Supplement to 'Efficacy and Safety of Masitinib in Progressive Forms of Multiple Sclerosis: A Randomized, Phase 3, Clinical Trial'

This appendix has been provided by the authors to give readers additional information.

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eMETHODS SUPPLEMENT

Protocol amendments for study AB07002

There were two major protocol amendments during the conduct of study AB07002. One amendment was related to the introduction of an independent parallel group in which patients received placebo or masitinib as a titrated treatment regimen. Each parallel group was effectively run as a separate study, distinct in matters of statistical analysis and control-arm. The other amendment was related to a change in the primary endpoint that was necessary for alignment with emergent recommended regulatory guidance on clinical investigations for treatment of MS. It is considered that the nature of these amendments will not have introduced any bias or ambiguity to interpretation of the study's key findings; no changes were data-driven and the introduction of a second independent parallel group had no impact on the data acquisition or analysis of the original parallel group.

i. Study AB07002 initially planned to enroll patients into a 6 mg/kg/day (starting dose) treatment-arm. However, following analysis of severe adverse event (AE) and discontinuation rates for all non-oncology clinical trials (not including the current AB07002 study), it was shown that single agent masitinib starting at a dose of 3 or 4.5 mg/kg/day had an incidence similar to placebo, whereas single agent masitinib starting at a dose of 6 mg/kg/day showed increased frequency of certain events (for example, neutropenia and skin toxicity) with respect to placebo (unpublished data). A related analysis also revealed that titrated doses from 3 or 4.5 mg/kg/day to 6 mg/kg/day improved tolerability and minimized discontinuations during the first 3 months of treatment when compared with a stable starting dose of 6 mg/kg/day. Indeed, this titrated dose regimen showed a similar discontinuation rate as when maintaining a stable dose of 3 or 4.5 mg/kg/day during and after the first 3 months.
An amendment to the protocol of study AB07002 was therefore an unavoidable consequence of these developments and was made with an objective to improve the benefit/risk balance. Change was implemented over two protocol versions. First, it was decided to terminate the 6 mg/kg/day (starting dose) treatment-arm (as per protocol version 5.0; May, 2012). Second, there was the addition of an independent parallel group in which patients were randomly assigned (1:2) to receive placebo or masitinib as a titrated treatment regimen, i.e. an initial dose of 4.5 mg/kg/day for 12 weeks that was then titrated to a planned dose of 6.0 mg/kg/day (as per protocol version 6.0; August, 2013).

ii. Study AB07002 initially planned to use the endpoint of Multiple Sclerosis Functional Composite (MSFC) for its primary analysis. However, during the study, the European Medicines Agency (EMA) 'Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis'* was issued in which use of the Kurtzke's Expanded Disability Status Scale (EDSS) as primary endpoint was clearly recommended. It was also stated that MSFC should be used as secondary measurement of disability. This guideline was adopted by Committee for Medicinal Products for Human Use (CHMP) in March 2015. Following this development, it was decided to change the primary analysis from an endpoint based on Multiple Sclerosis Functional Composite (MSFC) to an endpoint based on Expanded Disability Status Scale (EDSS). Analysis based on MSFC was consequently reassigned as a secondary endpoint. This change was implemented in the last protocol amendment (version 9; Sept 2016).

* European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/771815/2011, Rev. 2. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-multiple-sclerosis (accessed 09 September 2020).

eMETHODS SUPPLEMENT

Patient eligibility for study AB07002

Full patient eligibility criteria for study AB07002 (as per the amended protocol version 9.0) are presented below.

Inclusion criteria

1. Patient suffering from either primary progressive or secondary progressive multiple sclerosis without relapse within 2 years before inclusion according to the revised McDonald's criteria
2. Patient with EDSS score of [2.0 to 6.0] inclusive at baseline
3. Patient who had an EDSS score progression ≥ 1 point within 2 years before inclusion
4. Patient with normal organ function defined as:
   - Absolute neutrophils count (ANC) ≥ 2 x 10^9/L
   - Hemoglobin ≥ 10 g/dL
   - Platelets (PTL) ≥ 100 x 10^9/L
   - AST and ALT ≤ 3 ULN
   - Bilirubin ≤ 1.5x ULN
   - Creatinine clearance > 60 mL/min (Cockcroft and Gault formula)
   - Albuminemia > 1 x LLN
   - Proteinuria < 30 mg/dL (1+) on dipstick; in case of the proteinuria ≥1+ on the dipstick 24 hours proteinuria must be < 1.5 g/24 hours
   - Negative urinary cytology
5. Male or female patient aged between 18 and 75 years old, with a weight > 50 kg and BMI between 18 and 35 kg/m².
6. Patient able to understand the patient card and to follow the patient card procedures in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity.
7. Contraception
   - Female patient of childbearing potential (entering the study after a menstrual period and who has a negative pregnancy test), who agrees to use a highly effective method of contraception and an acceptable method of contraception by her male partner during the study and for 3 months after the last treatment intake.
   - Male patient with a female partner of childbearing potential who agrees to use a highly effective method of contraception and an acceptable method of contraception by his female partner during the study and for 3 months after the last treatment intake OR who agrees to use an acceptable method of contraception and a highly effective method of contraception by his female partner during the study and for 3 months after the last treatment intake.
   - Highly effective methods of contraception include:
     - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
     - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
     - Intrauterine device (IUD)
     - Intrauterine hormone-releasing system (IUS)
     - Bilateral tubal occlusion
     - Vasectomized male (azoospermia assessed medically)
     - Sexual abstinence (Its reliability should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
   - Acceptable methods of contraception include:
     - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
     - Male or female condom with or without spermicide
     - Cap, diaphragm or sponge with spermicide
8. Female patient of childbearing potential must have a negative pregnancy test at screening and baseline
9. Patient able and willing to comply with study procedures as per protocol
10. Patient able to understand, sign, and date the written informed consent form at screening visit prior to any protocol-specific procedures

Exclusion criteria

1. Patient suffering from a disease other than MS that would better explain the patient's neurological clinical signs and symptoms and/or MRI lesions
2. Patient who had a major surgery within 2 weeks of study entry
3. Patient with history of primary malignancy < 5 years, except treated basal cell skin cancer or cervical carcinoma in situ
4. Patient presenting with cardiac disorders defined by at least one of the following conditions:
   - Patient with recent cardiac history (within 6 months) of:
     - Acute coronary syndrome
     - Acute heart failure (class III or IV of the NYHA classification)
     - Significant ventricular arrhythmia (persistent ventricular tachycardia, ventricular fibrillation, resuscitated sudden death)
   - Patient with cardiac failure class III or IV of the NYHA classification
   - Patient with severe conduction disorders which are not prevented by permanent pacing (atrio-ventricular block 2 and 3, sino-atrial block)
   - Syncope without known etiology within 3 months
   - Uncontrolled severe hypertension, according to the judgment of the investigator, or symptomatic hypertension
5. Patient with any severe and/or uncontrolled medical condition
6. Patient with a known diagnosis of human immunodeficiency virus (HIV) infection
7. Patient with known hepatitis B, hepatitis C or tuberculosis
8. Pregnant or nursing female
9. Patient with history of poor compliance or history of drug/alcohol abuse, or excessive alcohol beverage consumption that would interfere with the ability to comply with the study protocol, or current or past psychiatric disease that might interfere with the ability to comply with the study protocol or give informed consent
10. Patient with any condition or concurrent medical events, including any clinically significant deviations from reference ranges in laboratory test, that on the opinion of the physician could be detrimental to the subjects
11. Patients requiring medication, which are prohibited in the current protocol, including corticosteroids used other than defined by the protocol, chemotherapies, immunomodulators or immunosuppressors, investigational drugs, live attenuated vaccines, drugs known to be at high risk of Stevens-Johnson syndrome.

Previous treatment wash-out criteria

12. Previous treatment with immunomodulators and/or immunosuppressors treatments including azathioprine, cladribine, cyclophosphamide, cyclosporine, methotrexate, mitoxantrone, natalizumab, mycophenolate mofetil, hematopoietic stem cell transplantation, plasma exchange or total lymphoid irradiation within 24 weeks prior to baseline
13. Interferon, glatiramer acetate, IV infusion of immunoglobulins or monthly bolus IV corticosteroids within 12 weeks prior to baseline
14. Treatment with any oral or systemic corticosteroids or adrenocorticotropic hormone (ACTH) within 4 weeks prior to baseline
15. Treatment with any investigational drug within 12 weeks prior to baseline

eMETHODS SUPPLEMENT

Dose adjustment procedures for the 4.5 mg/kg/day masitinib parallel group of study AB07002

Subjects enrolled received a total daily dose of 4.5 mg/kg masitinib or a matching placebo, to be taken during meals as shown below.

		4.5 mg/kg/day		
Patient's weight in kg		**Daily dose (mg)**	**Morning* (mg)**	**Evening* (mg)**
>50.0	≤55.5	200	100	100
> 55.5	77.7	300	100	200
> 77.7	99.9	400	200	200
> 99.9		500	200	200+100

**am: the tablets should be taken during breakfast; pm: the tablets should be taken during the dinner*

In the event of moderate or severe toxicity related to masitinib, treatment interruption or dose reduction was permitted according to predefined criteria.

For the 4.5 mg/kg/day subgroup, if a dose reduction was necessary the patient continued to receive masitinib at 3.0 mg/kg/day. The dose of study treatment to be administered according to patient's weight, after a dose reduction to 3.0 mg/kg/day (from randomized dose of 4.5 mg/kg/day), is shown below.

		4.5 → 3 mg/kg/day		
Patient's weight in kg		**Daily dose (mg)**	**Morning* (mg)**	**Evening* (mg)**
>50.0	≤55.5	STOP		
> 55.5	83.3	200	100	100
> 83.3		300	100	200

**am: the tablets should be taken during breakfast; pm: the tablets should be taken during the dinner*

Described below is the general dose reduction risk management plan for an adverse event suspected to be related to study treatment. Study treatment refers to masitinib or its matching placebo.

- At the first occurrence of moderate adverse event, study treatment (4.5 mg/kg/day) will be interrupted until said adverse event has returned to baseline value or mild intensity and then resumed at the same dose level.
- If the same moderate adverse event re-occurs, study treatment (4.5 mg/kg/day) will be interrupted until said adverse event has returned to baseline or mild intensity and then resumed with a dose reduction of 1·5 mg/kg/day.
- If the same moderate adverse event re-occurs after dose reduction, study treatment must be definitely discontinued
- In case of severe adverse event, study treatment (4.5 mg/kg/day) will be interrupted until said adverse event has returned to baseline level or mild intensity and then resumed with a dose reduction of 1·5 mg/kg/day.
- In case of severe adverse event re-occurs, discontinue definitely study treatment.
- In case of life-threatening or disabling adverse event, study treatment must be definitely discontinued.

A detailed description of safety rules for specific safety events or risk (regardless of the causal relationship to study treatment) including neutropenia, renal disorders, hypoalbuminemia, liver disorders, cardiac disorders, reproductive system disorders and pregnancy, skin toxicity, edema, nausea or vomiting, diarrhea, and carcinogenicity, are included in the study protocol.

SUPPLEMENTARY eTABLES

eTable 1: Baseline patient characteristics for the PPMS and nSPMS subgroups of the masitinib 4.5 mg/kg/day parallel group, ITT dataset (N=301)

		PPMS		nSPMS	
		M4.5 (n=79)	**PBO (n=45)**	**M4.5 (n=121)**	**PBO (n=56)**
Gender	% (n) (Female)	45.6% (36)	46.7% (21)	62.0% (75)	58.9% (33)
Age (years)	Mean (± SD)	49.3 (±9.69)	50.5 (±9.30)	50.1 (±9.62)	49.1 (±10.90)
	Range (min—max)	24—67	32—66	26—69	25—70
PPMS phenotype	% (n)	N/A	N/A	N/A	N/A
EDSS Score	Mean (± SD)	4.9 (±1.10)	5.0 (±1.14)	5.3 (±1.03)	5.3 (±0.99)
EDSS Category; % (n)	6	39.2% (31)	40.0% (18)	55.4% (67)	53.6% (30)
	5 and 5.5	16.5% (13)	24.4% (11)	23.1% (28)	17.9% (10)
	< 5.5	44.3% (35)	35.6% (16)	21.5% (26)	28.6% (16)
MSFC T25FW	Mean (± SD)	17.1 (±25.33)	26.8 (±48.04)	26.6 (±34.57)	19.4 (±27.24)
MSFC 9-HPT	Mean (± SD)	32.8 (±22.14)	37.1 (±24.48)	34.8 (±15.97)	31.8 (±16.60)
MSFC PASAT-3	Mean (± SD)	38.6 (±14.16)	36.2 (±16.96)	43.5 (±12.48)	43.2 (±11.32)
Time since MS onset	Mean (± SD)	9.0 (±6.75)	9.2 (±7.56)	17.3 (±9.03)	15.3 (±7.23)
(years)	Range (min—max)	1—27	2—36	3—41	3—37
Time since MS diagnosis	Mean (± SD)	4.9 (±5.24)	4.9 (±7.11)	11.9 (±7.92)	12.2 (±7.51)
(years)	Range (min—max)	0—26	0—34	1—41	1—30

PBO: Placebo. M4.5: Masitinib 4.5 mg/kg/day. MSFC: Multiple Sclerosis Functional Composite T25FW: Timed 25-foot walk test. 9-HPT: Nine-hole peg test. PASAT-3: Paced Auditory Serial Addition Test–3. Expanded Disability Status Scale (EDSS). ITT: Intention-to-treat dataset. PPMS: Primary Progressive Multiple Sclerosis. nSPMS: non-active Secondary Progressive Multiple Sclerosis. SD: standard deviation.

eTable 2: Summary of secondary endpoint analyses (repeated measures methodology) according to overall (progressive MS) population and nSPMS subgroup (masitinib 4.5 mg/kg/day parallel group)

	Progressive MS (Overall population)				nSPMS (Subgroup)			
	PBO (N=101)	M4.5 (N=199)	ΔLSM [95%CI]	*P* value	PBO (N=56)	M4.5 (N=120)	ΔLSM [95%CI]	*P* value
MSFC Score	0.042	0.031	-0.011 [-0.074, 0.052]	0.729	0.028	0.020	-0.008 [-0.093, 0.077]	0.854
9-HPT (seconds)	3.256	-1.027	-4.283 [-8.344, -0.221]	0.0388	2.331	-3.111	-5.442 [-10.030, -0.854]	0.020
T25W (seconds)	3.042	1.345	-1.697 [-5.534, 2.140]	0.385	3.083	0.960	-2.123 [-7.061, 2.815]	0.397
PASAT-3	2.806	2.209	-0.597 [-1.935, 0.741]	0.381	2.031	1.271	-0.760 [-2.347, 0.828]	0.346
MSQOL – Physical Health	-1.221	-0.976	0.246 [-1.918, 2.409]	0.823	-0.657	0.016	0.672 [-2.438, 3.783]	0.670
MSQOL – Mental Health	-1.107	-1.863	-0.755 [-3.421, 1.910]	0.578	-1.269	-0.399	0.870 [-2.663, 4.402]	0.628
EQ-VAS	-1.495	0.877	2.372 [-0.243, 4.987]	0.075	-0.547	3.047	3.595 [0.375, 6.814]	0.029

PBO: Placebo. M4.5: Masitinib 4.5 mg/kg/day. MSFC: Multiple Sclerosis Functional Composite T25FW: Timed 25-foot walk test. 9-HPT: Nine-hole peg test. PASAT-3: Paced Auditory Serial Addition Test–3. QoL: Quality of Life. MSQoL: Multiple Sclerosis Quality of Life. EQ-VAS: Health state Visual Analogue Scale

eTable 3: nSPMS subgroup: Time series analysis of change from baseline in secondary endpoints, measured every 12 weeks over 96 weeks (masitinib 4.5 mg/kg/day parallel group)

nSPMS	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Average M-P	M>P	P value
Timed 25-Foot Walk											
Masitinib	*0.58*	*1.04*	*-0.23*	*-0.50*	*-0.16*	*1.51*	*2.99*	*2.41*	-3.02	Yes	NS
Placebo	*0.55*	*1.89*	*1.99*	*4.06*	*4.02*	*6.03*	*6.16*	*7.06*			
Diff. of M-P	*0.03*	*-0.85*	*-2.22*	*-4.56*	*-4.18*	*-4.53*	*-3.17*	*-4.65*			
9-Hole Peg Test											
Masitinib	*-1.80*	*-2.08*	*-3.27*	*-1.98*	*-1.54*	*-2.41*	*0.62*	*0.45*	-4.27	Yes	0.0204
Placebo	*0.94*	*-1.73*	*1.77*	*1.87*	*3.82*	*4.88*	*3.44*	*7.13*			
Diff. of M-P	*-2.74*	*-0.34*	*-5.05*	*-3.85*	*-5.35*	*-7.29*	*-2.82*	*-6.68*			
PASAT-3											
Masitinib	*0.47*	*0.86*	*1.43*	*1.77*	*2.69*	*2.87*	*2.65*	*2.95*	-0.47	No	NS
Placebo	*0.56*	*2.67*	*2.82*	*2.67*	*3.35*	*2.54*	*2.41*	*2.45*			
Diff. of M-P	*-0.09*	*-1.81*	*-1.40*	*-0.90*	*-0.66*	*0.33*	*0.24*	*0.50*			
EQVAS											
Masitinib	*1.95*	*0.90*	*3.30*	*2.47*	*2.22*	*0.78*	*0.17*	*-0.58*	4.19	Yes	0.0289
Placebo	*-1.44*	*-1.39*	*-2.82*	*-5.42*	*-1.51*	*-2.40*	*-3.50*	*-3.82*			
Diff. of M-P	*3.39*	*2.29*	*6.12*	*7.89*	*3.73*	*3.18*	*3.67*	*3.24*			
MSQoL Physical Health Score											
Masitinib	*0.29*	*-0.29*	*0.72*	*0.80*	*-1.72*	*-2.09*	*-1.62*	*-1.34*	1.89	Yes	NS
Placebo	*-0.07*	*-0.86*	*-1.73*	*-4.18*	*-3.00*	*-3.91*	*-3.99*	*-2.67*			
Diff. of M-P	*0.36*	*0.56*	*2.45*	*4.98*	*1.28*	*1.81*	*2.37*	*1.33*			
MSQoL Mental Health Score											
Masitinib	*0.28*	*-1.06*	*-0.59*	*-0.85*	*-2.84*	*-2.96*	*-2.85*	*-3.22*	2.83	Yes	NS
Placebo	*-2.86*	*-4.15*	*-2.96*	*-7.05*	*-4.43*	*-4.96*	*-5.45*	*-4.84*			
Diff. of M-P	*3.14*	*3.09*	*2.37*	*6.20*	*1.59*	*2.00*	*2.60*	*1.62*			

nSPMS: non-active Secondary Progressive Multiple Sclerosis. SD: standard deviation. For the Timed 25-foot Walk and 9-Hole Peg tests, a positive value or increase from baseline indicates disability progression, while a negative differential between treatment-arms (M-P) favors masitinib. For the PASAT-3, EQ-VAS, and MSQOL tests, a negative value or decrease from baseline indicates disability progression, while a positive differential between treatment-arms (M-P) favors masitinib. NS: Not significant; p>0.05.

eTable 4: Most common adverse events for masitinib 4.5 mg/kg/day treatment relative to placebo over the 96-week treatment period (Safety dataset, regardless of severity, ordered with respect to between group difference in incidence)

Number (%) of patients with ≥1 event	M4.5 (n=199)	PBO (n=101)	Δ[M/P]	Δ[M–P] (%)
Diarrhea	29 (14.6)	5 (5.0)	2.92	9.6
Blood Phosphorus Decreased	24 (12.1)	3 (3.0)	4.03	9.1
Hemoglobin Decreased	21 (10.6)	2 (2.0)	5.3	8.6
Rash Maculo-Papular	18 (9.0)	1 (1.0)	9.0	8.0
Red Blood Cell Count Decreased	16 (8.0)	0	N/A	8.0
Nausea	21 (10.6)	4 (4.0)	2.65	6.6
Edema Peripheral	15 (7.5)	1 (1.0)	7.5	6.5
Pruritus	14 (7.0)	1 (1.0)	7.0	6.0
White Blood Cell Count Decreased	19 (9.5)	4 (4.0)	2.11	5.5
Hematocrit Decreased	15 (7.5)	2 (2.0)	3.75	5.5
Blood Sodium Increased	11 (5.5)	0	N/A	5.5
Vomiting	11 (5.5)	0	N/A	5.5
Lymphocyte Count Decreased	22 (11.1)	6 (5.9)	1.88	5.2
Hyperkalemia	0	5 (5.0)	N/A	-5.0
Hypertension	3 (1.5)	7 (6.9)	0.21	-5.4
Blood Bilirubin Decreased	4 (2.0)	10 (9.9)	0.2	-7.9
Hematocrit Increased	3 (1.5)	10 (9.9)	0.15	-8.4

Adverse events (AE) that differed in incidence by ≥5% between treatment groups are listed. AEs described using MedDRA preferred terms. Any given AE can be listed under multiple MedDRA preferred terms, which are not therefore cumulative. PBO: Placebo. M4.5: Masitinib 4.5 mg/kg/day. Δ[M–P]: Between group difference in incidence (positive value indicates greater incidence in masitinib treatment-arm). Δ[M/P]: masitinib to placebo reporting rate ratio (value of 1.0 indicates equality, >1 indicates greater incidence in masitinib treatment-arm. AEs were recorded until 28 days after treatment interruption. N/A: Not applicable.

eTable 5: Most common serious non-fatal adverse events for masitinib 4.5 mg/kg/day treatment relative to placebo over the 96-week treatment period (Safety dataset, ordered with respect to between group difference in incidence)

Number (%) of pts with ≥1 event	M4.5 (n=199)	PBO (n=101)	Δ[M/P]	Δ[M–P] (%)
Rash Maculo-Papular	3 (1.5%)	0	N/A	1.5%
Erythema Multiforme	2 (1.0%)	0	N/A	1.0%
GTT Increased	2 (1.0%)	0	N/A	1.0%
Neutropenia	2 (1.0%)	0	N/A	1.0%
P-P Erythrodysaesthesia	2 (1.0%)	0	N/A	1.0%
Urinary Tract Infection	2 (1.0%)	1 (1.0%)	1.0%	0.0%

Non-fatal serious adverse events (SAE) occurring in at least 2 patients over the 96-week treatment period are listed (excluded disease-related/progression events). SAEs described using MedDRA preferred terms. SAEs were recorded until 28 days after treatment interruption. PBO: Placebo. M4.5: Masitinib 4.5 mg/kg/day. Δ[M–P]: Between group difference in incidence (positive value indicates greater incidence in masitinib treatment-arm). Δ[M/P]: masitinib to placebo reporting rate ratio (value of 1.0 indicates equality, <1 indicates greater incidence in placebo arm. P-P Erythrodysaesthesia: Palmar-Plantar Erythrodysaesthesia GTT: Gamma-Glutamyl Transferase. N/A: Not applicable.

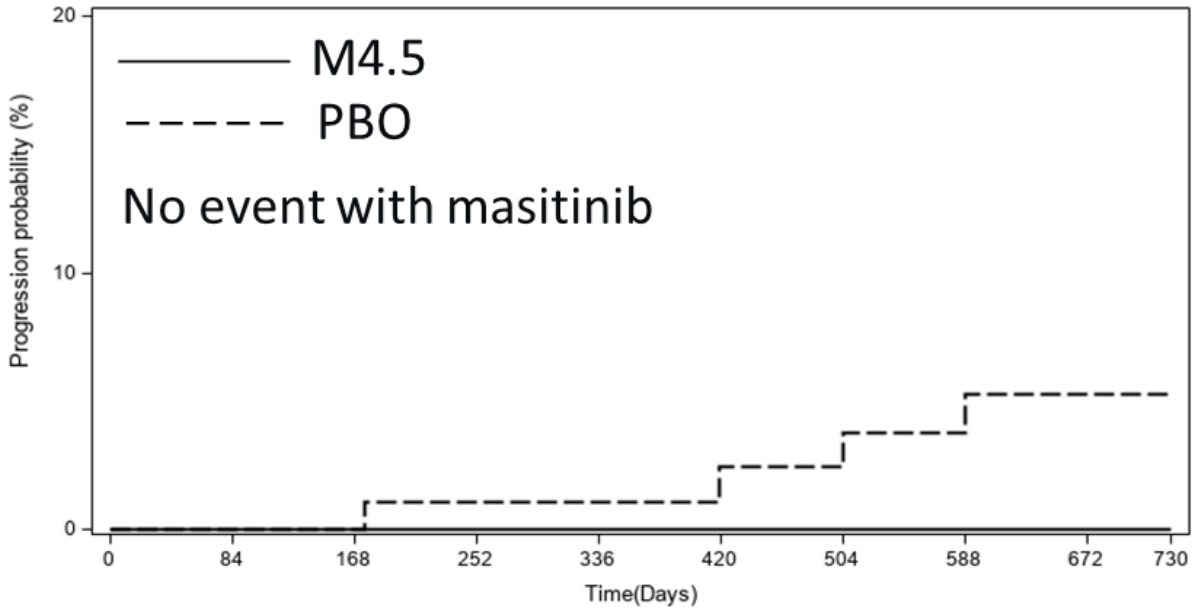
eTable 6: Assessment of adverse events related to infections and infestations based on clinical evidence for the masitinib 4.5 mg/kg/day parallel group (according to anatomical site and severity)

Patients with ≥1 event; % (n)	Severity	M4.5 (n=199)	PBO (n=101)	Δ[M/P]	Δ[M–P]
Infections and infestations	**Total**	**36.7% (73)**	**35.6% (36)**	**1.03**	**1.1%**
	Mild	*65.8% (48)*	*66.7% (24)*		
	Moderate	*32.9% (24)*	*33.3% (12)*		
	Severe	*1.4% (1)*	*0*		
Upper Respiratory Tract	**Total**	**20.6% (41)**	**17.8% (18)**	**1.16**	**2.8%**
	Mild	*75.6% (31)*	*83.3% (15)*		
	Moderate	*24.4% (10)*	*16.7% (3)*		
	Severe	*0*	*0*		
Lower Respiratory Tract	**Total**	**5.0% (10)**	**5.0% (5)**	**1.00**	**0.0%**
	Mild	*60.0% (6)*	*60.0% (3)*		
	Moderate	*40.0% (4)*	*40.0% (2)*		
	Severe	*0*	*0*		
Lower Urinary Tract	**Total**	**11.6% (23)**	**11.9% (12)**	**0.97**	**-0.3%**
	Mild	*52.2% (12)*	*58.3% (7)*		
	Moderate	*43.5% (10)*	*41.7% (5)*		
	Severe	*4.3% (1)*	*0*		
Other Infection	**Total**	**10.1% (20)**	**8.9% (9)**	**1.13**	**1.2%**
	Mild	*60.0% (12)*	*44.4% (4)*		
	Moderate	*40.0% (8)*	*55.6% (5)*		
	Severe	*0*	*0*		

Data presented as number of patients (%) with clinical evidence of at least one adverse event (AE). AEs were recorded until 28 days after treatment interruption. PBO: Placebo. M4.5: Masitinib 4.5 mg/kg/day. Δ[M–P]: Between-group difference in incidence (positive value indicates greater incidence in masitinib treatment arm). Δ[M/P]: masitinib to placebo reporting rate ratio.

SUPPLEMENTARY eFIGURE

eFigure 1: Kaplan-Meier analysis - cumulative probability of reaching an EDSS score ≥7.0 (12-week confirmed)



Expanded Disability Status Scale (EDSS). PBO: Placebo. M4.5: Masitinib 4.5 mg/kg/day.