Clinical trial results:
A 24-WEEK WITH POSSIBLE EXTENSION, PROSPECTIVE, MULTICENTRE, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, 2-PARALLEL GROUP WITH A RANDOMIZATION 1:1, PHASE 3 STUDY TO COMPARE EFFICACY AND SAFETY OF MASITINIB AT 6 MG/KG/DAY TO PLACEBO IN TREATMENT OF PATIENTS WITH SMOULDERING SYSTEMIC, INDOLENT SYSTEMIC OR CUTANEOUS MASTOCYTOSIS WITH HANDICAP

Summary

EudraCT number	2008-000972-25
Trial protocol	FR CZ SK LV AT DE GB IT BG HU GR ES
Global end of trial date	02 November 2015

Results information

Result version number	v1 (current)
This version publication date	27 June 2020
First version publication date	27 June 2020

Trial information

Trial identification

Sponsor protocol code	AB06006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00814073
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AB Science
Sponsor organisation address	3 Avenue George V, Paris, France, 75008
Public contact	Regulatory affairs manager, AB Science, 33 147 20 97 83, DL_MEDICALWRITERS@ab-science.com
Scientific contact	Regulatory affairs manager, AB Science, 33 147209783, DL_MEDICALWRITERS@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	12 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to compare the safety and efficacy of masitinib to placebo in adult patients with documented severe smouldering or indolent systemic mastocytosis unresponsive to optimal symptomatic treatments.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. In the event of severe toxicity related to masitinib, treatment interruption or dose reduction was permitted according to the predefined criteria in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	France: 121
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Latvia: 1

Worldwide total number of subjects	223
EEA total number of subjects	192

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)	204
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited in this study between 19 February 2009 and 15 July 2015, at 50 sites in France, USA, Poland, India, Czech-Republic, Slovakia, Russia, Germany, Italy, United Kingdom, Switzerland, Spain and Greece.

Pre-assignment

Screening details:

A total of 253 subjects were screened of which 30 subjects were screen failures. Out of the 223 subjects selected for randomization, 3 subjects were not randomized due to the withdrawal of consent before treatment allocation. The overall population consisted of 220 subjects randomized in the study, 110 subjects in each treatment group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Masitinib

Arm description:

Subjects received daily doses of masitinib at the dose of 6 mg/kg/day, taken twice daily (morning, evening) with a meal (breakfast, dinner).

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 6 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. The tablet had to be taken in a sitting position with a large glass of water (250 ml, or 8 oz.).

Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

Subjects received matching placebo, taken twice daily (morning, evening) with a meal (breakfast, dinner). The administration of the matching placebo was similar as the experimental drug (masitinib).

Number of subjects in period 1[1]	Masitinib	Placebo
Started	110	110
Completed	68	97
Not completed	42	13
Consent withdrawn by subject	4	2
Adverse event, non-fatal	26	7
Lost to follow-up	2	2
Lack of efficacy	6	2
Protocol deviation	4	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 253 subjects were screened of which 30 subjects were screen failures. Out of the 223 subjects selected for randomization, 3 subjects were not randomized due to the withdrawal of consent before treatment allocation. The overall population consisted of 220 subjects randomized in the study, 110 subjects in each treatment group.

Baseline characteristics

Reporting groups	
Reporting group title	Masitinib
Reporting group description:	
Subjects received daily doses of masitinib at the dose of 6 mg/kg/day, taken twice daily (morning, evening) with a meal (breakfast, dinner).	
Reporting group title	Placebo
Reporting group description:	
Subjects received daily doses of matching placebo, taken twice daily (morning, evening) with a meal (breakfast, dinner).	

Reporting group values	Masitinib	Placebo	Total
Number of subjects	110	110	220
Age categorical			
Units: Subjects			
Adults (18-64 years)	105	99	204
From 65-84 years	5	10	15
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	45.71	47.24	
standard deviation	± 11.29	± 13.20	-
Gender categorical			
Units: Subjects			
Female	78	76	154
Male	32	34	66
Mastocytosis disease characteristics: c-Kit mutation status			
C-Kit mutation status was classified in 2 subgroups: 1. Clonal: Subjects with D816V c-Kit mutation in at least one organ in which c-Kit sequencing was performed. Several sequencing procedures could be performed for a given patient and for the same organ. D816V c-Kit mutation found in all the organs in which c-Kit sequencing was done were classified as D816V "pure". Subjects with D816V variant found in one organ and the WT allele in a second organ were classified as D816V "chimeric". 2. Wild-type: Subjects with no D816V c-Kit mutation in the organ(s) in which c-Kit sequencing was performed			
Units: Subjects			
Clonal:D816V pure	83	85	168
Clonal: D816V chimeric	12	10	22
Not Clonal: WT	11	12	23
Unknown status	4	3	7

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population was defined as all randomized patients with systemic mastocytosis, based on the CDR classification. Only patients with indolent systemic mastocytosis meeting the prospectively declared inclusion criteria specified in this amendment were included for final analysis—ie, the ITT population. Patients were classified according to the treatment-arm to which they were randomized, irrespective of the actual treatment received.	

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population is the population that was designated for the primary analysis, across all version of the protocol. The mITT dataset included all ITT patients with exclusion of patients withdrawing prematurely from the study during the protocol period (week 0 to week 24) for a well-documented non–failure cause. Six patients from the ITT population were excluded from the mITT population based on this definition.

Reporting group values	ITT	mITT	
Number of subjects	135	129	
Age categorical Units: Subjects			
Adults (18-64 years)	127	122	
From 65-84 years	7	6	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	47.10	47.14	
standard deviation	± 12.16	± 12.00	
Gender categorical Units: Subjects			
Female	95	91	
Male	40	38	
Mastocytosis disease characteristics: c-Kit mutation status			
C-Kit mutation status was classified in 2 subgroups: 1. Clonal: Subjects with D816V c-Kit mutation in at least one organ in which c-Kit sequencing was performed. Several sequencing procedures could be performed for a given patient and for the same organ. D816V c-Kit mutation found in all the organs in which c-Kit sequencing was done were classified as D816V "pure". Subjects with D816V variant found in one organ and the WT allele in a second organ were classified as D816V "chimeric". 2. Wild-type: Subjects with no D816V c-Kit mutation in the organ(s) in which c-Kit sequencing was performed			
Units: Subjects			
Clonal:D816V pure	104	100	
Clonal: D816V chimeric	17	16	
Not Clonal: WT	9	8	
Unknown status	5	5	

End points

End points reporting groups

Reporting group title	Masitinib

Reporting group description:

Subjects received daily doses of masitinib at the dose of 6 mg/kg/day, taken twice daily (morning, evening) with a meal (breakfast, dinner).

Reporting group title	Placebo

Reporting group description:

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

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population was defined as all randomized patients with systemic mastocytosis, based on the CDR classification. Only patients with indolent systemic mastocytosis meeting the prospectively declared inclusion criteria specified in this amendment were included for final analysis—ie, the ITT population. Patients were classified according to the treatment-arm to which they were randomized, irrespective of the actual treatment received.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population is the population that was designated for the primary analysis, across all version of the protocol. The mITT dataset included all ITT patients with exclusion of patients withdrawing prematurely from the study during the protocol period (week 0 to week 24) for a well-documented non–failure cause. Six patients from the ITT population were excluded from the mITT population based on this definition.

Primary: Cumulative response on four handicaps (4H75%)

End point title	Cumulative response on four handicaps (4H75%)

End point description:

Cumulative response in at least one of 4 severe baseline handicaps from among pruritus, flushes, depression, or asthenia (referred to as 4H75) was equal to number of actual responses divided by total number of possible responses, between weeks 8 & 24. Missing data were considered as failure (MDF) and the p-value was obtained via a re-randomization (10,000 replicate) test. Response on a handicap defined as: an improvement with respect to the baseline values of ≥ 75% for pruritus, flushes, depression and asthenia, with handicaps at baseline being defined as pruritus score ≥ 9, number of flushes/week ≥ 8, HAMD-17 score ≥ 19, and Fatigue Impact Scale ≥ 75. To account for handicap imbalances between groups, observations for each handicap were weighted based on total number of patients with handicap and between-group difference in that handicap. Hence, total number of possible handicap observations for each group was equivalent.

Population analysed : mITT (129 subjects)

End point type	Primary

End point timeframe:

Up to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[1]	62[2]		
Units: percent				
number (not applicable)				
Main analysis	18.7	7.4		
Sensitivity of main analysis	18.7	7.5		

Notes:

[1] - mITT population

[2] - mITT population

Statistical analyses

Statistical analysis title	Re-randomization p-value

Statistical analysis description:

Main analysis: The difference between treatment groups (masitinib vs placebo) was tested using a Generalized Estimating Equations (GEE) model using Logit as the link function. This statistical model included all the responses (yes/no) on handicaps observed from week 8 to week 24; thus, from 5 to 20 responses per patient. Correlations between measurements within a subject were taken into account by using an exchangeable correlation matrix structure as hypothesized in the sample size calculation.

Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0076
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	10.83

Statistical analysis title	Re-randomization p-value

Statistical analysis description:

Sensitivity analysis: Same as main analysis but with Last Observation Carried Forward (LOCF) then with Observed Cases (data remain missing) instead of missing = failure if data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit.

Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0079
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	10.84

Secondary: Cumulative response on 3 handicaps (Pruritus or Flush or Depression): 3H75%

End point title	Cumulative response on 3 handicaps (Pruritus or Flush or Depression): 3H75%

End point description:

The analysis on response 3 handicaps (pruritus + flushes + depression) was done on the patients with handicap on pruritus and/or flushes and/or depression at baseline. The cumulative response by patient*handicap on pruritus and/or flushes and/or depression, among patients with at least one of these handicaps at baseline.
1. Response on a handicap defined as an improvement with respect to the baseline values ≥ 75% for pruritus and/or flushes and/or depression.
2. Handicaps at baseline defined as: pruritus score ≥ 9, number of flushes per week ≥ 8, and HAMD-17 score ≥ 19.
For every patient the response at each study visit (5 visits from week 8 to week 24) was calculated on each handicap present at baseline. Thus, from 5 to 15 responses were calculated per patient: 5 if the patient presented only 1 handicap at baseline (corresponding to the 5 visits) and 15 if the patient presented all 3 handicaps at baseline.

Population analysed : mITT population (129 subjects)

End point type	Secondary

End point timeframe:

From Week 8 to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[3]	62[4]		
Units: percent				
number (not applicable)				
Main Analysis	24.7	9.8		
Sensitivity analysis	32.4	10.4		

Notes:

[3] - mITT population

[4] - mITT population

Statistical analyses

Statistical analysis title	Observed p-value (GEE Model)
Comparison groups	Masitinib v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0071
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	6.92

Secondary: Cumulative response on 2 handicaps (Pruritus or Flush): 2H75%

End point title	Cumulative response on 2 handicaps (Pruritus or Flush): 2H75%

End point description:

The analysis on response 2 handicaps was done on the patients with handicap on pruritus and/or flushes at baseline.
The response on 2 handicaps (pruritus + flushes) is the cumulative response by patient*handicap on pruritus and/or flushes, among patients with either of these handicaps at baseline.
- Response was defined as an improvement with respect to the baseline values ≥ 75% for pruritus and/or flushes.
- Handicap at baseline was defined as: pruritus score ≥ 9 and flushes per week ≥ 8.

For every patient the response at each study visit (5 visits from week 8 to week 24) was calculated on each handicap present at baseline (from among pruritus and flushes) as defined above. Thus, from 5 to 10 responses were calculated per patient: 5 if the patient presented only 1 handicap at baseline (corresponding to the 5 visits) and 10 if the patient presented both handicaps at baseline (corresponding to the 2 handicaps * the 5 visits).

Population analysed : mITT population (129 subjects)

End point type	Secondary

End point timeframe:

Week 8 to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[5]	62[6]		
Units: percent				
number (not applicable)	27.2	10.7		

Notes:

[5] - mITT population

[6] - mITT population

Statistical analyses

Statistical analysis title	Observed p-value (GEE Model)
Comparison groups	Masitinib v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.038
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	6.55

Secondary: Cumulative response on pruritus among patients with this handicap at baseline

End point title	Cumulative response on pruritus among patients with this handicap at baseline

End point description:

The pruritus score analysis endpoint is the cumulative response on pruritus among patients with this handicap at baseline/
- Response was defined as an improvement with respect to the baseline values ≥ 75% for pruritus.
- Handicap at baseline was defined as: pruritus score ≥ 9.

For patients presenting this handicap at baseline (i.e. pruritus score ≥ 9), the response at each study visit (5 visits from week 8 to week 24) was calculated. Thus, 5 responses were calculated per patient.

Population analysed : mITT population (129 subjects)

End point type	Secondary
End point timeframe:	
Week 8 to Week 24	

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[7]	62[8]		
Units: percent				
number (not applicable)	22.0	7.3		

Notes:

[7] - mITT population

[8] - mITT population

Statistical analyses

Statistical analysis title	Observed p-value (GEE Model)
Comparison groups	Masitinib v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0322
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	8.88

Secondary: Long-term efficacy: Cumulative response rates (4H75%, 3H75% and pruritus) from W8 to W96

End point title	Long-term efficacy: Cumulative response rates (4H75%, 3H75% and pruritus) from W8 to W96

End point description:

This endpoint evaluated the sustainability of response in the long term, including the extension period. The following responses by patient*handicap were analyzed on the extension period up to W96 (2 years).

- Response on 4 handicaps (4H75%) up to week 96 (2 years)
- Response on 3 handicaps (3H75%) up to week 96 (2 years)
- Response on pruritus up to week 96 (2 years)

Population analysed : mITT population (129 subjects)

End point type	Secondary

End point timeframe:

Week 8 to Week 96

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[9]	62[10]		
Units: percent				
number (not applicable)				
4H75%	16.8	6.8		
3H75%	21.8	8.3		
Pruritus	19.2	6.2		

Notes:

[9] - mITT population

[10] - mITT population

Statistical analyses

Statistical analysis title	Observed p-value (GEE Model): 4H75%
Comparison groups	Masitinib v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0156
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	9.7

Statistical analysis title	Observed p-value (GEE Model): 3H75%
Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0031
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	6.81

Statistical analysis title	Observed p-value (GEE Model): pruritis
Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0338
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	8.59

Secondary: Efficacy evaluation based on objective markers of mast cell activity:

Change from baseline in tryptase level

End point title	Efficacy evaluation based on objective markers of mast cell activity: Change from baseline in tryptase level

End point description:

Tryptase is a measure of the burden of mast cells and of the activity of mast cells that can change in a 6-month period. It was analyzed for patients with a baseline level of greater than 20 µg/L.
The absolute change from baseline in serum tryptase level to last visit ([W0-W24 period]) in the mITT population is presented.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[11]	42[12]		
Units: microgram(s)/litre				
arithmetic mean (standard deviation)	-10 (± 46.9)	2.7 (± 20.0)		

Notes:

[11] - Only subjects with tryptase level ≥ 20 micro/L at baseline and Week 24 data (mITT population).

[12] - Only subjects with tryptase level ≥ 20 micro/L at baseline and Week 24 data (mITT population).

Statistical analyses

Statistical analysis title	Absolute change from baseline
Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0267
Method	GEE model

Other pre-specified: Cumulative response on flushes among patients with the handicap at baseline

End point title	Cumulative response on flushes among patients with the handicap at baseline

End point description:

For patients presenting this handicap at baseline (i.e. number of flushes per week ≥ 8), the response at each study visit (5 visits from week 8 to week 24) was calculated. Thus, 5 responses were calculated per patient. Response was defined as an improvement ≥ 75% at the visit.

Population analysed : mITT population (129 subjects)

End point type	Other pre-specified

End point timeframe:

Week 8 to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[13]	62[14]		
Units: percent weight/weight				
number (not applicable)	39.9	19.0		

Notes:

[13] - mITT population

[14] - mITT population

Statistical analyses

Statistical analysis title	Odds ration (GEE model)
Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	10.68

Other pre-specified: Cumulative response on depression among patients with this handicap at baseline

End point title	Cumulative response on depression among patients with this handicap at baseline

End point description:

For patients presenting this handicap at baseline (i.e. HAMD-17 ≥ 19), the response at each study visit (5 visits from week 8 to week 24) was calculated. Thus, 5 responses were calculated per patient. Response was defined as an improvement ≥ 75% at the visit.

Population analysed : mITT population (129 subjects)

End point type	Other pre-specified

End point timeframe:

Week 8 to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[15]	62[16]		
Units: percent				
number (not applicable)	18.6	7.6		

Notes:

[15] - mITT population

[16] - mITT population

Statistical analyses

Statistical analysis title	Odds ratio (GEE Model)
Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	11.08

Other pre-specified: Cumulative response on asthenia (FIS) among patients with this handicap at baseline

End point title	Cumulative response on asthenia (FIS) among patients with this handicap at baseline

End point description:

For patients presenting this handicap (asthenia) at baseline (i.e. FIS ≥ 75), the response at each study visit (5 visits from week 8 to week 24) was calculated. Thus, 5 responses were calculated per patient. Response was defined as an improvement ≥ 75% at the visit.

Population analysed : mITT population (129 subjects)

End point type	Other pre-specified

End point timeframe:

Week 8 to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[17]	62[18]		
Units: percent				
number (not applicable)	7.7	3.2		

Notes:

[17] - mITT population

[18] - mITT population

Statistical analyses

Statistical analysis title	Observed p-value (GEE Model)
Comparison groups	Masitinib v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	4.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	23.44

Other pre-specified: Quality of life: 75% improvement on the OPA score

End point title	Quality of life: 75% improvement on the OPA score

End point description:

OPA score corresponds to the 53rd question of the AFIRMM questionnaire. For the patients presenting the handicap at Baseline (ie. OPA "severe" or "intolerable"), the response at each study visit (5 visits from week 0 to week 24) was calculated. Response being defined as an OPA "normal" or "light" at the visit. If data were not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data were considered as failure (missing = failure as primary analysis). So, 5 responses were calculated by patient.
Improvement on quality of life was measured by a decrease by ≥75% in the OPA score (exploratory analysis). OPA score is a unidimensional questionnaire on the patient's assessment of pain, general health status and impact on life.

Population analysed: mITT population (129 subjects)

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[19]	62[20]		
Units: percent				
number (not applicable)	3.7	0.6		

Notes:

[19] - mITT population

[20] - mITT population

Statistical analyses

Statistical analysis title	Response rate for OPA score
Comparison groups	Masitinib v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	6.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	56.13

Other pre-specified: Long-term measures of mast cell activity nullification: Response on UP assessment: "Darier's sign" disappearance

End point title	Long-term measures of mast cell activity nullification: Response on UP assessment: "Darier's sign" disappearance

End point description:

"Darier's sign" disappearance (Yes/No) for subjects with "Darier's sign" at baseline, was analysed at different time points (Up to Week 24).
The percentage of subjects in whom the Darier's sign disappeared is presented for the mITT population.

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[21]	37[22]		
Units: percent				
number (not applicable)	18.9	2.7		

Notes:

[21] - Only subjects from mITT population with Darier's sign at baseline are included.

[22] - Only subjects from mITT population with Darier's sign at baseline are included.

Statistical analyses

Statistical analysis title	Observed p-value (GEE Model)
Comparison groups	Placebo v Masitinib
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0187
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	6.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	41.45

Other pre-specified: Long-term measures of mast cell activity nullification: Response on urticaria pigmentosa (UP)

End point title	Long-term measures of mast cell activity nullification: Response on urticaria pigmentosa (UP)

End point description:

Masitinib demonstrated activity on the objective long-term markers of mast cell activation including urticaria pigmentosa (UP) is presented here. Relative change from baseline in the body surface area covered by the UP corrected with Wallace formula is summarized for the mITT population (129 subjects).
The data are presented as percent change from baseline for the overall period (up to Week 24).

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to Week 24

End point values	Masitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[23]	36[24]		
Units: percent				
number (not applicable)	-12.3	15.9		

Notes:

[23] - Only those subjects from mITT population with values at Baseline and at Week 24 are included.

[24] - Only those subjects from mITT population with values at Baseline and at Week 24 are included.

Statistical analyses

Statistical analysis title	Observed p-value
Comparison groups	Masitinib v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.021
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	6.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	56.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main period (up to Week 24)

Adverse event reporting additional description:

Adverse events have been reported for Overall population (safety population + Others) which includes all patients with severe systemic mastocytosis as well as other mastocytosis patients (non severe systemic mastocytosis and cutaneous mastocytosis), who took at least one dose of study medication (masitinib or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13

Reporting groups

Reporting group title	Masitinib

Reporting group description:

Subjects received daily doses of masitinib at the dose of 6 mg/kg/day, taken once daily (morning) or twice daily (morning/evening) with a meal (breakfast/dinner).

Reporting group title	Placebo

Reporting group description:

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

Serious adverse events	Masitinib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 110 (29.09%)	15 / 110 (13.64%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 110 (2.73%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic oedema			

subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type I hypersensitivity			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactoid reaction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			

subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Trigeminal neuralgia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 110 (2.73%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 110 (2.73%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glossitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			

subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichenoid keratosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			

subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 110 (1.82%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis acute			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Masitinib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 110 (99.09%)	109 / 110 (99.09%)	
Vascular disorders			
Flushing			
subjects affected / exposed	10 / 110 (9.09%)	2 / 110 (1.82%)	
occurrences (all)	13	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 110 (26.36%)	20 / 110 (18.18%)	
occurrences (all)	36	22	
Oedema peripheral			

subjects affected / exposed	20 / 110 (18.18%)	8 / 110 (7.27%)	
occurrences (all)	26	10	
Face oedema			
subjects affected / exposed	14 / 110 (12.73%)	2 / 110 (1.82%)	
occurrences (all)	15	2	
Fatigue			
subjects affected / exposed	13 / 110 (11.82%)	20 / 110 (18.18%)	
occurrences (all)	19	22	
Pyrexia			
subjects affected / exposed	10 / 110 (9.09%)	1 / 110 (0.91%)	
occurrences (all)	12	1	
Oedema			
subjects affected / exposed	6 / 110 (5.45%)	1 / 110 (0.91%)	
occurrences (all)	8	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 110 (10.00%)	6 / 110 (5.45%)	
occurrences (all)	12	6	
Dyspnoea			
subjects affected / exposed	7 / 110 (6.36%)	6 / 110 (5.45%)	
occurrences (all)	7	7	
Psychiatric disorders			
Depression			
subjects affected / exposed	11 / 110 (10.00%)	7 / 110 (6.36%)	
occurrences (all)	11	7	
Insomnia			
subjects affected / exposed	11 / 110 (10.00%)	10 / 110 (9.09%)	
occurrences (all)	11	11	
Sleep disorder			
subjects affected / exposed	4 / 110 (3.64%)	6 / 110 (5.45%)	
occurrences (all)	4	7	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	24 / 110 (21.82%)	9 / 110 (8.18%)	
occurrences (all)	43	15	
Blood glucose increased			

subjects affected / exposed	23 / 110 (20.91%)	19 / 110 (17.27%)		
occurrences (all)	31	28		
Blood triglycerides increased				
subjects affected / exposed	20 / 110 (18.18%)	23 / 110 (20.91%)		
occurrences (all)	22	35		
Alanine aminotransferase increased				
subjects affected / exposed	21 / 110 (19.09%)	6 / 110 (5.45%)		
occurrences (all)	33	8		
Blood phosphorus decreased				
subjects affected / exposed	21 / 110 (19.09%)	6 / 110 (5.45%)		
occurrences (all)	29	7		
Aspartate aminotransferase increased				
subjects affected / exposed	19 / 110 (17.27%)	5 / 110 (4.55%)		
occurrences (all)	26	7		
White blood cell count decreased				
subjects affected / exposed	15 / 110 (13.64%)	6 / 110 (5.45%)		
occurrences (all)	27	6		
Blood alkaline phosphatase increased				
subjects affected / exposed	15 / 110 (13.64%)	10 / 110 (9.09%)		
occurrences (all)	24	11		
Gamma-glutamyltransferase increased				
subjects affected / exposed	15 / 110 (13.64%)	16 / 110 (14.55%)		
occurrences (all)	19	23		
Lymphocyte count decreased				
subjects affected / exposed	11 / 110 (10.00%)	6 / 110 (5.45%)		
occurrences (all)	15	6		
Blood bilirubin increased				
subjects affected / exposed	12 / 110 (10.91%)	8 / 110 (7.27%)		
occurrences (all)	15	14		
Weight decreased				
subjects affected / exposed	11 / 110 (10.00%)	2 / 110 (1.82%)		
occurrences (all)	11	2		
Neutrophil count decreased				

subjects affected / exposed	8 / 110 (7.27%)	3 / 110 (2.73%)	
occurrences (all)	14	3	
Blood cholesterol increased			
subjects affected / exposed	7 / 110 (6.36%)	16 / 110 (14.55%)	
occurrences (all)	8	25	
Blood calcium decreased			
subjects affected / exposed	7 / 110 (6.36%)	3 / 110 (2.73%)	
occurrences (all)	8	3	
Lymphocyte count increased			
subjects affected / exposed	4 / 110 (3.64%)	6 / 110 (5.45%)	
occurrences (all)	4	7	
Blood sodium decreased			
subjects affected / exposed	1 / 110 (0.91%)	6 / 110 (5.45%)	
occurrences (all)	1	7	
Blood calcium increased			
subjects affected / exposed	2 / 110 (1.82%)	10 / 110 (9.09%)	
occurrences (all)	2	13	
Neutrophil count increased			
subjects affected / exposed	0 / 110 (0.00%)	6 / 110 (5.45%)	
occurrences (all)	0	7	
Cardiac disorders			
Palpitations			
subjects affected / exposed	7 / 110 (6.36%)	5 / 110 (4.55%)	
occurrences (all)	7	6	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 110 (22.73%)	31 / 110 (28.18%)	
occurrences (all)	28	39	
Paraesthesia			
subjects affected / exposed	8 / 110 (7.27%)	3 / 110 (2.73%)	
occurrences (all)	11	7	
Dizziness			
subjects affected / exposed	5 / 110 (4.55%)	8 / 110 (7.27%)	
occurrences (all)	6	10	
Sciatica			

subjects affected / exposed	1 / 110 (0.91%)	6 / 110 (5.45%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 110 (20.00%)	12 / 110 (10.91%)	
occurrences (all)	36	19	
Lymphopenia			
subjects affected / exposed	16 / 110 (14.55%)	8 / 110 (7.27%)	
occurrences (all)	31	14	
Neutropenia			
subjects affected / exposed	12 / 110 (10.91%)	13 / 110 (11.82%)	
occurrences (all)	17	16	
Leukopenia			
subjects affected / exposed	6 / 110 (5.45%)	6 / 110 (5.45%)	
occurrences (all)	7	6	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 110 (3.64%)	7 / 110 (6.36%)	
occurrences (all)	4	7	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	28 / 110 (25.45%)	7 / 110 (6.36%)	
occurrences (all)	32	8	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	51 / 110 (46.36%)	26 / 110 (23.64%)	
occurrences (all)	63	34	
Diarrhoea			
subjects affected / exposed	50 / 110 (45.45%)	26 / 110 (23.64%)	
occurrences (all)	67	31	
Abdominal pain			
subjects affected / exposed	24 / 110 (21.82%)	17 / 110 (15.45%)	
occurrences (all)	27	19	
Vomiting			
subjects affected / exposed	24 / 110 (21.82%)	15 / 110 (13.64%)	
occurrences (all)	28	19	
Abdominal pain upper			

subjects affected / exposed	7 / 110 (6.36%)	10 / 110 (9.09%)	
occurrences (all)	7	10	
Constipation			
subjects affected / exposed	4 / 110 (3.64%)	11 / 110 (10.00%)	
occurrences (all)	4	11	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	23 / 110 (20.91%)	14 / 110 (12.73%)	
occurrences (all)	30	15	
Rash			
subjects affected / exposed	15 / 110 (13.64%)	4 / 110 (3.64%)	
occurrences (all)	18	6	
Dry skin			
subjects affected / exposed	10 / 110 (9.09%)	1 / 110 (0.91%)	
occurrences (all)	11	1	
Eczema			
subjects affected / exposed	6 / 110 (5.45%)	2 / 110 (1.82%)	
occurrences (all)	7	2	
Urticaria			
subjects affected / exposed	6 / 110 (5.45%)	2 / 110 (1.82%)	
occurrences (all)	7	2	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	8 / 110 (7.27%)	5 / 110 (4.55%)	
occurrences (all)	9	6	
Haematuria			
subjects affected / exposed	7 / 110 (6.36%)	7 / 110 (6.36%)	
occurrences (all)	8	7	
Leukocyturia			
subjects affected / exposed	5 / 110 (4.55%)	7 / 110 (6.36%)	
occurrences (all)	6	8	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	29 / 110 (26.36%)	8 / 110 (7.27%)	
occurrences (all)	33	13	
Arthralgia			

subjects affected / exposed	15 / 110 (13.64%)	18 / 110 (16.36%)	
occurrences (all)	19	21	
Back pain			
subjects affected / exposed	9 / 110 (8.18%)	12 / 110 (10.91%)	
occurrences (all)	10	12	
Bone pain			
subjects affected / exposed	9 / 110 (8.18%)	6 / 110 (5.45%)	
occurrences (all)	9	8	
Myalgia			
subjects affected / exposed	9 / 110 (8.18%)	8 / 110 (7.27%)	
occurrences (all)	10	9	
Pain in extremity			
subjects affected / exposed	8 / 110 (7.27%)	5 / 110 (4.55%)	
occurrences (all)	10	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 110 (10.91%)	7 / 110 (6.36%)	
occurrences (all)	12	8	
Bronchitis			
subjects affected / exposed	3 / 110 (2.73%)	7 / 110 (6.36%)	
occurrences (all)	3	8	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	19 / 110 (17.27%)	18 / 110 (16.36%)	
occurrences (all)	25	24	
Hypertriglyceridaemia			
subjects affected / exposed	13 / 110 (11.82%)	21 / 110 (19.09%)	
occurrences (all)	16	26	
ANOREXIA			
subjects affected / exposed	10 / 110 (9.09%)	2 / 110 (1.82%)	
occurrences (all)	10	2	
Hypophosphataemia			
subjects affected / exposed	8 / 110 (7.27%)	2 / 110 (1.82%)	
occurrences (all)	9	2	
Hypercholesterolaemia			

subjects affected / exposed	7 / 110 (6.36%)	16 / 110 (14.55%)	
occurrences (all)	9	17	
Hypoglycaemia			
subjects affected / exposed	2 / 110 (1.82%)	11 / 110 (10.00%)	
occurrences (all)	3	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2013	To increase the benefit/risk ratio following discussion with EMA (Scientific advice) for indications in non-oncology, the protocol was amended to include only mastocytosis patients with smoldering systemic and indolent systemic mastocytosis. The inclusion criteria for Handicaps were strengthened (Pruritus score from ≥ 6 to ≥ 9; Flushes frequency per week from ≥ 7 to ≥ 8 ; Hamilton score from ≥ 14 to ≥ 19). Number of patients was changed to 150 with documented smoldering or indolent systemic mastocytosis with a severe handicap (75 patients per group). Limit of hemoglobin level was added to inclusion criteria in order to avoid enrolling anemic patients. The threshold of liver enzymes for the inclusion of the patients was modified to better stick to the CTCAE classification (mild / grade 1 liver enzymes increase is allowed at the inclusion). The threshold of albumin has been increased to avoid hypoalbuminia that could potentially interfere with PK of masitinib. The age limit has been set in order to avoid enrolling elderly patients in this indication. BMI level and minimal weight has been set. Subsequent dose reductions in case of occurrence of Adverse Event was allowed and specified. Specific surveillance for adverse events was clarified and risk management plans were updated.
13 February 2015	Protocol version 7.0 including amendment No. 6 incorporated the following changes: - Clarification of contraceptive methods that must be used by patients during the study and for 3 months after the last treatment intake was added for male and female patients. - Maximum IMP exposure duration was limited to 2 years. After 2 years, patients were allowed to continue the treatment on a case by case basis only if a documented favorable benefit/risk ratio is established by the investigator. - New safety rules: Chest X-ray removed from screening; if chest X-ray performed within 3 months prior to baseline, not required at baseline. Risk management plan/procedures for carcinogenicity as potential adverse events were supplemented with NMP test at the baseline visit, every 12 weeks, and at the final visit; frequency of urinary cytology was increased to every 12 weeks and specific search for transitional and/or malignant cells was emphasized. - Hormonal work up to address the risk of uterine carcinoma was added. - Prescription of broad-spectrum antibiotherapy was considered and executed by clinical study physicians in case subjects will present themselves with signs or symptoms suggesting the occurrence of severe neutropenia and/or severe skin toxicity. - Information about the AB Science pregnancy surveillance program (for confirmed pregnancy). - Frequency for (optional depending on patients` consent) semen analysis for male patients was increased to the baseline visit, every 12 weeks, and final visit. Live attenuated vaccines were added to prohibited concomitant treatments. - Pelvic ultrasound in women of childbearing potential added to safety assessment at baseline and final visit. A serum pregnancy test was added to screening procedures. Introduced rebound evaluation assessment of symptoms after treatment discontinuation. Updated severe skin toxicity questionnaire.

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/28069279