	6	9
Adverse event, non-fatal	7	12	1
Prohibited Concomitant treatment	2	-	1
Non compliance	2	3	-
Cancer not related	-	1	2
Lost to follow-up	-	1	-
Procedure	-	-	3
Lack of efficacy	19	19	15
Protocol deviation	2	1	2
Travel	1	4	8

Baseline characteristics

Reporting groups	
Reporting group title	Masitinib 3.0 mg/kg/d
Reporting group description: masitinib 3 mg/kg/d administered as an add-on to riluzole	

Reporting group title	Masitinib 4.5 mg/kg/d
Reporting group description: masitinib 4.5 mg/kg/d administered as an add-on to riluzole	
Reporting group title	Placebo
Reporting group description: placebo administered as an add-on to riluzole	

Reporting group values	Masitinib 3.0 mg/kg/d	Masitinib 4.5 mg/kg/d	Placebo
Number of subjects	131	130	133
Age categorical Units: Subjects			
Adults (18-64 years)	105	103	103
From 65-84 years	26	27	30
Age continuous Units: years			
arithmetic mean	55.7	55.5	55.2
standard deviation	± 10.2	± 10.6	± 10.6
Gender categorical Units: Subjects			
Female	50	47	53
Male	81	83	80
ΔFS<1.1 before randomisation			
Proportion of patients with Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised progression rate (ΔFS) from disease-onset to baseline of less than 1.1 points/month			
Units: Subjects			
Yes	110	103	114
No	21	27	19
Site of onset			
Site of ALS onset (spinal versus bulbar)			
Units: Subjects			
Bulbar	21	23	24
Spinal	110	107	109
ΔFS before randomisation			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) progression rate from disease-onset to baseline			
Units: points/month			
arithmetic mean	0.65	0.73	0.71
standard deviation	± 0.48	± 0.63	± 0.53
ALSFRS-R score at baseline			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score at baseline			
Units: points			
arithmetic mean	37.4	37.5	38.1

standard deviation	± 5.7	± 5.5	± 5.5

Reporting group values	Total		
Number of subjects	394		
Age categorical Units: Subjects			
Adults (18-64 years)	311		
From 65-84 years	83		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	150		
Male	244		
ΔFS<1.1 before randomisation			
Proportion of patients with Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised progression rate (ΔFS) from disease-onset to baseline of less than 1.1 points/month			
Units: Subjects			
Yes	327		
No	67		
Site of onset			
Site of ALS onset (spinal versus bulbar)			
Units: Subjects			
Bulbar	68		
Spinal	326		
ΔFS before randomisation			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) progression rate from disease-onset to baseline			
Units: points/month arithmetic mean standard deviation	- -		
ALSFRS-R score at baseline			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score at baseline			
Units: points arithmetic mean standard deviation	- -		

Subject analysis sets

Subject analysis set title	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose

(masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal Progressor' M4.5 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	'Normal and Fast Progressor' Masitinib 4.5 mg/kg/d cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal and Fast' M4.5 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	'Normal Progressor' Masitinib 3.0 mg/kg/d cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal Progressor' M3.0 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	'Normal and Fast Progressor' Masitinib 3.0 mg/kg/d cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-

off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal and Fast' M3.0 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Reporting group values	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population)	Control (placebo) for the 'Normal Progressor' M4.5 cohort	'Normal and Fast Progressor' Masitinib 4.5 mg/kg/d cohort
Number of subjects	106	114	130
Age categorical			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous			
Units: years			
arithmetic mean	54.8	55.4	55.5
standard deviation	± 10.8	± 10.5	± 10.6
Gender categorical			
Units: Subjects			
Female	37	45	47
Male	69	69	83
ΔFS<1.1 before randomisation			
Proportion of patients with Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised progression rate (ΔFS) from disease-onset to baseline of less than 1.1 points/month			
Units: Subjects			
Yes	106	114	106
No	0	0	24
Site of onset			
Site of ALS onset (spinal versus bulbar)			
Units: Subjects			
Bulbar	21	24	23
Spinal	85	90	107
ΔFS before randomisation			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) progression rate from disease-onset to baseline			
Units: points/month			
arithmetic mean	0.49	0.49	0.73
standard deviation	± 0.25	± 0.24	± 0.63
ALSFRS-R score at baseline			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score at baseline			
Units: points			
arithmetic mean	38.3	39.3	37.5
standard deviation	± 5.3	± 4.6	± 5.5

Reporting group values	Control (placebo) for the 'Normal and Fast' M4.5 cohort	'Normal Progressor' Masitinib 3.0 mg/kg/d cohort	Control (placebo) for the 'Normal Progressor' M3.0 cohort
Number of subjects	133	110	114
Age categorical			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous			
Units: years			
arithmetic mean	55.2	54.9	55.4
standard deviation	± 10.6	± 10.3	± 10.5
Gender categorical			
Units: Subjects			
Female	53	40	45
Male	80	70	69
ΔFS<1.1 before randomisation			
Proportion of patients with Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised progression rate (ΔFS) from disease-onset to baseline of less than 1.1 points/month			
Units: Subjects			
Yes	114	110	114
No	19	0	0
Site of onset			
Site of ALS onset (spinal versus bulbar)			
Units: Subjects			
Bulbar	24	18	24
Spinal	109	92	90
ΔFS before randomisation			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) progression rate from disease-onset to baseline			
Units: points/month			
arithmetic mean	0.71	0.48	0.49
standard deviation	± 0.69	± 0.25	± 0.24
ALSFRS-R score at baseline			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score at baseline			
Units: points			
arithmetic mean	38.1	38.6	39.3
standard deviation	± 5.5	± 5.1	± 4.6

Reporting group values	'Normal and Fast Progressor' Masitinib 3.0 mg/kg/d cohort	Control (placebo) for the 'Normal and Fast' M3.0 cohort	
Number of subjects	131	133	
Age categorical			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous			
Units: years			
arithmetic mean	55.7	55.2	
standard deviation	± 10.2	± 10.6	

Gender categorical Units: Subjects			
Female	50	53	
Male	81	80	
ΔFS<1.1 before randomisation			
Proportion of patients with Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised progression rate (ΔFS) from disease-onset to baseline of less than 1.1 points/month			
Units: Subjects			
Yes	110	114	
No	21	19	
Site of onset			
Site of ALS onset (spinal versus bulbar)			
Units: Subjects			
Bulbar	21	24	
Spinal	110	109	
ΔFS before randomisation			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) progression rate from disease-onset to baseline			
Units: points/month			
arithmetic mean	0.65	0.71	
standard deviation	± 0.48	± 0.69	
ALSFRS-R score at baseline			
Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score at baseline			
Units: points			
arithmetic mean	37.4	38.1	
standard deviation	± 5.7	± 5.5	

End points

End points reporting groups

Reporting group title	Masitinib 3.0 mg/kg/d
Reporting group description: masitinib 3 mg/kg/d administered as an add-on to riluzole	

Reporting group title	Masitinib 4.5 mg/kg/d
Reporting group description: masitinib 4.5 mg/kg/d administered as an add-on to riluzole	

Reporting group title	Placebo
Reporting group description: placebo administered as an add-on to riluzole	

Subject analysis set title	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal Progressor' M4.5 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	'Normal and Fast Progressor' Masitinib 4.5 mg/kg/d cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal and Fast' M4.5 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	'Normal Progressor' Masitinib 3.0 mg/kg/d cohort

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal Progressor' M3.0 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	'Normal and Fast Progressor' Masitinib 3.0 mg/kg/d cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Subject analysis set title	Control (placebo) for the 'Normal and Fast' M3.0 cohort
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

An important prognostic factor in ALS is the ALSFRS-R progression rate from disease-onset to baseline (ΔFS) (i.e., speed of functional deterioration).
Four efficacy population were therefore predefined according to masitinib dose and ΔFS, using the cut-off < 1.1 points/month to define 'Normal Progressors' and ≥ 1.1 points/month to define 'Fast Progressors'. The high-dose (masitinib 4.5 mg/kg/d) 'Normal Progressor' cohort, and associated control cohort, was prospectively declared as the primary efficacy population (subject analysis set). The broader 'Normal and Fast Progressor' masitinib 4.5 mg/kg/d cohort, and corresponding ΔFS-tiered low-dose (masitinib 3.0 mg/kg/d) cohorts were predefined as secondary subject analysis sets.

Primary: ΔALSFRS-R (primary efficacy population of 'Normal Progressor' patients receiving masitinib 4.5 mg/kg/d versus Control)

End point title	ΔALSFRS-R (primary efficacy population of 'Normal Progressor' patients receiving masitinib 4.5 mg/kg/d versus Control)

End point description:

The primary endpoint was decline in ALSFRS-R from baseline to week-48 (ΔALSFRS-R). Missing data were imputed via last observation carried forward (LOCF) methodology for those patients discontinuing because of toxicity or lack of efficacy before week 48. Any patient dying after randomization had an ALSFRS-R score of zero imputed. ΔALSFRS-R was calculated using a model of analysis of covariance (ANCOVA), adjusted on the baseline covariates (site of onset, ALSFRS-R score, age, geographical region, and ΔFS), expressing results as difference of least-squares means (ΔLSM) between treatments (masitinib versus placebo) with corresponding 95% two-sided confidence intervals (CI) and statistical test P-value.

End point type	Primary

End point timeframe:

48 weeks

End point values	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population)	Control (placebo) for the 'Normal Progressor' M4.5 cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99[1]	102[2]		
Units: points				
least squares mean (standard error)	-9.24 (± 1.357)	-12.63 (± 1.371)		

Notes:

[1] - Assessable patients for primary endpoint according to rules for missing data imputation

[2] - Assessable patients for primary endpoint according to rules for missing data imputation

Statistical analyses

Statistical analysis title	Least squares mean difference (LSMD)
Statistical analysis description:	
Between treatment-arm difference of least-squares means difference from baseline	
Comparison groups	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population) v Control (placebo) for the 'Normal Progressor' M4.5 cohort
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0158
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	6.13
Variability estimate	Standard error of the mean
Dispersion value	1.391

Statistical analysis title	LSMD using Jump to Reference method
Statistical analysis description:	
Sensitivity analysis on the primary efficacy endpoint using the recommended technique of jump-to-reference. This multiple imputation Jump to Reference approach imputed missing data for reason of discontinuation due to lack of efficacy or toxicity, using estimates from the control group. This is justifiable under the assumption that patients who stop taking therapy for lack of efficacy will no longer benefit from it in the future, and thus will tend to have outcomes similar to the control.	
Comparison groups	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population) v Control (placebo) for the 'Normal Progressor' M4.5 cohort

Number of subjects included in analysis	201
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0386
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	5.46

Statistical analysis title	LSMD using Multiple Imputation method

Statistical analysis description:

Sensitivity analysis on the primary efficacy endpoint using the recommended techniques of multiple imputation and jump-to-reference.
Multiple imputation is the most widely used sensitivity analysis technique and is highly recommended by all health authorities. The multiple imputation approach used is based on factors the explained maximum variability in primary endpoint.

Comparison groups	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population) v Control (placebo) for the 'Normal Progressor' M4.5 cohort
Number of subjects included in analysis	201
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.436
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	6.33

Secondary: Progression free survival (PFS) on the primary efficacy population of ‘Normal Progressor’ patients receiving masitinib 4.5 mg/kg/d versus Control

End point title	Progression free survival (PFS) on the primary efficacy population of ‘Normal Progressor’ patients receiving masitinib 4.5 mg/kg/d versus Control

End point description:

Time-to-event analysis, defined here as a deterioration of 9 points from baseline in ALSFRS-R or death. This endpoint is driven by both death and a fixed disease progression on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) scale.

End point type	Secondary

End point timeframe:

48 weeks

End point values	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population)	Control (placebo) for the 'Normal Progressor' M4.5 cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105[3]	113[4]		
Units: months				
median (confidence interval 95%)	20 (14 to 30)	16 (11 to 19)		

Notes:

[3] - Assessable patients for above referenced endpoint according to rules for missing data imputation

[4] - Assessable patients for above referenced endpoint according to rules for missing data imputation

Statistical analyses

Statistical analysis title	Delay in disease progression
Comparison groups	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population) v Control (placebo) for the 'Normal Progressor' M4.5 cohort
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0159
Method	Wilcoxon (Mann-Whitney)

Secondary: ΔALSAQ-40

End point title	ΔALSAQ-40

End point description:

Change from baseline in ALS Assessment Questionnaire 40-item (ALSAQ-40) score. (Jenkinson C, Fitzpatrick R, Brennan C, Swash M. Evidence for the validity and reliability of the ALS assessment questionnaire: the ALSAQ-40. Amyotroph Lateral Scler Other Motor Neuron Disord 1999; 1: 33–40)

End point type	Secondary

End point timeframe:

48 weeks

End point values	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population)	Control (placebo) for the 'Normal Progressor' M4.5 cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	102		
Units: points				
least squares mean (standard error)	19.42 (± 2.818)	27.18 (± 2.847)		

Statistical analyses

Statistical analysis title	Least squares mean difference (LSMD)
Statistical analysis description:	
Between treatment-arm difference of least-squares means difference from baseline	
Comparison groups	'Normal Progressor' Masitinib 4.5 mg/kg/d (Primary Population) v Control (placebo) for the 'Normal Progressor' M4.5 cohort
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.45
upper limit	-2.06
Variability estimate	Standard error of the mean
Dispersion value	2.888

Other pre-specified: ΔALSFRS-R (secondary analysis set of 'Normal and Fast Progressor' patients receiving masitinib 4.5 mg/kg/d versus Control)

End point title	ΔALSFRS-R (secondary analysis set of 'Normal and Fast Progressor' patients receiving masitinib 4.5 mg/kg/d versus Control)

End point description:

ΔALSFRS-R for predefined secondary analysis set (step 2: efficacy analyses conducted using a stepwise fixed sequence method to control the global family-wise error rate at the 0.05 level for the primary analysis). Missing data were imputed via last observation carried forward (LOCF) methodology for those patients discontinuing because of toxicity or lack of efficacy before week 48. Any patient dying after randomization had an ALSFRS-R score of zero imputed. ΔALSFRS-R was calculated using a model of analysis of covariance (ANCOVA), adjusted on the baseline covariates (site of onset, ALSFRS-R score, age, geographical region, and ΔFS), expressing results as difference of least-squares means (ΔLSM) between treatments (masitinib versus placebo) with corresponding 95% two-sided confidence intervals (CI) and statistical test P-value.

End point type	Other pre-specified

End point timeframe:

48 weeks

End point values	'Normal and Fast Progressor' Masitinib 4.5 mg/kg/d cohort	Control (placebo) for the 'Normal and Fast' M4.5 cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120[5]	119[6]		
Units: points				
least squares mean (standard error)	-10.89 (± 1.411)	-12.97 (± 1.42)		

Notes:

[5] - Assessable patients for above referenced endpoint according to rules for missing data imputation

[6] - Assessable patients for above referenced endpoint according to rules for missing data imputation

Statistical analyses

Statistical analysis title	Least squares mean difference
Statistical analysis description:	
Between treatment-arm difference of least-squares means difference from baseline	
Comparison groups	Control (placebo) for the 'Normal and Fast' M4.5 cohort v 'Normal and Fast Progressor' Masitinib 4.5 mg/kg/d cohort
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1202
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	4.73
Variability estimate	Standard error of the mean
Dispersion value	1.339

Other pre-specified: ΔALSFRS-R (secondary analysis set of 'Normal Progressor' patients receiving masitinib 3.0 mg/kg/d versus Control)

End point title	ΔALSFRS-R (secondary analysis set of 'Normal Progressor' patients receiving masitinib 3.0 mg/kg/d versus Control)

End point description:

ΔALSFRS-R for predefined secondary analysis set (step 3: efficacy analyses conducted using a stepwise fixed sequence method to control the global family-wise error rate at the 0.05 level for the primary analysis). Missing data were imputed via last observation carried forward (LOCF) methodology for those patients discontinuing because of toxicity or lack of efficacy before week 48. Any patient dying after randomization had an ALSFRS-R score of zero imputed. ΔALSFRS-R was calculated using a model of analysis of covariance (ANCOVA), adjusted on the baseline covariates (site of onset, ALSFRS-R score, age, geographical region, and ΔFS), expressing results as difference of least-squares means (ΔLSM) between treatments (masitinib versus placebo) with corresponding 95% two-sided confidence intervals (CI) and statistical test P-value.

End point type	Other pre-specified

End point timeframe:

48 weeks

End point values	'Normal Progressor' Masitinib 3.0 mg/kg/d cohort	Control (placebo) for the 'Normal Progressor' M3.0 cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	106[7]	102[8]		
Units: points				
least squares mean (standard error)	-8.61 (± 1.478)	-11.34 (± 1.430)		

Notes:

[7] - Assessable patients for above referenced endpoint according to rules for missing data imputation

[8] - Assessable patients for above referenced endpoint according to rules for missing data imputation

Statistical analyses

Statistical analysis title	Least squares mean difference
Statistical analysis description: Between treatment-arm difference of least-squares means difference from baseline	
Comparison groups	'Normal Progressor' Masitinib 3.0 mg/kg/d cohort v Control (placebo) for the 'Normal Progressor' M3.0 cohort
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0661
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	5.65
Variability estimate	Standard error of the mean
Dispersion value	1.478

Other pre-specified: ΔALSFRS-R (secondary analysis set of 'Normal and Fast Progressor' patients receiving masitinib 3.0 mg/kg/d versus Control)

End point title	ΔALSFRS-R (secondary analysis set of 'Normal and Fast Progressor' patients receiving masitinib 3.0 mg/kg/d versus Control)

End point description:

ΔALSFRS-R for predefined secondary analysis set (step 4: efficacy analyses conducted using a stepwise fixed sequence method to control the global family-wise error rate at the 0.05 level for the primary analysis). Missing data were imputed via last observation carried forward (LOCF) methodology for those patients discontinuing because of toxicity or lack of efficacy before week 48. Any patient dying after randomization had an ALSFRS-R score of zero imputed. ΔALSFRS-R was calculated using a model of analysis of covariance (ANCOVA), adjusted on the baseline covariates (site of onset, ALSFRS-R score, age, geographical region, and ΔFS), expressing results as difference of least-squares means (ΔLSM) between treatments (masitinib versus placebo) with corresponding 95% two-sided confidence intervals

(CI) and statistical test P-value.

End point type	Other pre-specified

End point timeframe:

48 weeks

End point values	'Normal and Fast Progressor' Masitinib 3.0 mg/kg/d cohort	Control (placebo) for the 'Normal and Fast' M3.0 cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	119[9]	126[10]		
Units: points				
least squares mean (standard error)	-10.27 (± 1.448)	-12.07 (± 1.409)		

Notes:

[9] - Assessable patients for above referenced endpoint according to rule for missing data imputation

[10] - Assessable patients for above referenced endpoint according to rules for missing data imputation

Statistical analyses

Statistical analysis title	Least squares mean difference

Statistical analysis description:

Between treatment-arm difference of least-squares means difference from baseline

Comparison groups	'Normal and Fast Progressor' Masitinib 3.0 mg/kg/d cohort v Control (placebo) for the 'Normal and Fast' M3.0 cohort
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1918
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	4.51
Variability estimate	Standard error of the mean
Dispersion value	1.375

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to week-48	
Adverse event reporting additional description:	
Adverse events (AE) were recorded until 28 days after treatment interruption with any AE not resolved at the death of the patients recorded as an AE leading to death. 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	Placebo
Reporting group description:	
Placebo plus riluzole	
Reporting group title	Masitinib 4.5 mg/kg/d
Reporting group description:	
Masitinib 4.5 mg/kg/day plus riluzole	
Reporting group title	Masitinib 3.0 mg/kg/d
Reporting group description:	
Masitinib 3.0 mg/kg/day plus riluzole	

Serious adverse events	Placebo	Masitinib 4.5 mg/kg/d	Masitinib 3.0 mg/kg/d
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 133 (27.07%)	50 / 129 (38.76%)	28 / 131 (21.37%)
number of deaths (all causes)	12	10	11
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Pleural Mesothelioma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Surgical and medical procedures			
Wisdom Teeth Removal			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Euthanasia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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			
Respiratory Failure			
subjects affected / exposed	6 / 133 (4.51%)	13 / 129 (10.08%)	8 / 131 (6.11%)
occurrences causally related to treatment / all	0 / 6	0 / 13	0 / 9
deaths causally related to treatment / all	0 / 4	0 / 5	0 / 4
Dyspnoea			
subjects affected / exposed	1 / 133 (0.75%)	4 / 129 (3.10%)	2 / 131 (1.53%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Acute Respiratory Failure			

subjects affected / exposed	1 / 133 (0.75%)	1 / 129 (0.78%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Chronic Respiratory Failure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Obstructive Airways Disorder			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia Aspiration			
subjects affected / exposed	1 / 133 (0.75%)	1 / 129 (0.78%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Pulmonary Oedema			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory Arrest			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Increased Bronchial Secretion			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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 disorders			
Anxiety			

subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Panic Attack			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 133 (0.00%)	2 / 129 (1.55%)	0 / 131 (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
Weight Decreased			
subjects affected / exposed	2 / 133 (1.50%)	1 / 129 (0.78%)	2 / 131 (1.53%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration Bronchial			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Haemoglobin Decreased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T Increased			

subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Urine Cytology Abnormal			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 133 (0.00%)	2 / 129 (1.55%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face Injury			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Intestinal Obstruction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Ligament Sprain			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Rib Fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Scapula Fracture			

subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Wrist Fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Ankle Fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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			
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 133 (0.75%)	1 / 129 (0.78%)	4 / 131 (3.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 3
Cardiopulmonary Failure			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Myocardial Infarction			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	2 / 131 (1.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amnesia			

subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amyotrophic Lateral Sclerosis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Injury			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Cauda Equina Syndrome			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Spasticity			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnic Coma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	2 / 131 (1.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic Anaemia			

subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Normochromic Normocytic Anaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	9 / 133 (6.77%)	11 / 129 (8.53%)	14 / 131 (10.69%)
occurrences causally related to treatment / all	0 / 9	0 / 11	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Diarrhoea			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal Haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Pneumoperitoneum			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Pneumonia			

subjects affected / exposed	3 / 133 (2.26%)	1 / 129 (0.78%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pneumonia Bacterial			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Skin Infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Cystitis Bacterial			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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 Tract Infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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 Tract Infection Viral			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			

subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	0 / 131 (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
Skin and subcutaneous tissue disorders			
Drug Reaction With Eosinophilia And Systemic Symptoms			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry Skin			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Eczema			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Mechanical Urticaria			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Pruritus Generalised			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Rash Generalised			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Rash Maculo-Papular			
subjects affected / exposed	1 / 133 (0.75%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seborrhoeic Dermatitis			

subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Toxic Skin Eruption			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 129 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 133 (0.75%)	2 / 129 (1.55%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 133 (1.50%)	2 / 129 (1.55%)	2 / 131 (1.53%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis Haemophilus			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Gastroenteritis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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

Oral Candidiasis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Oropharyngeal Candidiasis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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
Hip Fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 129 (0.78%)	0 / 131 (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

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

Non-serious adverse events	Placebo	Masitinib 4.5 mg/kg/d	Masitinib 3.0 mg/kg/d
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 133 (57.89%)	114 / 129 (88.37%)	30 / 131 (22.90%)
Investigations			
Weight Decreased			
subjects affected / exposed	10 / 133 (7.52%)	11 / 129 (8.53%)	12 / 131 (9.16%)
occurrences (all)	10	11	12
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 133 (6.77%)	11 / 129 (8.53%)	8 / 131 (6.11%)
occurrences (all)	10	12	17
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 133 (6.02%)	9 / 129 (6.98%)	6 / 131 (4.58%)
occurrences (all)	10	10	7
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 133 (0.75%)	9 / 129 (6.98%)	3 / 131 (2.29%)
occurrences (all)	1	9	3
General disorders and administration site conditions			

Oedema Peripheral			
subjects affected / exposed	1 / 133 (0.75%)	9 / 129 (6.98%)	7 / 131 (5.34%)
occurrences (all)	1	10	8
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 133 (4.51%)	16 / 129 (12.40%)	9 / 131 (6.87%)
occurrences (all)	6	17	10
Diarrhoea			
subjects affected / exposed	6 / 133 (4.51%)	10 / 129 (7.75%)	10 / 131 (7.63%)
occurrences (all)	6	12	12
Dyspepsia			
subjects affected / exposed	3 / 133 (2.26%)	9 / 129 (6.98%)	3 / 131 (2.29%)
occurrences (all)	3	10	4
Abdominal Pain Upper			
subjects affected / exposed	3 / 133 (2.26%)	8 / 129 (6.20%)	4 / 131 (3.05%)
occurrences (all)	3	9	5
Dysphagia			
subjects affected / exposed	7 / 133 (5.26%)	6 / 129 (4.65%)	4 / 131 (3.05%)
occurrences (all)	7	6	4
Skin and subcutaneous tissue disorders			
Rash Maculo-Papular			
subjects affected / exposed	0 / 133 (0.00%)	11 / 129 (8.53%)	6 / 131 (4.58%)
occurrences (all)	0	14	7
Rash			
subjects affected / exposed	4 / 133 (3.01%)	10 / 129 (7.75%)	2 / 131 (1.53%)
occurrences (all)	4	10	2
Psychiatric disorders			
Depression			
subjects affected / exposed	9 / 133 (6.77%)	11 / 129 (8.53%)	12 / 131 (9.16%)
occurrences (all)	9	11	12
Insomnia			
subjects affected / exposed	6 / 133 (4.51%)	5 / 129 (3.88%)	9 / 131 (6.87%)
occurrences (all)	6	5	9
Anxiety			
subjects affected / exposed	1 / 133 (0.75%)	7 / 129 (5.43%)	5 / 131 (3.82%)
occurrences (all)	1	7	5
Infections and infestations			

Viral Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 133 (4.51%)	7 / 129 (5.43%)	9 / 131 (6.87%)
occurrences (all)	6	7	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2013	Protocol amendments were implemented during the study with data remaining blinded throughout, i.e. no changes were data-driven. There were two key amendments: including a non-premeditated passage from a phase 2 to a demonstrative phase 2/3 design, requiring appropriate adjustment in sample size and statistical hypothesis (amendment dated 02 July 2013 following recruitment of 34/394 (9%) patients, of which none had completed the 48-week treatment period).
08 October 2014	Protocol amendments were implemented during the study with data remaining blinded throughout, i.e. no changes were data-driven. There were two key amendments including implementation of a prospectively tiered design based on aggressiveness phenotype (amendment dated 08 October 2014 following recruitment of 142/394 (36%) patients, of which 46/394 (12%) had completed the 48-week treatment period). This amendment involved categorization of patients according to ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) progression rate (ΔFS), calculated from disease-onset to baseline with a dichotomizing cut-off at 1.1 points/month. Accordingly, patients receiving masitinib 4.5 mg/kg/day with post-onset ΔFS<1.1 points/month (comprising an estimated 84% of the ALS population) were predefined as the primary efficacy population. All necessary information was available from patient records, meaning no retrospective data-collection was necessary, with stratification (minimization algorithm) implemented for the remaining (64%) patient recruitment to ensure balanced treatment-arms. This prospectively defined two-tiered approach defines a more homogenous target population (primary analysis), reducing variability and therefore sample size requirements, while concurrently permitting evaluation (secondary analysis) of the broader, more heterogeneous population. The rationale for this amendment assumed that heterogeneity in ALS disease aggressiveness reflects differing disease mechanisms, with dysregulated immunity being one possibly factor, leading to an unpredictable and likely divergent treatment-effect across the overall population. Furthermore, the right-skewed (positive-skew) characteristic of ΔFS histogram distributions was a common observation in clinical practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31280619

http://www.ncbi.nlm.nih.gov/pubmed/34457038