Supplement to Olivier Lortholary, et al., “Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study”

This supplement contains the following items:

1. Statistical analysis plan for study AB06006
2. Protocol for study AB06006
3. Summary of protocol changes for study AB06006
STATISTICAL ANALYSIS PLAN
FOR FINAL ANALYSIS

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 (CUTANEOUS MASTOCYTOSIS PATIENTS ARE NOT PART OF MAIN ANALYSIS AND CLAIM AS PER PROTOCOL AMENDMENT VERSION 6.0).

Phase of development: Phase 3

Indication: Patients with Smouldering, Indolent Systemic or Cutaneous mastocytosis with handicap (cutaneous mastocytosis patients are not part of main analysis and claim as per protocol amendment version 6.0).

Sponsor AB Science
3, avenue George V
F – 75008 Paris

First patient enrolled 19th February 2009

Main / coordinating investigator Olivier Lortholary, Necker Hospital, Paris
1. DOCUMENTATION

1.1. General Information

Protocol AB06006

Related documents
- Protocol v7.0
- ICH-E9
- CRF V5.0 dated 28MAR2014
- MDH V1.0 dated 25MAR2013 and Validation plan V1.0 dated 06JAN2015

Document Owner AB Science Biometry Unit

1.2. Version History and Approvals

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<th>Version n° and date</th>
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<td>Initial version, was in draft 0.11 at time of Blind Data Review meeting.</td>
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<tr>
<td>1.0 dated 23NOV2015</td>
<td>Version finalized after Blind Data Review meeting and before database lock.</td>
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1.3. Approvals

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<tr>
<td>Inna IVANINA</td>
<td>Clinical Project Manager</td>
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<tr>
<td>Eckhard PECHER</td>
<td>Head of Biometry</td>
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<tr>
<td>Ophélie CALAS-ZEROUG</td>
<td>AB Science Biostatistician</td>
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2. PROTOCOL SYNOPSIS (7.0 FRANCE)

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Study Title:
A 24-week with possible extension, prospective, multicenter, 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 (cutaneous mastocytosis patients are not part of main analysis and claim as per protocol amendment version 6.0).

Study Code Number: AB06006

Coordinating investigator: Olivier Lortholary MD, PhD – Necker Hospital - Paris

Clinical Study Centres: Up to 100 sites in Europe, United-States, India, Latin America, South Africa

Study periods: duration of treatment: 24 weeks

Safety and efficacy objectives:
The objective is to compare the safety and efficacy of masitinib to placebo in patients with documented Smouldering or Indolent Systemic mastocytosis (cutaneous mastocytosis patients are not part of main analysis and claim as per protocol amendment version 6.0) with severe handicap on the following endpoints:

Primary endpoint:
- Cumulative response by patient*handicap:

Secondary endpoints:
- Cumulative response on pruritus among patients with the handicap at Baseline
- Cumulative response on OPA score among patients with “severe” or “intolerable” handicap at Baseline
- Quality of Life (QoL) : QLQ-C30 global score, functional scores and symptom scores at each visit
- AFIRMM questionnaire:
  • global score
  • for each of the 52 items : cumulative response among patients with “severe” or “intolerable” handicap at Baseline
- Cumulative response on micturitions among patients with the handicap at Baseline
- Cumulative response on stools among patients with the handicap at Baseline
- Urticaria Pigmentosa (UP) evaluation at week 12, 24 and then every 12 weeks
- Mastocytosis symptoms rebound effect evaluation from 1 month after study/treatment discontinuation. Severity of symptom sand time of occurrence of the rebound effect after study/treatment discontinuation will be evaluated. Patient overall wellbeing from treatment period will be also evaluated.

Safety profile of masitinib: Occurrence of Adverse Events, vital signs, ECG, Chest X-Ray and biological parameters.
Efficacy endpoints will be analysed on the overall patient population (cutaneous mastocytosis patients are not part of main analysis and claim as per protocol amendment version 6.0) and additionally on patients bearing activation point mutations in the phosphotransferase domain of c-Kit such as the main mutation Asp-816-Val (D816V) versus patients for whom the detection of kit816 is negative or unknown in the organ biopsied.

Methodology/Study Design:
This is a prospective, multicentre, randomized; double blinded, placebo-controlled, 2-parallel group with a randomization 1:1, phase 3 study comparing the efficacy and the safety of masitinib at 6 mg/kg/day versus placebo in the treatment of patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap (cutaneous mastocytosis patients are not part of main analysis and claim as per protocol amendment version 6.0).
A total of 150 patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap will be randomized in two treatment groups:
- Group 1: 75 patients will receive masitinib at 6 mg/kg/day
- Group 2: 75 patients will receive placebo

Treatment allocation:
Because handicap/scores at baseline regarding pruritus, flushes, depression and fatigue might influence the study outcome, they must be equally balanced in the two treatment groups. Hence, randomization procedures include a minimization process aimed at reducing any difference in the distribution of the handicaps/scores at baseline and country in patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap.

Inclusion criteria:
1. Patient with one of the following documented mastocytosis as per WHO classification:
   - Smouldering Systemic Mastocytosis
   - Indolent Systemic Mastocytosis
2. Patient with documented mastocytosis and evaluable disease based upon histological criteria: typical infiltrates of mast cells in a multifocal or diffuse pattern in skin and/or bone marrow biopsy
3. Patient with documented treatment failure of his/her handicap(s) with at least one of the following therapy used at optimized dose:
   - Anti H1
   - Anti H2
   - Proton pump inhibitor
   - Osteoclast inhibitor
   - Cromoglycate Sodium
   - Antileukotriene
4. Handicapped status defined as at least two of the following handicaps, including at least one among pruritus, flushes, depression and fatigue:
   - Pruritus score ≥ 9
   - Number of flushes per week ≥ 8
   - Hamilton rating scale for depression (HAMD-17) score ≥ 19
   - Number of stools per day ≥ 4
   - Number of micturition per day ≥ 8
   - Fatigue Impact Scale total score (asthenia) ≥ 75
5. Patients with OPA > 2 (moderate to intolerable general handicap)

6. ECOG ≤ 2

7. Patient with adequate organ function:
   - Absolute neutrophils count (ANC) ≥ 2.0 x 10^9/L,
   - Haemoglobin ≥ 10 g/dL
   - Platelets (PTL) ≥ 100 x 10^9/L
   - AST/ALT ≤ 3x ULN (≤ 5 x ULN in case of liver mast cell involvement),
   - Bilirubin ≤ 1.5x ULN
   - Creatinine clearance >60mL/min (Cockcroft and Gault formula)
   - Albumin >1 x LLN
   - Urea ≤ 1.5x ULN
   - Proteinuria< 30mg/dL on the dipstick; in case of proteinuria ≥ 1+ on dipstick, 24 hours proteinuria should be ≤1.5g/24 hours

8. Male or female patient aged 18 to 75 years, weight > 50 kg, BMI between 18 and 35 kg/m²

9. Female patient of childbearing potential (entering the study after a menstrual period and who have a negative pregnancy test), who agrees to use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. Acceptable forms of contraception include:
   - A documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository)
   - Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) should also be used
   - Double barrier method: Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
   - Any other contraceptive method with a documented failure rate of <1% per year
   - Abstinence when this is in line with the preferred and usual lifestyle of the patient.

10. Male patients must use medically acceptable methods of contraception if your female partner is pregnant, from the time of the first administration of the study drug until three months following administration of the last dose of study drug. Acceptable methods include:
   - Condom;
   - If you have undergone surgical sterilization (vasectomy with documentation of azoospermia) a condom should also be used.

Male patients must use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. The acceptable methods of contraception are as follows:
   - Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
   - Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
   - Your female partner uses oral contraceptives (combination oestrogen/progestosterone pills), injectable progestrone or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
Medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);

Your female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) should also be used;

Your female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);

Abstinence when this is in line with the preferred and usual lifestyle of the patient.

11. Patient must be able and willing to comply with study visits and procedures per protocol

12. Patient must understand, sign, and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures performed

13. Patient must understand the patient card and follow the patient card procedures in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity during the first 2 months of treatment

14. Patient affiliated to a social security regimen

Exclusion criteria:

1. Patient with one of the following mastocytosis:
   - Cutaneous Mastocytosis
   - Not documented Smouldering Systemic Mastocytosis or Indolent Systemic Mastocytosis
   - Systemic Mastocytosis with an Associated clonal Hematologic Non Mast cell lineage Disease (SM-AHNMD)
   - Mast cell leukaemia (MCL)
   - Aggressive systemic mastocytosis (ASM)

2. Previous treatment with any Tyrosine Kinase Inhibitor

3. 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

4. Patient who had major surgery within 2 weeks prior to screening visit

5. Vulnerable population defined as:
   - Life expectancy < 6 months
   - Patient with < 5 years free of malignancy, except treated basal cell skin cancer or cervical carcinoma in situ
   - Patient with any severe and/or uncontrolled medical condition
Patient with known diagnosis of human immunodeficiency virus (HIV) infection

6. 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, or institutionalized by court decision

7. Patient with any condition that the physician judges could be detrimental to subjects participating in this study; including any clinically important deviations from normal clinical laboratory values or concurrent medical events

Previous treatment

8. Change in the symptomatic treatment of mastocytosis or administration of any new treatment of mastocytosis within 4 weeks prior to baseline

9. Treatment with any investigational agent within 4 weeks prior to baseline

Centralization of c-Kit sequencing and mast cell counting:
For all patients, askin biopsy will be performed at screening, except for patients without cutaneous lesion for whom a bone marrow aspirate or biopsy will be mandatory, in order to document potential c-kit mutation (only at screening) and mast cell counting. Additionally, skin biopsy (or bone marrow aspirate or biopsy) will be performed at week 24, or at end of visit for mast cell counting.

Optionally, a bone marrow aspirate or biopsy could be performed in addition to the skin biopsy at screening (and at week 24, or at end of study visit) to document mast cell counting.

The c-kit sequencing and mast cell counting will be performed centrally in order to ensure consistency in the study results. The procedure to follow for performing skin, optionally bone marrow aspirate and bone marrow biopsy is described in protocol appendix 13.8.

Myocardial contractibility study:
As part of the international study, French patients enrolled in this study, will enter a specific cardiac surveillance in order to study potential effect of masitinib on myocardial contractibility. Echocardiogram will be performed for assessing myocardial contractibility features and especially the Left Ventricular Ejection Fraction.

2D and M-mode echocardiography which provide qualitative and semi quantitative measurements of ventricular systolic function could be used. However, whenever it’s possible, three-dimensional echocardiography should be preferred. This technique has excellent correlation with radionuclide angiography for calculation of left ventricular ejection fraction in patients and has observer variability similar to that of radionuclide angiography (9).

As per study protocol, patients will have to perform at baseline and at week 24 a Doppler echocardiography. This examination should be conducted in the supine position, with the same ultrasound system and preferably by the same physician. All patients should be haemodynamically stable. Tracings should be recorded during expiration. Para-sternal and apical views have to be obtained according to the recommendations of the American Society of Echocardiography. Values should be presented as means from three consecutive cardiac cycles. Left ventricular ejection fraction should be calculated according to the same integration method for the two measurements (i.e. baseline, week 24 and end of study visit).

The following echocardiogram endpoints should be measured:
- Left Ventricular Ejection Fraction at week 0, week 24 and end of study visit (primary)
- Fractional shortening (midwall mFS) at week 0, week 24 and end of study
- Systolic and diastolic left ventricular diameters at week 0, week 24 and end of study
- Optionally, left ventricular contractility during Isovolumic Contraction at week 0, week 24 and end of study
Background information and statistical considerations are provided in the study protocol.

**Duration of Treatment, extension phase and maximum exposure duration:**

Eligible patients will be treated with masitinib or matching placebo for 24 weeks with possible extension. Patients who completed the Week 24 period, with regular assessments and evaluation can enter a double blind extension phase:

- In case of positive clinical benefit/response established by investigator
- If required by the investigator and agreed by the patient.

The maximum exposure to treatment is 2 years.

Exposure to treatment for more than 2 years will be possible only if:

- A Substantial amendment is approved by Competent Authority
- The benefit/risk for the study is positive based on available data
- The individual benefit/risk is still assessed as positive by investigator and documented

The informed consent form has been resigned to remind patient about potential long term risks.

**Treatment administration:**

Subjects enrolled will receive a total daily dose of 6 mg/kg masitinib or a matching placebo, to be taken during meals as indicated in the table below:

<table>
<thead>
<tr>
<th>Patient’s weight in kg</th>
<th>Daily dose (mg)</th>
<th>Morning* (mg)</th>
<th>Evening** (mg)</th>
</tr>
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<tr>
<td>≤41.6</td>
<td>200</td>
<td>100</td>
<td>100</td>
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<tr>
<td>&gt; 41.6</td>
<td>58.3</td>
<td>300</td>
<td>100</td>
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<tr>
<td>&gt; 58.3</td>
<td>74.9</td>
<td>400</td>
<td>200</td>
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<td>&gt; 74.9</td>
<td>91.6</td>
<td>500</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 91.6</td>
<td>600</td>
<td>200+100</td>
<td>200+100</td>
</tr>
</tbody>
</table>

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

**Dose reduction**

Should a dose reduction be necessary, the patient will receive 4.5 mg/kg/day. The daily dose and the administration of the study treatment, according to the patient’s weight, is displayed in the table below:

<table>
<thead>
<tr>
<th>Patient’s weight in kg</th>
<th>Daily dose (mg)</th>
<th>Morning* (mg)</th>
<th>Evening** (mg)</th>
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<tbody>
<tr>
<td>≤41.6</td>
<td>STOP</td>
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<tr>
<td>&gt; 41.6</td>
<td>58.3</td>
<td>200</td>
<td>100</td>
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<td>&gt; 58.3</td>
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<td>&gt; 99.9</td>
<td>500</td>
<td>200</td>
<td>200+100</td>
</tr>
</tbody>
</table>
name of company: ab science
name of finished product: masitinib
name of active ingredient: ab1003

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

no dose escalation will be authorized for patients who have had a dose reduction for safety reasons.

procedure in case of missed or vomited doses of study treatment tablets:

- in case the morning dose has been missed, it can be taken until 2 pm. on the same day. should it be later than 2 pm, the missed dose will not be made up and study treatment will be resumed at the evening dose on the same day.
- in case the evening dose is missed, it should not be made up the day after in addition to the morning dose. the study treatment will be resumed the day after as scheduled in the protocol.
- should the patient vomit within 10 minutes after the last study treatment dose intake, another dose should be taken.

should the patient vomit later than 10 minutes following the last study treatment dose intake, study treatment will be resumed at the next theoretical dose intake, but the last dose will not be replaced

procedures to manage potential adverse reaction:
study treatment refers to masitinib or its matching placebo.

surveillance:

- complete blood count at screening, baseline, w1, w2, w3, w4, w5, w6, w7, w8, w10, and every 4 weeks until the end of study treatment.
- hepatic work up (ast, alt, gamma gt, total bilirubin, ap, ldh) at screening, baseline, w2, w4, w6, w8 and every 4 weeks until the end of study treatment.
- bnp at baseline and ecg at baseline then every 12 weeks.
- chest x-ray (only posterior-anterior view) at baseline (not required if chest x-ray performed within 3 months prior to baseline) and at the end of the study.
- at each visit, cardiac symptoms are carefully checked by medical interview and clinical examination.
- at baseline and at each patient visit, the physical exam of the patient must include a careful thyroid palpation.
- urinary cytology and nmp22 test at baseline and then every 12 weeks.
- beta hcg at screening, baseline, at the end of the study and in case of suspicion of pregnancy.
- in non-menopausal women using non-hormonal contraceptive method, hormonal work-up at baseline then every 12 weeks.
- optional spermogram at baseline then every 12 weeks.

patient card and procedures to follow by the patient during the first 2 months
all patients will receive a card mentioning the risk of severe neutropenia and the risk of severe skin toxicity with masitinib and the procedures to follow in case of signs or symptoms suggesting the occurrence of those 2 risks.

call from site to patient once a week for the first 2 months

during the two first months of treatment, the study staff should call the patient every week to verify with the patient the weekly workups (i.e. absolute neutrophils count) and to enquire about all signs which might be due to an underlying infection and ensure the absence of skin detachment and/or ulcerations.

in case a patient experiences either a severe neutropenia or severe skin toxicity, a specific pharmacogenomic blood sample should be collected and sent to the central lab on the day of the collection. the tube to be used for pharmacogenomic analysis must be either an edta tube (4 ml) or 2 paxgene dna/rna tube (2x2.5 ml), provided by ab science.

statistical analysis plan - version n°1.0
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### Neutropenia regardless of the causal relationship to study treatment:

- In case of absolute neutrophils count between 0.5 and 1x10^9/L, study treatment will be interrupted until absolute neutrophils count has returned above 1.5x10^9/L, and then restarted at the same dose.
- If duration of neutropenia > 4 weeks, the dose of study treatment will be decreased by one step.
- In case of absolute neutrophils count < 0.5x10^9/L, study treatment will be definitely discontinued.
- The investigator must inform the sponsor immediately (within 24 hours by fax using a Serious Adverse Event form) even if he/she considers the neutropenia as non-serious.
- In case of associated fever, oral ulceration, sore throat or infection, a complete blood count should be performed in order to check the neutrophil count. In case of neutropenia, the above mentioned rules should be applied.
- The patient should be instructed to follow the procedures described in the patient card in case of signs or symptoms of severe neutropenia.
- In any case, all concomitant treatment potentially inducing neutropenia must be stopped.

### Renal disorders regardless of the causal relationship to study treatment

- In case of one of the 4 following events occur:
  - proteinuria ≥ 30 mg/dL on dipstick confirmed by a 24 hours proteinuria > 1.5g/24 hours
  - creatinin clearance < 50 mL/min (Cockroft and Gault formula)
  - albumin < 0.75 x LLN
  - urea > 1.5 x ULN

Study treatment will be interrupted until return to baseline; then treatment will be restarted at the same dose.

- If one of the 4 events occurs a second time, study treatment will be interrupted until adverse event has returned to baseline, and then restarted with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day).
- If one of the 4 events occurs a third time: study treatment will be permanently discontinued. In case of severe renal disorders, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day). If severe renal disorders re-occurs after dose reduction, study treatment must be definitely discontinued.
- If renal disorders are disabling or life-threatening, study treatment must be definitely discontinued.

### Hypoalbuminemia regardless of the causal relationship to study treatment

- In case of hypoalbuminemia between 0.75 and 1 LLN, the dose of study treatment should be reduced (new dose: 4.5 mg/kg/day).
- In case of hypoalbuminemia lower than 0.75 LLN, study treatment must be definitely discontinued.

### Liver disorders regardless of the causal relationship to study treatment

- In case of grade 2 liver enzymes increase; i.e. transaminases (AST or ALT or both) ≤5 ULN, and/or in case of bilirubin increase ≤ 3 ULN, study treatment should be maintained.
- In case of grade 3 liver enzymes increase, i.e. transaminases (AST or ALT or both) increase > 5 ULN and < 20 ULN, and/or in case of bilirubin increase > 3 ULN and < 10 ULN, study treatment should be interrupted until transaminases levels return to ≤ 3 ULN and bilirubin level returns ≤ 1.5 ULN. Hepatic surveillance tests will be performed every week. Then resume study treatment with a dose reduction (new dose: 4.5 mg/kg/day).
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**NAME OF FINISHED PRODUCT:** MASITINIB  
**NAME OF ACTIVE INGREDIENT:** AB1003

- In case of second grade 3 liver enzymes increase, i.e. transaminases (AST or ALT or both) increase higher than 5 ULN and < 20 ULN and/or a second bilirubin increase >3 ULN and <10 ULN occur when study treatment is resumed, study treatment must be definitely discontinued.

- In case of grade 4 transaminases increase (i.e. AST or ALT > 20 ULN and/or bilirubin> 10 ULN), study treatment must be definitely discontinued

- **Cardiac disorders, regardless of the causal relationship to study treatment.**

At each visit, cardiac symptoms are carefully checked by medical interview and clinical examination.

In the event of cardiac event:

- In the event of thoracic pain
  i. Perform an ECG: if there is any change compared to the previous ECG(s), a cardiologist should be consulted
  ii. Perform a dosage of troponin: if the result is higher to LLN, a cardiologist should be consulted

If an acute coronary syndrome is confirmed, study treatment should be definitely discontinued

- In the event of dyspnoea or signs of cardiac failure
  i. Perform a clinical examination: if there is clinical signs of cardiac failure, study treatment should be definitely discontinued and a cardiologist should be consulted
  ii. Perform an ECG: if there is any change compared to the previous ECG(s), a cardiologist should be consulted
  iii. Perform a dosage of BNP (or NT proBNP):
    1. If BNP is between 100 and 400 pg/mL (NT proBNP between 400 and 2000 pg/mL) without clinical signs of cardiac failure, control the dosage one week later: if there is an increase higher than 30% when compared to baseline value, a cardiologist should be consulted and the discontinuation of study treatment should be discussed according to the benefit risk ratio for the patient
    2. If BNP is higher than 400 pg/mL (NT proBNP higher than 2000 pg/mL) without clinical signs of cardiac failure, study treatment should be interrupted and a cardiologist should be consulted with an ECG and an echocardiography for the discussion of discontinuation or not of study treatment, according to the benefit/risk ratio for the patient.
  iv. Perform a dosage of troponin: if the result is higher to LLN, a cardiologist should be consulted
  v. Perform an echocardiography:
    1. If LVEF < 50%: study treatment should be definitely discontinued and a cardiologist should be consulted
    2. If LVEF between 50 and 60%, without clinical signs of cardiac failure, maintain study treatment and control the LVEF two weeks later:
      a. If clinical signs of cardiac failure appear: discontinue study treatment and a cardiologist should be consulted
      b. If LVEF is still between 50 and 60%: control the LVEF one month later, maintain study treatment, control the LVEF every 3 months
      c. If LVEF is equal or higher than 60%: maintain study
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 NAME OF FINISHED PRODUCT: MASITINIB  
 NAME OF ACTIVE INGREDIENT: AB1003

- Treatment, control the LVEF 3 month later.
  - If LVEF is lower than 50%: discontinue study treatment and a cardiologist should be consulted.

- In the event of isolated lower limbs oedema
  - Check clinical signs of cardiac failure
  - Perform a dosage of BNP (or NT proBNP)
  - If there is any suspicion of a cardiac origin, a cardiologist should be consulted.

- In the event of blood pressure increased
  - Adapt the anti-hypertensive medications
  - If high blood pressure persists, a cardiologist should be consulted and the discontinuation of study treatment should be discussed according to the benefit risk ratio for the patient.

- In the event of other potential cardiac adverse events, like syncope without known aetiology, severe conduction disorders, persistent ventricular tachycardia, resuscitated sudden death, study treatment should be interrupted and a cardiologist should be consulted.
  - In the event of severe conduction disorders, study treatment may be resumed after pacing
  - In the other cases, study treatment must be definitely discontinued.

- Reproductive system disorders and pregnancy

- If pregnancy is suspected during the study, study treatment must be immediately withheld until the result of a laboratory pregnancy test is available. Should pregnancy be confirmed, the patient must be withdrawn from study. Thereafter, the patient (and/or partner, if applicable) must be asked to participate in the AB Science pregnancy surveillance program and the baby and patient’s health will be followed at least up to 3 months after birth.

- Menstrual cycle of pre-menopausal women not using hormonal contraceptive should be recorded at each study visit. In case of irregular cycles without known cause after exploration (such as pre-menopausal or history of irregular cycles), study treatment must be definitely discontinued. In addition, FSH, LH, estradiol and progesterone level of all pre-menopausal women not using hormonal contraceptive will be assessed at baseline and every 12 weeks during the course of the study, in front of the date of last menstruations.

- A pelvic ultrasound will be performed in women of childbearing potential at baseline and final visit

- Regarding male patients enrolled in the present study, they will be asked to perform a semen analysis (i.e. sperm count, morphology and motility analysis) at baseline, every 12 weeks and final visit. This procedure will be optional depending on the patient consent.

- Skin toxicity regardless of the causal relationship to study treatment

In case of mucous ulceration, and/or skin detachment and/or suspicion of erythema multiforme or Stevens-Johnson syndrome, Lyell syndrome or DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) regardless of the severity of the event:

- Study medication must be interrupted and the patient must consult a dermatologist. Study treatment can be re-challenged after mandatory agreement of the dermatologist.

- The investigator must inform the sponsor immediately (within 24 hours by fax using a Serious Adverse Event form), even if he/she considers the skin toxicity as non-serious. AB Science will contact the investigator and the dermatologist in order to document the case (specific questionnaire see Appendix, photography of the lesions, cutaneous biopsy, ...)

- Should an epidermal necrolysis (erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome) be suspected, study treatment must be definitely discontinued.

- Should a DRESS syndrome be suspected, study treatment must be definitely discontinued.
In case of Grade 1 (CTC-AE classification) maculo-papular rash or desquamation:
- Study treatment will be maintained and patient will be treated with hydroxyzine 100 mg/day for 8 days

In case of Grade 2 (CTC-AE classification) maculo-papular rash or desquamation:
- Study treatment will be interrupted, and patient will be treated with hydroxyzine 100 mg/day for 8 days combined with prednisone for 8 days (1 mg/kg for 2 days, 0.5 mg/kg for the next 2 days, then 20 mg/day for 2 days, and last 10 mg/day for 2 days). After return to baseline or grade ≤ 1, study treatment will be resumed at the same dose level as before interruption
- In case of reoccurrence of a Grade 2 maculo-papular rash or desquamation, study treatment must be interrupted and the same symptomatic treatment should be initiated. After return to baseline or grade ≤ 1, study treatment will be resumed with at the same dose reduction (new dose: 4.5 mg/kg/day).
- If grade 2 maculo-papular rash or desquamation re-occurs, study treatment must be interrupted and the same symptomatic treatment should be initiated. After return to baseline or grade ≤ 1, study treatment will be resumed with a dose reduction (new dose: 4.5 mg/kg/day).
- If Grade 2 maculo-papular rash or desquamation re-occurs after dose reduction, study treatment must be definitely discontinued.

In case of Grade 3 skin toxicity, except mucous ulceration, and/or skin detachment and/or suspicion of erythema multiforme or Stevens-Johnson syndrome, Lyell syndrome or DRESS, study treatment should be interrupted and a dermatologist should be consulted to confirm the diagnosis, assess the risk and define the symptomatic treatment for the patient. The dermatologist will give his/her opinion on whether patient could resume study treatment depending on skin lesions and patient safety. If the dermatologist agrees that study treatment should resume, study treatment will be resumed with a dose reduction (new dose: 4.5 mg/kg/day).
If Grade 3 skin toxicity re-occurs after dose reduction, study treatment must be definitely discontinued.
- Oedema regardless of the causal relationship to study treatment
  - In the event of isolated lower limbs oedema:
  - Check clinical signs of cardiac failure
  - Perform a dosage of BNP (or NT proBNP)
    If there is any suspicion of a cardiac origin, a cardiologist should be consulted.
  - In case of moderate oedema, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose
  - If moderate oedema re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If moderate oedema re-occurs after dose reduction, study treatment must be definitely discontinued.
  - In case of severe oedema, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If severe oedema re-occurs, discontinue definitely study treatment
  - In case of incapacitating or life-threatening oedema or angioedema, discontinue definitely study treatment.
- Nausea or vomiting regardless of the causal relationship to study treatment
  - In case of nausea or vomiting, anti-emetics are recommended according to the usual practice.
  - In case of moderate nausea or vomiting, interrupt study treatment until return to baseline or mild intensity.
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- If moderate nausea or vomiting re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
- If moderate nausea or vomiting re-occurs after dose reduction, study treatment must be definitely discontinued.
- In case of severe nausea or vomiting, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
- If severe nausea or vomiting re-occurs, discontinue definitely study treatment
- In case of disabling or life threatening nausea or vomiting, discontinue definitely study treatment

- Diarrhoea regardless of the causal relationship to study treatment
  - In case of diarrhoea, anti-diarrheal medications are recommended according to usual practice.
  - In case of moderate diarrhoea, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose
  - If moderate diarrhoea re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If moderate diarrhoea re-occurs after dose reduction, study treatment must be definitely discontinued.
  - In case of severe diarrhoea, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If severe diarrhoea re-occurs, discontinue definitely study treatment
  - In case of incapacitating or life threatening diarrhoea, discontinue definitely study treatment

- Dehydration
In case of dehydration, study treatment should be interrupted and symptomatic treatment should be initiated.

- Pulmonary disorders
In case of aggravation of pre-existing symptoms, or new pulmonary symptoms without known aetiology (cough, dyspnoea, fever), study treatment will be interrupted until results of the etiological work-up are received.

- Ocular disorders
In case of moderate ocular disorders lasting for more than 1 week, or in case of severe ocular disorders, an ophthalmologist should be consulted to decide about patient care.

- Carcinogenicity
Risk of bladder cancer
A carcinogenicity study in male mice has shown potential risk of bladder carcinogenicity. This risk was not evidenced in human experience. However, urinary cytology including a specific search for transitional and/or malignant cells and a NMP22 test will be performed at baseline visit, every 12 weeks and at the final visit.

Risk of thyroid cancer / adenoma
At baseline and at each patient visit, the physical exam of the patient must include a careful thyroid palpation. Should a thyroid nodule be detected, an endocrinologist must be consulted for further diagnosis and treatment, if applicable.

Risk of uterine carcinoma
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At baseline and every 12 weeks, a hormonal work up including progesterone, estradiol, FSH and LH must be performed in non-menopausal female patients treated with masitinib and using a non-hormonal contraceptive method.

- Risk management plan for adverse event not described above and suspected to be related to study treatment

Please note that the previous rules apply regardless of the causal relationship to study treatment, while this rule applies only for adverse events suspected to be related to study treatment.

- At the first occurrence of moderate adverse event, study treatment will be interrupted until adverse event has returned to baseline value or mild intensity, then resumed at the same dose level.
- If the same moderate adverse event re-occurs, study treatment will be interrupted until adverse event has returned to baseline or mild intensity, then resumed with a dose reduction (4.5 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 will be interrupted until adverse event has returned to baseline level or mild intensity, then resumed with a dose reduction (4.5 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

In case of severe adverse event suspected to be related to study treatment, an evaluation of the benefit/risk ratio by the investigator and an agreement of the Pharmacovigilance Department of the Sponsor will be necessary before resuming study treatment.

In case of serious, unexpected adverse event, the treatment will be interrupted. The treatment could only be resumed when the adverse event has returned to baseline value and after the Independent Data Monitoring Committee would have given his approval.

Concomitant treatments allowed during the study (at stable doses):

1. Mandatory concomitant medication:

An oral antihistamine (cetirizine 10 mg/day) must be combined systematically with the study drug for 60 days. Cetirizine will be initiated at the same time as study treatment. To avoid the possible sedative effect of anti-histamine, the treatment will be taken in the evening, at bedtime.

2. Other concomitant treatments:

All symptomatic treatments such as:
- Anti H1
- Anti H2
- Proton pump inhibitor
- Osteoclast inhibitor (biphosphonates)
- Cromoglycate Sodium
- Antileukotriene
- Adrenaline in case of anaphylactic shocks
- Other therapies used for the symptomatic care

They should be maintained at the same dose during the study. No change in the symptomatic treatment of mastocytosis or administration of any new treatment of mastocytosis should occur.

Prohibited concomitant treatments:
- Anticancer agent (including chemotherapy, high dose of corticosteroids, biologics agent)
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- 2CDA
- Interferon
- Any investigational treatment related or not related to mastocytosis
- Live attenuated vaccines
- Drugs known to be at high risk of Stevens-Johnson syndrome: allopurinol, lamotrigine, carbamazepine, phenytoin, phenobarbital, sulfasalazine, sulfamide, oxicam and nevirapine; or to be at high risk of DRESS syndrome: minocycline, nodafenil, dapsone.

**Treatments which should be given with high caution:**
- Drugs known to interact with the same CYP450 isoenzymes (2C9, 2D6 and 3A4) than masitinib whether inducers, inhibitors or substrates.
- Acetaminophen/paracetamol
- Any nephrotoxic drug

**Independent Data Monitoring Committee**

An Independent Data monitoring committee (IDMC) with expertise and experience in the diagnosis and management of mastocytosis, and without direct involvement in the conduct of the study will be set up specifically to monitor safety data throughout the duration of a study. All adverse events occurring during the trial will be forwarded to this Committee.

The Committee recommends a closer follow-up on the events occurring during the study with an evaluation of the data quarterly independently from the sponsor and reserves the possibility of alerting the Scientific Committee of AB Science in the event of observation of highly unexpected events compared to the initial assumptions in early term of lack of efficacy, limiting toxicity or early efficacy. In case of alert:
- AB SCIENCE should consider discussing an action with Competent Authority(ies) in advance.
- If this alert concerns early efficacy, Head of Biometry should develop appropriate stopping rules and adjustment of type I error before examining the data.

The IDMC will review analyses by treatment group twice during the study. The IDMC will recommend the discontinuation of the study due to lack of efficacy; lack of efficacy being defined as a conditional power < 10%. If needed the sample size might be revisited further to IDMC analysis.

**Criteria for Evaluation:**

**Efficacy:**

Handicaps are defined as:
- Main handicaps: pruritus score ≥ 9, number of flushes per week ≥ 8, HAMD-17 score ≥ 19, Fatigue Impact Scale ≥ 75
- Other handicaps: micturition≥ 8, stools ≥ 4

Response on a handicap is defined as an improvement ≥ 75% for pruritus, flushes, Hamilton and fatigue

**Primary variable:**

- Cumulative response by patient*handicap

For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing =
failure as primary analysis).

Week 4 is not considered for the calculation of this response as:

- All patients take anti-histamines between Baseline and week 4 even if they didn’t take such treatment before study entry
- Based on phase II studies, first month of treatment is under efficient

So, from 5 to 20 responses will be calculated by patient: 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients presents the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits.

**Sensitivity analysis**:
- same 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.
- *Secondary variables*

  - Cumulative response on pruritus among patients with the handicap at Baseline

Cumulative response is calculated for pruritus as pruritus is considered as the most objective and representative measure in mastocytosis benefiting from a validated measure.

For the patients presenting the handicap at Baseline (ie. score ≥ 9), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

**Sensitivity analysis**:
- same 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.

  - OPA score

OPA score corresponds to the 53rd question of the AFIRM questionnaire.

For the patients presenting the handicap at Baseline (ie. OPA “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an OPA “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

**Sensitivity analysis**:
- same 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.

  - Quality of Life (QoL) : QLQ-C30

Value at time point, absolute and relative change from Baseline for each scale (functional scales i.e. physical, role, cognitive, emotional and social; symptom scales i.e. fatigue, nausea/vomiting, pain and global scale) and each individual items (8, 11, 13, 16, 17 and 28).

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

**AFIRM questionnaire**

For the global score, value at time point, absolute and relative change from Baseline will be given. If
data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

For each of the 52 items, cumulative response among patients with “severe” or “intolerable” handicap at Baseline will be given. For the patients presenting the handicap at Baseline (i.e. answer “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an answer “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

**Sensitivity analysis:** same 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.

- Cumulative response on micturition among patients with the handicap at Baseline
  
  For the patients presenting the handicap at Baseline (i.e. ≥ 8), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.
  
  **Sensitivity analysis:** same 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.

- Cumulative response on stools among patients with the handicap at Baseline
  
  For the patients presenting the handicap at Baseline (i.e. ≥ 6), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.
  
  **Sensitivity analysis:** same 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.

- Urticaria Pigmentosa (UP) evaluation
  
  Percentage of patients with UP improvement at time point.

- Mastocytosis symptoms rebound effect evaluation
  
  Percentage of patients who experiencing a rebound effect on at least one symptom after study/treatment discontinuation. Mean number of symptoms showing a rebound per discontinued patients. Percentage of patients who experiencing a rebound effect per symptom. Mean time of the occurrence of the rebound effect after study/treatment discontinuation. Symptom severity will be described. Patient overall wellbeing from treatment period will be also described.

**Safety:**

Masitinib safety profile will be compared to placebo on the following parameters:

- Occurrence of Adverse Events (AEs)
Follow-Up
Patients who completed the Week 24 period, with regular assessments and evaluation can enter a double blind extension phase:
- In case of positive clinical benefit/response established by investigator
- If required by the investigator and agreed by the patient.

The maximum exposure to treatment is 2 years. Exposure to treatment for more than 2 years will be possible only if:
- A Substantial amendment is approved by Competent Authority
- The benefit/risk for the study is positive based on available data
- The individual benefit/risk is still assessed as positive by investigator and documented

The informed consent form has been resigned to remind patient about potential long term risks. In this case the follow-up of patients will be identical with assessments every 12 weeks.

- Patients with AEs or clinically significant abnormal laboratory test results at the final visit will be followed up by telephone calls, site visit, and/or additional evaluation until resolved or stabilized.

Analysis datasets:
Protocols v5.0 and v6.0 changed handicaps definition from mild to moderate to severe. Additionally protocol v6.0 restricted the inclusion of patients with documented Smouldering or Indolent Systemic mastocytosis. With previous versions of the protocol, patients with cutaneous mastocytosis could be included. Protocol v6.0 restricted the inclusion to documented Smouldering or Indolent Systemic mastocytosis as there was no or limited cutaneous mastocytosis in the 2 phase 2 studies and in an effort to improve the benefit/risk balance.

Thus, the objective of the study is to compare the safety and efficacy of masitinib to placebo in patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap. Therefore patients including before protocol v6.0 and presenting a cutaneous mastocytosis, a non-documented Smouldering or Indolent Systemic mastocytosis or a documented Smouldering or Indolent Systemic mastocytosis with non-severe handicap will be supportive. Efficacy and safety analysis of these patients will be exploratory and will consist in the presentation of individual listing.

- Intention-To-Treat (ITT) dataset

The ITT population will be defined as all patients randomized presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0. Patients will be classified according to the treatment arm to which they have been randomized, irrespective of the actual treatment received. The documented lack of taking at least one dose of the study drug after randomization and patients with no efficacy measure after randomization will be discussed.

- Modified Intent-To-Treat (mITT) dataset

The mITT dataset will include all ITT patients but patients withdrawing prematurely from the study for a well-documented non-treatment-related cause will be excluded. Among these causes, we could list withdrawal of consent for other reason than lack of efficacy or toxicity related to treatment, death for reason not related to treatment or no treatment intake.

- Per Protocol (PP) dataset

The PP data set consists of all patients of the mITT data set without any major protocol deviation. This is the set of patients who participated in the study as intended. Patients terminating the study prematurely will be included in the PP data set provided that there is no protocol deviation. Before
locking the data base, the precise reasons for excluding patients from the PP data set will be fully defined and documented by the Data Review Committee.

Protocol deviations will be defined as:

- inclusion and non-inclusion criteria were not met
- intake of forbidden medication
- non-respect of visit dates
- missing value for main criterion without premature termination
- non-respect of protocol design
- any other deviations during the course of the study

Data Review Committee will classify as “minor” or “major” all the deviations of the study. This classification should be done prior to the unblinding the data.

Safety population

The safety population consists of all patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 who took at least one dose of study medication (masitinib or placebo).

Sample Size:

**Primary analysis**: A total of 142 patients (71 in masitinib group and 71 in placebo group) presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 will provide a 80% power with a two-sided 5% alpha in order to compare masitinib to placebo as primary analysis (GEE model for the cumulative response by patient*handicap : 4 handicaps / 5 visits), under the following hypotheses:

- Same response rate for all the 4 handicaps all along the study ie. 8.5% for placebo vs. 21% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 42.6% for the first study, 23.7% for the second and 30.6% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (24%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.

- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)

- 1:1 design ratio


Taking into account a percentage of non-evaluable patients around 5%, 150 patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 (75 in masitinib group and 75 in placebo group) will be randomized in the study.

**Secondary analysis**: This sample size is sufficient to ensure a power ≥ 80% with an overall two-sided 5% alpha for the cumulative response on pruritus among patients with the handicap at Baseline.

1. GEE model : 5 visits
2. Same response rate all along the study ie. 6% for placebo vs. 24% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 25.0% for the first study, 38.5% for the second and 35.8% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2
### Statistical Methods:

For analysis on pruritus, flushes, Hamilton and FIS:

- Handicaps are defined as: pruritus score $\geq$ 9, number of flushes per week $\geq$ 8, HAMD-17 score $\geq$ 19, Fatigue Impact Scale $\geq$ 75
- Response on a handicap is defined as an improvement $\geq$ 75% for pruritus, flushes, Hamilton and fatigue.

#### Primary analysis:

The primary analysis will be done on the mITT population. It is based on the cumulative response by patient*handicap:

- For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above
- So, from 5 to 20 responses will be calculated by patient: 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients presents the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 4 to week 24: so from 5 to 20 responses by patient (as described above). Beside the treatment, the following factors and covariables will be included in the model: handicap, visit and corresponding interactions. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is $\leq$ 5%.

Sensitivity analysis will be provided with Last Observation Carried Forward (LOCF) and Observed Cases (data remain missing) instead of missing=failure. Sensitivity analyses will also be provided on ITT and PP populations.

#### Secondary analysis:

The secondary analysis will be done on the mITT population. It is based on the cumulative response on pruritus among patients with the handicap at Baseline:

- For the patients presenting the handicap at Baseline (ie. score $\geq$ 9), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above.
- So, 5 responses will be calculated by patient.

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as...
primary analysis).

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 4 to week 24; so from 5 by patient (as described above). Beside the treatment, the following factors and covariables will be included in the model: handicap, visit and corresponding interactions. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is \( \leq 5\% \).

Sensitivity analysis will be provided with Last Observation Carried Forward (LOCF) and Observed Cases (data remain missing) instead of missing=failure. Sensitivity analyses will also be provided on ITT and PP populations will be provided as secondary analysis.

Control of overall family-wise type I error rate:

To guard against spurious inflation of the Type I error rate, if primary analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

| Primary analysis | Cumulative response by patient*handicap on mITT population. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

If this analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

Sensitivity analysis :

- same 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
- same analysis on ITT and PP populations instead of mITT |

| Secondary analysis | Cumulative response on pruritus among patients with the handicap at Baseline (i.e. score \( \geq 9 \)). If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). If this analysis is conclusive at a 5% level, analyses of efficacy will be continued with exploratory analyses.

Sensitivity analysis :

- same 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
- same analysis on ITT and PP populations instead of mITT |

| Exploratory analyses | Analyses on OPA, QLQ, AFIRM, micturition, stools, Urticaria Pigmentosa and mastocytosis symptoms rebound effect.

These analyses are exploratory. |

| Subgroup analysis: | Subgroup analysis is planned for studying the efficacy of the study treatment in patients bearing activation point mutations in the phosphotransferase domain of c-Kit such as the main mutation |
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Asp-816-Val (D816V) in at least one organ versus patients for whom the detection of kit816 is negative in the organ biopsied or unknown. This subgroup analysis will be conducted on all variables. Potential chimeric patients (D816V in one tissue and WT in a second one) will be considered as patient bearing c-kit mutation.
### Table 3: Response definition for Mast Cell Infiltration and Tryptase level

<table>
<thead>
<tr>
<th>Sign</th>
<th>Pathological if at baseline</th>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
<th>Stable Disease (SD)</th>
<th>Progressive Disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>5% or more pathological mast cells (PMC) on bone marrow biopsy, assessed either on morphological ground or by immunohistochemistry or by immunocytology (c-Kit+ and CD25+)</td>
<td>PMC &lt; 5%</td>
<td>PMC &gt; 5% and decrease ≥ 25% from baseline</td>
<td>PMC &gt; 5% and stable number (baseline number ±25%)</td>
<td>Increase ≥ 25% from baseline</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin lesions (extension % body surface or tumor size)</td>
<td>All skin lesions and related symptoms disappeared (=0)</td>
<td>Reduction &gt;25% of skin lesions and related symptoms (decrease by at least 1 pt of the scale score)</td>
<td>All others cases</td>
<td>Progression &gt;25% of skin lesions and/or related symptoms (Increase by at least 1 pt of the scale score)</td>
</tr>
<tr>
<td>Tryptase level</td>
<td>Serum level ≥ 20 µg/ml</td>
<td>Level &lt; 20 µg/ml</td>
<td>Level ≥ 20 µg/ml, and decrease ≥ 25%</td>
<td>Level ≥ 20 µg/ml, and -25% &lt; change ≤ +25%</td>
<td>Increase &gt; 25%</td>
</tr>
</tbody>
</table>

*0 (no symptoms), 1 (mild, infrequent, no therapy required), 2 (mild/moderate and frequent, may be successfully managed by standard therapy), 3 (severe and frequent, requiring extensive local and systemic therapy), and 4 (requiring immediate therapy and hospitalization, severe adverse event, SAE).

### Table 4: Definition of Symptomatic treatment failure with respect to patient enrolment

<table>
<thead>
<tr>
<th>Overall Biological Response</th>
<th>Bone marrow</th>
<th>Skin</th>
<th>Tryptase level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
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<tr>
<td>Partial Response</td>
<td>At least one PR without any PD</td>
<td></td>
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<tr>
<td>Stable Disease</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>At least one PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A failure is, for one handicap, a failure to at least one treatment.

### Handicap

<table>
<thead>
<tr>
<th>Handicap</th>
<th>Anti H1</th>
<th>Anti H2</th>
<th>Proton Pump Inhibitor</th>
<th>Cromoglycate</th>
<th>Antileukotriene</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>RUD</td>
<td>1 month</td>
<td></td>
<td></td>
<td></td>
<td>Local corticosteroid 6 weeks</td>
</tr>
<tr>
<td>Flashes</td>
<td>RUD</td>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton score</td>
<td>RUD</td>
<td>3 month</td>
<td>RUD 6 weeks</td>
<td>RUD 6 weeks</td>
<td>RUD 6 weeks</td>
<td>Anti depressive drug 3 months</td>
</tr>
<tr>
<td>Nbr stools</td>
<td>RUD</td>
<td>6 weeks</td>
<td>RUD 6 weeks</td>
<td>RUD 6 weeks</td>
<td>RUD 6 weeks</td>
<td></td>
</tr>
<tr>
<td>Nbr micturitions</td>
<td>RUD</td>
<td>1 month</td>
<td>RUD 6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RUD: Recommended Usual Dose.
## STUDY FLOW-CHART

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment period</th>
<th>Treatment period</th>
<th>Extension period</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>Baseline</td>
<td>Week 0</td>
<td>W1, W2, W3, W5, W6, W7, W10</td>
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<tr>
<td>Patient Visit</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Written Informed Consent</td>
<td></td>
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<tr>
<td>Call to patient</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Medical History</td>
<td>x</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Inclusion/exclusion</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient able to follow the patient card procedures</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Mast cell infiltration assessment:

- Skin biopsy: x
- And/or Bone marrow aspirate/biopsy (optional): x
- Tryptase level: x

### Decision to randomize the patient

x

### Handicap assessment:

- Pruritus score: x
- Flashes/week: x
- HAMD-17: x
- Fatigue Impact Scale: x
- Stools/day: x
- Micturitions/day: x
- Anaphylactic shock: x
- QLQ-C30 scores: x
- Overall Patient Assessment: x
- AFIRMM Score V2: x
- UP evaluation: x

### Safety assessment:

- Adverse events: x
- Concomitant treatment: x
- Physical examination including vital signs and weight: x
- ECG: x
- Doppler echocardiography: x
- NT pro BNP (or BNP): x
- Chest X-ray[5]: x
- Haematology: x
- Liver enzymes: x
- Biochemistry: x
- Urinalysis (dipstick)[2]: x
- Urinary Cytology and NMP22 test: x
- Spermogram (optional): x

[1] (Final visit)
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
<th>Week 11</th>
<th>Week 12</th>
<th>Every 12 weeks</th>
<th>Week 24</th>
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<tr>
<td>Menstrual cycle</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
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<tr>
<td>FSH/LH/estradiol/progesterone assessments</td>
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<td></td>
<td></td>
<td>every 12 weeks</td>
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<tr>
<td>Pregnancy test (serum)</td>
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<td></td>
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<td>x</td>
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<td>Pelvic ultrasound</td>
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<td></td>
<td></td>
<td></td>
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<td>Study Treatment dispensation</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Treatment compliance</td>
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</tbody>
</table>

(1) If the final visit is performed on week 24, all assessment will not be repeated.
(2) In case of proteinuria >1+ (30 mg/dL) on the dipstick, 24-H protein will be measured.
(3) In non-menopausal women using non-hormonal contraceptive method.
(4) Additionally, at any time in case of suspicion of pregnancy.
(5) In case a chest X-ray has been performed within 3 months prior to baseline, it might be used as baseline chest X-ray. For chest X-ray only Posterior-Anterior view is required.
(6) Mastocytosis symptoms rebound effect assessment should be performed by telephone call or during site visit starting from one month after treatment discontinuation (for any reason)/end of the study; appropriate pages in CRF should be completed.
(7) In women of childbearing potential.
Localisation of the blood and urinary tests (C: Central Lab / L: Local lab):

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment period</th>
<th>Treatment period</th>
<th>Extension period</th>
<th>End of study</th>
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</tr>
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</tr>
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<tr>
<td>NT proBNP or BNP</td>
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<td></td>
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</tr>
<tr>
<td>FSH / LH / Estradiol / Progesterone</td>
<td>L / Every 12 weeks</td>
<td></td>
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<td>L</td>
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<tr>
<td><strong>Urinalysis</strong></td>
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<tr>
<td>Specific gravity</td>
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<td></td>
<td>L</td>
</tr>
<tr>
<td>Blood</td>
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<td></td>
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<td>Test</td>
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<tr>
<td>Leukocytes</td>
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<tr>
<td>Ketones</td>
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</tr>
<tr>
<td>Nitrites</td>
<td></td>
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</tr>
<tr>
<td>Urinary cytology and NMP22 test</td>
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<td>L</td>
<td>L / W12 only</td>
<td>L</td>
</tr>
</tbody>
</table>

(1) If the final visit is performed on week 24, all assessment will not be repeated.
(2) If proteinuria ≥ 1+ (30 mg/dL) on the dipstick, 24-hour proteinuria should be performed.
(3) Only at week 2 and week 6.
(4) Only for pre-menopausal women not using hormonal contraceptive.
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ANALYSES WILL BE PERFORMED AS DESCRIBED IN SECTION 8.1.1.

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4. ABBREVIATIONS

AE  
Adverse event
AFIRMM  
Association Française pour les Initiatives de Recherche sur le
Mastocyte et Les Mastocytoses
CDR  
Central Document Review
CI(1-α)%  
Confidence interval (level (1-α) %)
CMH  
Cochran-Mantel-Haenszel
CRF  
Case Report/Record Form
ECG  
Electrocardiogram
GEE  
Generalized Estimating Equations
IDMC  
Independent Data Monitoring Committee
ITT  
Intention-to-treat
LVEF  
Left Ventricular Ejection Fraction
LOCF  
Last Observation Carried Forward
MDF  
Missing Data equal to Failure
mITT  
Modified Intention-to-treat
NA  
Not Applicable
OPA  
Overall Patient Assessment
OR  
Odds Ratio
PP  
Per Protocol
Q1  
1st quartile
Q3  
3rd quartile
QLQ-C30  
Quality of Life Questionnaire – Core questionnaire
QOL  
Quality Of Life
SAE  
Serious Adverse Event
SAF  
Safety population
SD  
Standard Deviation
5. INTRODUCTION

This statistical analysis plan specifies and completes the analyses planned in the statistical section of the protocol. This statistical analysis plan was written before database lock and the blind breaking.

The statistical analyses will be performed under the supervision of AB Science biostatistician.

6. POPULATIONS

Initial versions up to version 4.0 of the protocol included mastocytosis patients with moderate and severe handicaps.

Following scientific advice with the EMA, protocols v5.0 and v6.0 changed handicaps definition to severe.

To increase benefit/risk ratio following discussion with authorities for indications in non-oncology, protocol was amended to include only mastocytosis patients with severe handicaps.

EMA was consulted on this question through scientific advice in October 2011 (EMA/CHMP/H/SA/573/2/FU/2/2011/PA/SME/II) and EMA validated the increase of severity of handicaps. EMA mentioned that “the increase of the baseline severity of population is in general desirable”.

The implementation of this increase was performed in V5.0 and V6.0 of the protocol.

Handicaps specified in inclusions criteria of study protocol V4.0 to V6.0 were strengthened:

- Pruritus score from \( \geq 6 \) to \( \geq 9 \)
- Flashes frequency per week from \( \geq 7 \) to \( \geq 8 \)
- Hamilton score from \( \geq 10 \) to \( \geq 19 \)
- FIS score from \( \geq 40 \) to \( \geq 75 \)

It took two protocol versions to reach the desirable severity level of handicap; protocol version 5.0 still had some level of handicaps incompatible with severe handicaps.

For example:

- For Hamilton score, definition of severity is a score \( \geq 19 \). In protocol version 5.0 the severity level for inclusion was \( \geq 14 \), a score of 14 corresponding to moderate depression level.
- For flushes frequency per week, a frequency \( \geq 7 \) (protocol version 5.0) was interpreted as one per day, when \( \geq 8 \) is more than one per day.

Still, in an effort to improve the benefit/risk balance, protocol v6.0 restricted the inclusion of patients with documented Smouldering or Indolent Systemic mastocytosis.

Systemic mastocytosis patients are more severely impaired as demonstrated by AFIRMM published results of a case-control study (Hermine et al. PLoS ONE 2008) showing more severe symptoms in systemic mastocytosis patients than in cutaneous patients. The OPA score results on patients participating in the AFIRMM pathophysiological study show that the systemic mastocytosis (SM) patients experienced more severe handicap than the cutaneous mastocytosis (CM) patient, 28% (23/82) of SM patients experienced severe to intolerable handicap against 15% (5/33) of the CM patients (p-value=0.0386). The AFIRMM score results on patients participating in the AFIRMM pathophysiological study show that the systemic mastocytosis (SM) patients experienced more severe
handicap than the cutaneous mastocytosis (CM) patient, AFIRMM score was 124 in median for SM patients against 84 for the CM patients (p-value=0.0225, Wilcoxon test). The OPA and AFIRMM scores results show that systemic mastocytosis patients experienced more severe handicap than the cutaneous mastocytosis patients.

The objective of study AB06006 is to compare the safety and efficacy of masitinib to placebo in patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap not responsive to optimal symptomatic treatment.

Safety data of the patients included before protocol v6.0 and presenting a cutaneous mastocytosis, or a non-documented Smouldering or Indolent Systemic mastocytosis, or a documented Smouldering or Indolent Systemic mastocytosis with non-severe handicap, will be supportive and descriptive.

### 6.1. **Severity assessment**

Patient will be classified as severe if he/she suffers of at least one of the main handicaps as defined on the four symptoms above:

- Pruritus score ≥ 9
- Number of flushes per week ≥ 8
- Hamilton rating scale for depression(HAMD-17) score ≥ 19
- Fatigue Impact Scale total score (asthenia) ≥ 75

### 6.2. **Smouldering or Indolent Systemic mastocytosis assessment**

A central review of patient cases was performed to homogenize the diagnosis of severe smouldering and indolent systemic mastocytosis patients. In this part, is provided extracts of the Note to File on Central reading definition of systemic mastocytosis.

#### 6.2.1. Justification of criteria used to define systemic mastocytosis

The key inclusion criteria defined in the protocol are:

1. Patient with one of the following documented mastocytosis as per WHO classification:
   - Smouldering Systemic Mastocytosis
   - Indolent Systemic Mastocytosis

2. Patient with documented mastocytosis and evaluable disease based upon histological criteria: typical Infiltrates of mast cells in a multifocal or diffuse pattern in skin and/or bone marrow biopsy.

The first inclusion criterion was applied to exclude aggressive forms of mastocytosis according to WHO classification. The second criterion was meant to select patients with the criteria previously used in phase 2 studies and in AFIRMM study (refer to Appendix 1 to 4).

The criteria for systemic mastocytosis retained in study AB06006 v6 of the protocol were based on the following objectives:

- To confirm results of phase 2 studies in the population of systemic mastocytosis defined in phase 2

The objective of the phase 3 was to confirm that masitinib is effective for patients having systemic mastocytosis as defined in phase 2. The definition used in phase 2 does not refer to WHO.
classification but to patients having more than one organ infiltrated by mast cells. This population encompass more patients than with WHO definition for systemic mastocytosis.

- To restrict the claim to severe systemic mastocytosis as opposed to non-severe systemic mastocytosis or cutaneous mastocytosis

In an effort to increase the benefit/risk balance, the amendment 6 was implemented to restrict the claim to patients with severe form of systemic mastocytosis and therefore excluded patients with cutaneous mastocytosis or non-severe systemic mastocytosis. The fact that cutaneous mastocytosis was less severe was demonstrated through the AFIRMM epidemiology study. In this AFIRMM study, the systemic mastocytosis (SM) patients experienced more severe handicap than the cutaneous mastocytosis (CM) patient, 28% (23/82) of SM patients experienced severe to intolerable handicap against 15% (5/33) of the CM patients (p-value=0.0386) based on OPA score. AFIRMM score was more severe between patients with SM and CM (median 124 [n = 82] vs. 84 [n = 33]; P = 0.0225), (refer to Note to file Version 1.0 dated 07/10/2014, §3 on Justification of the amendments of the protocol and Hermine et al. PLoS ONE 2008).

Furthermore, the AFIRMM definition of systemic mastocytosis was defined as patients who had more than one organ infiltrated by mast cells and was not referring to WHO classification

6.2.2. Need for Central Document Review (CDR)

Investigators were using available data to define whether a subject with mastocytosis is systemic or cutaneous, but sometime did not use the same rules to identify the patients as systemic.

In their practice, investigators did not rely entirely on WHO classification to classify patients as having systemic mastocytosis. Among the 135 patients with severe systemic mastocytosis according the CDR, 108 (80%) fulfilled the criteria for WHO classification of systemic mastocytosis.

The relevance of WHO classification for systemic mastocytosis as was previously highlighted by AB Science during scientific advice with EMA (Procedure N° EMEA/H/SA/573/2/FU/2/2011/PA/SME/II, Refer to Appendix 5)

Therefore, there was a necessity to develop a central homogeneous definition of systemic mastocytosis respecting criterion 1 and 2 of the protocol.

To be noted: criterion 2 allows several possibilities for the combination of organs (bone marrow, skin, digestive organs) and allows to diagnose systemic for patients who have mastocytes in bone marrow without any abnormality.

The primary analysis will be performed on the Central Documentation Review (CDR) systemic severe population.

6.2.3. Definition of central document review (CDR) for classification as systemic mastocytosis

The retained classification of systemic mastocytosis is based on an excess of mast cells or a presence of abnormal mast cells in at least two organs.

All patients have excess presence of mast cells in the skin, expressing D816V mutation or not. The Central Documentation Review is therefore based on findings the bone marrow or digestive organs.

Central Documentation Review defines systemic mastocytosis based on the following criteria, present in the records of the patients:

1. Bone marrow biopsy or aspirate associated with at least a sign of abnormality of mast cells:
   - Signs of abnormality of mast cells are:
a) Abnormal aggregates of mast cells in a sample in bone marrow:
The criteria is deemed satisfied if the aggregate i) is quantified and is strictly above 15 mast cell
per aggregated (corresponding to WHO major criterion), or ii) is not quantified but is described
as nodule, seat, cluster, focus, or granuloma and therefore pathological

b) >25% atypical mast cells in a sample of bone marrow (corresponding to WHO minor criterion)

c) c-Kit point mutation at codon 816 in bone marrow (corresponding to WHO minor criterion)

d) Abnormal mast cells in the sample of bone marrow while microscopic testing that can be
described by the following words: Spindled ; Abnormal ; Atypical ; Fusiform ; Dystrophic ;
Pathologic ; Dysmorphic (corresponding to WHO minor criterion)

e) Abnormal immunohistochemistry signs: mast cells in bone marrow express CD2 or/and CD25
present (corresponding to WHO minor criterion)

f) Abnormal infiltration of mast cells in the bone marrow
   The criteria is deemed satisfied if the infiltration i) is quantified and is strictly above 3% in the
   biopsy, or ii) is not quantified but is abnormal as described with infiltration , contingent of mast
   cells, or proliferation and therefore pathological.

2. Detection of c-kit 816 in the bone marrow without evidence of mast cells in bone marrow but with
evidence of c-Kit 816 in skin, justifying clonality

3. Excess of mast cells in digestive organs

The level of tryptase serum above 20ng/mL, which is part of the WHO classification, is not retained in
the CDR classification because this criterion is not specific to systemic mastocytosis, since 32% of
cutaneous mastocytosis have elevated tryptase level above 20ng/mL (AFIRMM study in 593 patients).
Patients with rare and normal presence of mast cells in the bone marrow biopsy or aspirate and
without signs of abnormality of mast cells are not retained in population of systemic mastocytosis as
defined by the CDR, as per recommendation of the medical experts.

The Central Documentation Review has been reviewed and validated before unblinding by Olivier
Hermine, head of reference mastocytosis center in France and Olivier Lortholary international
coordinator of the study. Sample size

6.3. Sample size

6.3.1. Definition of the sample size in the protocol

Primary analysis : A total of 142 patients (71 in masitinib group and 71 in placebo group) presenting a
documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by
protocol v6.0

Taking into account a percentage of non-evaluable patients around 5%, 150 patients presenting a
documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by
protocol v6.0 (75 in masitinib group and 75 in placebo group) will be randomized in the study.

6.3.2. Justification of the actual sample size

The actual number of patients in the ITT population is 135 patients, based on Central Review
Documentation of patients with severe systemic mastocytosis.

Starting in 2015, after implementation of version 6 of the protocol, the Central Review Documentation
started to be initiated because end of recruitment was anticipated due to the rarity of new patients.
Indeed, mastocytosis is an orphan disease, and patients with systemic mastocytosis associated with severe symptoms are even more rare.

- As of March 2015, 112 sites were opened worldwide (including sites in India and South America).
- Only 40 sites were able to recruit at least 1 patient with systemic mastocytosis severe handicaps and only 8 sites were able to recruit more than 5 patients with systemic MCO severe handicaps.
- All options/efforts to recruit patients with systemic mastocytosis severe handicaps were exhausted
- Recruitment in the study had been on-going since March 2009, equivalent to seven years.
- Opening of recruitment in Romania was expected to provide an additional 6 patients to the study, but the application was still processed by the competent authority after 18 months (initial study submission was performed 27 Sep 2013)

At the IDMC meeting on 22 June 2015, the sponsor explained to the IDMC members why the enrolment was going to be closed (slide 28 and 29 of the presentation)

The ITT population under Central Review Documentation remained at **135 patients**.

### 6.4. Statistical analysis populations

The primary data set to be analyzed for efficacy in this study will be the mITT data set as per protocol.

#### 6.4.1. Intent-To-Treat population (ITT)

The ITT population is defined as all patients with severe systemic mastocytosis randomized, based on Central Review Documentation of patients with severe systemic mastocytosis (refer to the Note to File on Number of Patients in the ITT population).

Patients are classified according to the treatment arm to which they have been randomized, irrespective of the actual treatment received.

Particular case of patient 70102 was discussed during the Blind Review. This patient was screened and randomized in October 2014 but was not treated due to a wasp bite. Patient came again on site and was randomized in December 2014 on another patient number: 70104. He was then treated with study drug and is still ongoing in the study (in extension part). It was decided by the sponsor to keep patient 70104 and to ensure all screening/baseline data were collected under this patient number. Patient 70102 is considered as excluded from ITT.

The actual number of patients in the ITT population is 135 patients, based on Central Review Documentation of patients with severe systemic mastocytosis.

#### 6.4.2. modified Intent-To-Treat population (mITT)

The mITT population is the population that was designated for the primary analysis, across all version of the protocol.
The protocol indicates that the “mITT dataset will include all ITT patients but patients withdrawing prematurely from the study for a well-documented non treatment-related cause will be excluded”.

The first modification relates to the clarification of terminology from treatment Related / Not Related to treatment Failure / Non Failure cause. In the protocol, there was a distinction between reasons related to treatment and reasons not related to treatment, whereas we will classify withdrawal reasons according to failure or non-failure causes. The clarification is needed since a discontinuation for AE non related to treatment will be classified in failure.

The second modification relates to study procedures, which were considered as not related to the treatment, and are now considered as a cause of failure. Indeed, a discontinuation for reason “fed up with procedure” will be classified as failure since in case of registration there will still be procedure associated with the treatment with masitinib.

The mITT definition is clarified as follows:

The mITT dataset includes all ITT patients but patients withdrawing prematurely from the study during the protocol part (Week0-Week24) for a well-documented non-failure cause.

Among these non-failure causes, we could list:
- Lost to follow-up
- Violation of inclusion and/or exclusion criteria
- Withdrawal of informed consent due to travel or move
- No treatment intake

Other reasons will be considered as failure causes, such as:
- Adverse events related to treatment
- Adverse events not related to treatment
- Lack of efficacy
- Non-compliance with protocol
- Withdrawal of informed consent due to study procedure
- Withdrawal of informed consent for reason not specified

6 patients are excluded from the mITT population based on this definition. They are the followings:

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Reason of exclusion of the mITT</th>
<th>Last visit performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>00134</td>
<td>No treatment intake</td>
<td>W0 (baseline)</td>
</tr>
<tr>
<td>13001</td>
<td>No treatment intake</td>
<td>W0 (baseline)</td>
</tr>
<tr>
<td>01016</td>
<td>Lost to follow-up</td>
<td>W0 (baseline)</td>
</tr>
<tr>
<td>01026</td>
<td>Lost to follow-up</td>
<td>W8</td>
</tr>
<tr>
<td>09505</td>
<td>Lost to follow-up</td>
<td>W4</td>
</tr>
<tr>
<td>16903</td>
<td>Patient was withdrawn from the Protocol by the investigator due to violation of inclusion/exclusion criteria</td>
<td>W0 (baseline)</td>
</tr>
</tbody>
</table>
Patient 16903 did not respect inclusion criteria #7: Absolute neutrophils count (ANC) ≥ 2.0 x 10⁹/L at baseline). At baseline, the patient had a grade 2 neutropenia (neutrophil count =1170 M/L), just slightly above grade 3 (neutrophil count = 500 - 1000 M/L).

Consequently, the actual number of patients in the mITT population is 129 patients, based on Central Review Documentation of patients with severe systemic mastocytosis.

Of note, none of the 6 patients excluded with mITT population have available data at week 8 and after, except patient 1026. This patient 1026 has data available at week 4 and week 8 and is lost to follow-up after week 8. The data at week 4 is no taken into account for efficacy assessment as per protocol. Because the patient is lost to follow-up, the data after week 8 is not replaced given the definition adopted for missing data (refer to Note to File on Missing Data equal to Failure (MDF) method for patient present at visit but with data missing). Consequently, there is marginal difference expected between the analysis in the ITT and the mITT population.

Consequently, the primary analysis in the mITT population, which is planned in the protocol, is maintained.

### 6.4.3. Per-Protocol population (PP)

The PP data set consists of all patients of the mITT data set without any major protocol deviation. This is the set of patients who participated in the study as intended. Patients terminating the study prematurely will be included in the PP data set provided that there is no major protocol deviation. Before locking the data base, the precise reasons for excluding patients from the PP data set will be fully defined and documented by the Data Review Committee.

Data Review Committee will classify as “minor” or “major” all the deviations of the study. This classification should be done prior to the unblinding.

This meeting was held on October 28th 2015.

The main deviation (major) is the discontinuation of patients when the investigator did not respect the protocol safety procedures, including dose reduction. The patient is stated in major protocol deviation if the three following criteria are met:

- Investigator Protocol violation who discontinued patient despite protocol saying to continue with or without dose reduction
- Patients did not express willingness to discontinue study
- Investigator recognized violation

Since primary analysis uses MDF, this violation can cause a major bias on the interpretation of the results.

### Patients excluded of the PP population from the mITT population:

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Reason of exclusion of the PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>00123</td>
<td>Non respect by the investigator of protocol safety rules, including dose reduction</td>
</tr>
<tr>
<td>00128</td>
<td>Non respect by the investigator of protocol safety rules, including dose reduction</td>
</tr>
<tr>
<td>00135</td>
<td>Non respect by the investigator of protocol safety rules, including dose reduction</td>
</tr>
<tr>
<td>01407</td>
<td>Non respect by the investigator of protocol safety</td>
</tr>
</tbody>
</table>
Consequently, the actual number of patients in the PP population is 124 patients, based on Central Review Documentation of patients with severe systemic mastocytosis.

6.4.4. Concomitant treatments and PP population

Symptomatic treatments have been introduced or increased in a lot of patients. It was not authorized per protocol but was not considered a major protocol deviation by Blind Review Committee. Given the severity of the handicaps, it was considered ethical. However this increase or introduction of symptomatic treatments adds more value to the demonstration of the efficacy of masitinib with optimal symptomatic treatments before baseline and also in the course of the study up to Week 24 and in extension. An update of the label to “optimal symptomatic treatment before and even during treatment” was validated by the Data Review Committee on October 28th 2015.

6.4.5. Population not discontinued within 3 months (>3M)

The >3M population will include all mITT patients excluding patients withdrawn before Week 12 or at Week 12 visit, whatever the reason of discontinuation.

The reason for this population is that masitinib tolerability is increasing with time, there is a sharp drop of adverse events after 3 months, as explained in MASITINIB MESYLATE (AB1010) Investigator’s Brochure for Non-oncology studies, July 2015:

- The incidence rates of AE (per patient-year) reported are 3.27 and 2.56 during the first 3 months versus 0.24 and 0.34 after the third month in open label or uncontrolled studies (masitinib arm) and blinded studies respectively.
- The incidence rates of AEs leading to discontinuations (per patient-year) are 1.52 and 0.57 during the first 3 months versus 0.12 and 0.05 after the third month in open label or uncontrolled studies (masitinib arm) and blinded studies respectively.

In this protocol, study drug initial dosage was 6mg/kg/day. However, an alternative to reach 6 mg/kg/day could have been to start at 3 mg/kg/day and increase dose until 6mg/kg/day at Week 12 to minimize adverse events and discontinuations during the first three months.

Patients excluded of the >3M population from the mITT population:

<table>
<thead>
<tr>
<th>Patient number</th>
</tr>
</thead>
<tbody>
<tr>
<td>00113</td>
</tr>
<tr>
<td>00123</td>
</tr>
<tr>
<td>00404</td>
</tr>
<tr>
<td>00601</td>
</tr>
<tr>
<td>01009</td>
</tr>
<tr>
<td>01029</td>
</tr>
<tr>
<td>01407</td>
</tr>
<tr>
<td>01601</td>
</tr>
<tr>
<td>06001</td>
</tr>
<tr>
<td>06004</td>
</tr>
</tbody>
</table>
6.4.6. Safety population (SAF) and “SAF SS+Others” population

The safety population (SAF) includes all patients with severe systemic mastocytosis who took at least one dose of study medication (masitinib or placebo).

Absence of documented treatment intake will be stated if one of the 2 following criteria is fulfilled in the End of Study Form:

- date of last intake can be “NA/NA/NA” or “A”
- date of last intake is empty and flag “date of treatment intake NA” is ticked

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Reason of exclusion of the SAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>00134</td>
<td>No treatment intake</td>
</tr>
<tr>
<td>13001</td>
<td>No treatment intake</td>
</tr>
</tbody>
</table>

Patients excluded of the SAF populations from the ITT population:

The “SAF SS+Others” includes all patients who took at least one dose of study medication (masitinib or placebo), regardless the severe and/or systemic criteria.

Analyses performed on this population will be only supportive and descriptive.
7. STATISTICAL METHODOLOGY

7.1. General considerations

The statistical analysis will be performed under the supervision of AB Science biostatistician. The statistical analysis plan will be written before database lock and before unblinding.

The type I ($\alpha$) error will be 5% (two-sided) for efficacy and quality of life (results will be presented with a two-sided 95% CI). Unless otherwise specified, no statistical test will be performed for safety analyses.

Quantitative endpoints will be presented by treatment group in terms of mean, standard-deviation, median, extreme values and number of missing data. Qualitative endpoints will be presented by treatment group in terms of number and percentage for each modality. Percentage will be calculated among filled data, if not otherwise specified.

The primary data set to be analyzed for efficacy in this study will be the mITT data set, according to study protocol. Efficacy analyses will also be carried out on the PP and $> 3M$ data sets.

All data analyses and reporting procedures will use SAS v9.4 or latest version.

7.2. Specific topics

7.2.1. Use of repeated measures in the statistical analysis

Use of repeated measures in the statistical analysis, in line with the EMA guideline on clinical trial on small population (CHMP/EWP/83561/2005), was planned in the protocol version 6.0 to counteract the rarity of the population.

In the protocol up to the version 5.0, the main statistical analysis was the response on at least one handicap at week 24.

As the population included in the protocol version 6.0 was restricted to severe systemic patients, an even smaller population than the patients suffering of moderate to severe cutaneous and systemic mastocytosis, the main statistical analysis will be performed on repeated measurements over time and over handicaps, as recommended in the EMA guideline on clinical trial on small population (CHMP/EWP/83561/2005). In this guideline EMA recommends to “minimize bio-noise” in the context of a small population study, by using repeated measures analysis. In the guideline it is mentioned that “Repeated measurements over time – or in different body locations – may also improve the efficiency of an analysis”.

The implementation of the repeated measures analysis was performed in V6.0 of the protocol, with main statistical analysis being the analysis of response repeated over handicap and over time from week 8 to week 24.

Then, cumulative response by patient*handicap is the primary variable/endpoint for the analysis. For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS).
7.2.2. Analysis on the W8-W24 time window

In the protocol version 6.0, the primary analysis is planned to be performed from W8 to W24, to assess of the efficacy of the treatment after two months of treatment.

Early efficacy assessment (W4) was not planned to be included in the primary analysis as:

- All patients were required to take anti-histamines between Baseline and week 4 even if they didn’t take such treatment before study entry
- Based on phase II studies, first month of treatment is less efficient

In addition, the non-inclusion of early efficacy measurement (W4) in the analysis was addressed in EMA scientific advice in June 2006 (EMEA/CHMP/H/SA/573/2/FU/1/2006/PA/II). The EMA advised AB science as follows: “The company proposes not to include the results from the first 8 weeks because there are known side effects of AB1010 in the early part of treatment. … Patients who drop out of the study during the first 8 weeks should still be included in the primary analysis.”

As advised by the EMA, missing data equal to failure method will be applied to the early discontinued patients, as defined in Section 7.3.2.1.

7.2.3. Increase in the cut-off point for response up to 75% improvement of the baseline handicap

To increase benefit/risk ratio following discussion with authorities for indications in non-oncology and to enhance the clinical relevance of the response, protocol was amended to increase the cut-off point for response up to 75% improvement of the baseline handicap.

EMA was consulted on this question through scientific advice in October 2011 (EMA/CHMP/H/SA/573/2/FU/2/2011/PA/SME/II) and EMA validated the increase in the cut-off point for response up to 75% improvement of the baseline handicap. EMA mentioned that “the proposed increase in the cut-off point for response criteria would lead to more strict definition of product efficacy and, to this respect is regarded, a priori, as conservative, more clinically relevant and thus in principle desirable”.

The implementation of this increase was done in V5.0 and V6.0 for the four handicaps (pruritus score, flushes frequency per week, Hamilton score and FIS score).

It took two protocol versions to reach the desirable cut-off point for response; protocol version 5.0 still had some cut-off point for response below 75%. For instance, in protocol version 5.0, the response for Hamilton score was stated as an improvement of two severity categories (HAMD-17 categories: 0-7 Normal, 8-13 Mild Depression, 14-18 Moderate Depression, 19-22 Severe Depression, ≥ 23 Very Severe Depression), that corresponds for a baseline level of 14 to an improvement of 50%, and for a baseline level of 19 to an improvement of 30%, even lower that the initial cut-off point for response of 50%. Therefore in protocol 6.0 and 7.0, Hamilton response was define using a cut-off point equal to 75% improvement, as the other symptoms.
7.3. **Precision on differences between SAP and protocol**

7.3.1. **Missing Data equal to Failure (MDF) method for patient present at visit but with data missing**

Protocol indicates that “If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).”

We modified the protocol definition of MDF for patients who are present at visit and for whom data is missing. In this case, protocol indicates to consider the response as a failure, whereas we will not replace the data, which is preferable, as non-observed values can be considered as Missing Completely At Random (MCAR).

MDF definition should be precised in the SAP as compared to protocol for application to the ITT population and for the population in extension and in alignment with the definition of mITT population (refer to Note to File on definition of mITT and PP population).

The second modification relates to the clarification of terminology from treatment Related / Not Related to treatment Failure / Non Failure cause. In the protocol, there was a distinction between reasons related to treatment and reasons not related to treatment, whereas we will classify withdrawal reasons according to failure or non-failure causes. The clarification is needed since a discontinuation for AE non related to treatment will be classified in failure.

The third modification relates to study procedures, which were considered as not related to the treatment, and are now considered as a cause of failure. Indeed, a discontinuation for reason “fed up with procedure” will be classified as failure since in case of registration there will still be procedure associated with the treatment with masitinib.

The cause of failure / non failure for MDF are therefore defined as follows:

**Failure causes:**
- Adverse events related to treatment
- Adverse events not related to treatment
- Lack of efficacy
- Non-compliance with the protocol
- Withdrawal of informed consent due to study procedures
- Withdrawal of informed consent for reason not specified
- End of study period without extension: This is considered as failure to be conservative since all patients had the possibility to go in the extension phase
- ANSM request. Four patients wrongly declared by the investigator as having cutaneous mastocytosis and therefore discontinued at the request of ANSM. Yet these patients fulfilled the criteria of systemic mastocytosis according to the Central Review Documentation but are considered as failed to be conservative. These patients were discontinued in extension phase without impact on the main analysis.

**Non-failure causes:**
- Lost to follow up
- Violation of inclusion and/or exclusion criteria
- Withdrawal of consent due to travel or move
- No treatment intake
7.3.2. **mITT definition**

The mITT definition is specified in this SAP regarding timing of withdrawal. In the protocol it was mentioned that patients were excluded from the mITT dataset if prematurely withdrawn (for a non-failure cause) whenever during the study, whereas in this SAP, patients are excluded from mITT if withdrawn (for a non-failure cause) during the protocol part (Week0-Week24).

The mITT dataset will include all ITT patients excluding patients prematurely withdrawn during the protocol part (Week0-Week24) for a well-documented non-failure cause. Patients withdrawn during the extension period for a failure reason will not be excluded from the mITT population.

7.4. **Specific procedures for statistical analysis**

7.4.1. **Management of missing data for efficacy analysis**

7.4.1.1. **Qualitative variables**

For qualitative binary variables, such as a response (yes/no), main analysis will be performed with the Missing Data equal to Failure (MDF) method.

Missing Data equal to Failure (MDF) method is defined as follows:

A. Replacement of missing value due to patients withdrawn from the study:
   - Case 1: discontinuation for a documented failure cause.
     - In this case, missing data will be imputed as failure (missing = failure as primary analysis).
     - Among documented failure causes there are:
       - Adverse events related to treatment
       - Adverse events not related to treatment
       - Non-compliance with the protocol
       - Lack of efficacy
       - Withdrawal of informed consent due to study procedures
       - Withdrawal of informed consent for reason not specified
       - End of study period without extension
       - ANSM request.
     - Among documented non-failure causes, there are:
       - Lost to follow up
       - Violation of inclusion and/or exclusion criteria
       - Withdrawal of consent due to travel or move
       - No treatment intake
     - Case 2: discontinuation for a documented non-failure cause. In this case, non-observed values can be considered as Missing At Random (MAR), and no imputation will be done (Observed Cases)
   
     "Lost to follow up", is when site did its best effort to collect information of patient status, but failed.

   B. Replacement of missing value due to patients present at the visit or who did not attend the visit without discontinuation (i.e. last visit is after the missing visit)
If data is missing, the data will not be replaced.
Note: if the patient could have reached the visit (according to time since baseline), MDF will be applied up to this visit the patient could have reached. This rule applies for extension.

### 7.4.1.2. Quantitative variables

For quantitative variables, main analysis will be performed with the Last Observation Carried Forward (LOCF) method.

Last Observation Carried Forward (LOCF) method is defined as follows:

A. Replacement of missing value for patients withdrawn from the study:

- Case 1: discontinuation for a documented failure cause. In this case, missing data will be imputed with the Last Observation Carried Forward (LOCF) method. To be noted, if the last available data is the baseline value, the baseline value will be carry forward.
- Case 2: discontinuation for a documented non-failure cause. In this case, non-observed values can be considered as Missing At Random (MAR), and no imputation will be done (Observed Cases).

B. Replacement of missing value due to patients present at the visit or who did not attend the visit without discontinuation (i.e. last visit is after the missing visit)

If data is missing, the data will not be replaced (Observed Cases).

Note: if the patient could have reached the visit (according to time since baseline), LOCF will be applied up to this visit the patient could have reached. This rule applies for extension.

### 7.4.2. Baseline and post baseline data selection

For efficacy data, the baseline value used for the analysis will be the last available value (among screening or baseline value) before study treatment intake.

For safety data, same rule will be applied, unless specified differently in the SAP dedicated section.

### 7.4.3. Adjustment

The primary analysis will be adjusted on the following variables:

- Handicap (pruritus, flushes, Hamilton, FIS) as per eCRF
- Visit (W8, W12, W16, W20, W24)

Note: the “corresponding interactions” between handicap and visit variables, planned to be included in primary analysis statistical model in the protocol, will be no longer included in the model to prevent for non-convergence of it.
7.4.4. Weighting of the primary and secondary efficacy analysis

As a central review of the systemic status of the patients was performed after the randomization was finished, an imbalance between treatment groups in the number of patients with a given handicap (either pruritus, flushes, Hamilton, or FIS) could occur.

To account for this possible imbalance, each observation will be weighted according to the following formula:

\[
\text{Weight}_i = \frac{N_{\text{tot}}}{2N_{\text{trt}_i}}
\]

Where:

- \(N_{\text{tot}}\): is the total number of patients with a given handicap (either pruritus, flushes, Hamilton, or FIS)
- \(N_{\text{trt}_i}\): is the number of patients with a given handicap (either pruritus, flushes, Hamilton, or FIS) in the treatment group \(i\) (either masitinib or placebo)

For example, if there is an imbalance for a handicap, with 40 patients with this handicap in the treatment group 1, and 50 patients in the treatment group 2, for a total number of patients of 90 with this handicap. Weights allocated to each observation will be equal to \(45/40 = 1.125\) in the treatment group 1 and \(45/50 = 0.9\) in the treatment group 2.

The primary analysis will be performed with weighted statistical model, using weights computed as defined above.

The secondary efficacy analysis on “2 Handicaps” response will also be performed with weighted statistical model using the same method restricted to flush and pruritus handicaps.

7.4.5. Management of missing data in incomplete dates

For incomplete dates the following conventions will be used:

For efficacy data: the Data Review Committee will statute on this data case by case.

For baseline data (ex: date of diagnosis, previous therapies for Mastocytosis):

- For missing start day: ‘01’ is used.
- For missing start day and month: missing data will not be replaced
- For missing end day: ‘last day of the month’ is used unless last day of the month is posterior to randomization date, in that case the data is not replaced.
- For missing end day and month: missing data will not be replaced

For adverse events data and concomitant treatment data, the following conventions will be only used to classify adverse events and concomitant treatments in the different analysis subgroups (e.g.: concomitant treatment ongoing at study drug first intake, adverse event occurring between study drug first intake and last intake+28 days, AEs occurring either during protocol part or extension...)

- For fully missing start date, such AE/concomitant treatment will be analyzed as occurring under study treatment and:
• Before W24 if AE/concomitant treatment is reported in the CRF part “[W0-W24]”

• After W24 if the patient went on extension and if AE/concomitant treatment is reported in the CRF part “Extension”

○ For missing start month:
  • If year of AE/concomitant treatment start is anterior to year of first intake: in that case the AE/concomitant treatment is considered as starting before first intake
  • If year of AE/concomitant treatment start is posterior to year of last intake (for patients who terminated study): in that case the AE/concomitant treatment is considered as starting more than 28 days after last intake
  • Otherwise (year first intake <= year start <= year last intake), the AE/concomitant treatment is considered as starting under study treatment and:
    – Before W24 if AE/concomitant treatment is reported in the CRF part “[W0-W24]”
    – After W24 if the patient went on extension and if AE/concomitant treatment is reported in the CRF part “Extension”

○ For missing start day (if start month is not missing), following conservative approach will be used:
  • If year+month (MMYYYY) of AE/concomitant treatment start is anterior to year+month of first intake: in that case the adverse event/concomitant treatment is considered as starting before first intake
  • If year+month of AE/concomitant treatment start is posterior to year+month of last intake (for patients who terminated study): in that case the AE/concomitant treatment is considered as starting more than 28 days after last intake
  • Otherwise (year+month first intake <= year+month start <= year+month last intake), the adverse event/concomitant treatment is considered as starting under study treatment and:
    – Before W24 if AE/concomitant treatment is reported in the CRF part “[W0-W24]”
    – After W24 if the patient went on extension and if AE/concomitant treatment is reported in the CRF part “Extension”

For exposure data:
  • Missing first intake date (for randomized patients only) will be replaced using max(date screening, date baseline, date rando).
• Incomplete last intake date will be replaced, missing day will be replaced by max (first day of the month (‘01’), last date reported in administration eCRF page), providing month is not missing.

7.4.6. Specifications for analysis

(1) Calculation of specific variables for analysis
Duration or time of occurrence, in days, will be calculated as: end_date – start_date +1.
Duration or time of occurrence, in weeks, will be calculated as: (end_date – start_date +1) / 7.
Duration or time of occurrence, in months, will be calculated as: (end_date – start_date +1) / 30.4375.
Duration or time of occurrence, in years, will be calculated as: (end_date – start_date +1) / 365.242.

Body Mass Index (BMI, in kg/m²) will be calculated as weight (kg) / height (m)².
Creatinine clearance (mL/min) will be calculated as [(140 – age (years)) * weight (kg) * K] / Creatinine (µmol/L), with K=1.23 for men and 1.04 for women.

(2) Convention for stools, micturitions and tryptase
In case of a post-baseline non-numeric result < x at a particular visit, the value will be set to x.
Tryptase values are coming from two source databases:
- External database, corresponding to the data entry from laboratory reports (SPELAB2)
- eCRF data (SPELAB)
Data in SPELAB2 will be taken in priority for the analyses. If no data are available in SPELAB2, data will be taken from SPELAB.
Last visit on W0-W24 period will be defined as follows:
- W24 if visit has been done
- In case value at W24 is missing, data will be replaced by value at final Visit if patient discontinued study before or at W24

7.4.7. Management of laboratory data
In this study, two sources of laboratory data were used:
- Central laboratory analysis performed by Synevo: Labconnect
- Local laboratory analysis performed in each investigational site
Analysis of laboratory data (see part 11 for baseline description and part 13.6 for safety analysis) will be performed using central laboratory results.
8. EFFICACY ANALYSIS

8.1. Primary analysis

The primary endpoint is the cumulative response by patient*handicap. It will be performed on the following populations:

<table>
<thead>
<tr>
<th>Primary Analysis</th>
<th>Statistical population for the analysis</th>
<th>Replacement of missing data method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>mITT</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #1</td>
<td>PP</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #2</td>
<td>&gt;3M</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #3 (primary analysis only)</td>
<td>ITT</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #4</td>
<td>mITT</td>
<td>Observed Cases (OC) (missing data remain missing)</td>
</tr>
</tbody>
</table>

8.1.1. Protocol period analysis: cumulative response

Analyses will be performed as described in Section 8.1.1.

Cumulative response from W8 to W24

Response on a handicap is defined as: an improvement with respect to the baseline values ≥ 75% for pruritus, flushes, Hamilton and FIS. Handicaps at baseline being defined as: pruritus score ≥ 9, number of flushes per week ≥ 8, HAMD-17 score ≥ 19, Fatigue Impact Scale ≥ 75

For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above.

So, from 5 to 20 responses will be calculated by patient: 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients presents the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits. Exchangeable correlation structure will be used for primary analysis.
Description of the statistical model

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 8 to week 24: so from 5 to 20 responses by patient (as described above). Correlations between measurements within a subject will be taken into account by using an exchangeable correlation matrix structure as hypothesized in sample size calculation.

To account for a possible imbalance between treatment groups in the number of patients with a given handicap (either pruritus, flushes, Hamilton, or FIS), each observation will be weighted as described in Section 7.4.4.

The following factors and variables will be included in the model:
- handicap (pruritus, flushes, Hamilton, FIS) as per eCRF
- and visit (W8, W12, W16, W20, W24).

We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

If GEE method fails to estimate treatment effect, for example, algorithm does not converge; Cochran-Mantel-Haenszel test will be used as backup method. The CMH test for repeated tests of independence will be used to test the difference between masitinib and placebo after controlling for handicap and visit variables. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

Rerandomization test

For the primary analysis on mITT population with Missing Data equal to Failure as method for replacement of missing values, the p-value of the statistical test will be obtained with a re-randomization test. This test will only be performed for the primary analysis, along with a test without re-randomization as sensitivity analysis. No re-randomization test will be applied to any sensitivity or secondary analysis.

This method involves the reshuffling of observed data and computing the test statistic (GEE model or Cochran-Mantel-Haenszel test), with the following conditions:
- Re-running of the minimization algorithm in order to assign a treatment group for each randomized patient
  - Maintenance of the real order (=observed) of arrival of the patients (e.g. patient 001-001-01 randomized in first)
  - Maintenance of the randomness set for minimization algorithm (here 25%)
- Maintenance of the response data for the statistical analysis

Following steps will be set up:
- **Step 1:** Statistical test (GEE model or CMH test) will be performed on observed data, and test statistic will be provided along with p-value.

- **Step 2:** The minimization algorithm will be run to obtain a new “randomization list” (assignment of each patient to a treatment group) for the analyzed population (mITT population). The statistical test statistic will be computed at each re-randomization.
This step 2 (re-randomization and computation of the test statistic) will be performed 10,000 times, to obtain 10,000 replicate statistical test statistics.

- **Step 3:** The proportion of replicates for which the value of the test statistic would be at least as large as the value of the test statistic from the original data will be calculated. In this proportion the observed test statistic will be also counted as one replicate in numerator and denominator.

  That proportion is the p-value for the randomization test.

  This last step determines how often the resampled test statistic is as extreme as the observed value of the same statistic.

The hypothesis of no treatment difference will be rejected at the 5 % level of significance if the p-value of the re-randomization test is <= 5 %.

**Descriptive statistics:**

A summary table will be provided with cumulative response rate per visit.

8.1.2. **Extension period analysis**

Other key analysis is the analysis of sustainability of response in extension. Therefore, the primary variable, response by patient*handicap, will be also analyzed on the extension period up to W96 (2 years).

**Statistical test:**

GEE model, or CMH test in case the first fails, as for cumulative response from W8 to W24.

**Descriptive statistics:**

A summary table will be provided with cumulative response rate per visit from W36 to W96.

8.2. **Secondary analyses**

8.2.1. **Introduction**

In the protocol, the pruritus score was proposed as secondary analysis. It is well recognized that pruritus and flushes are the most relevant symptoms of the mastocytosis, as they are direct markers of the Mast Cells (MC) activity.

Pooled phase II (AB04010+AB06013) results on similar criteria as phase III, have shown that masitinib is more efficacious on pruritus and flushes, markers of MC activity, the response 2 handicaps on pruritus and flushes is reported to be higher than the response 2 handicaps on FIS and Hamilton.

**Phase II pooled analysis (AB04010+AB06013) summary results – Response per handicap - Systemic severe patients**
### Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Cumulative response rate from W8 to W24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Response 75% (MDF) 28.6%</td>
</tr>
<tr>
<td>Flashes</td>
<td>Response 75% (MDF) 52.8%</td>
</tr>
<tr>
<td>Hamilton</td>
<td>Response 75% (MDF) 16.7%</td>
</tr>
<tr>
<td>FIS</td>
<td>Response 75% (MDF) 8.0%</td>
</tr>
</tbody>
</table>

Results from: Olivier Hermine & al. Masitinib for the treatment of severe systemic mastocytosis: Pooled phase 2 study simulation of phase 3 population and response criteria. EMBRN International Mast Cell and Basophil Meeting (21-23 October 2015, Marseille.

**Phase II pooled analysis (AB04010+AB06013) summary results – Response 4 handicaps and 2 handicaps - Systemic severe patients**

<table>
<thead>
<tr>
<th></th>
<th>Response 75% (MDF)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Handicaps</td>
<td></td>
<td>26.1%</td>
</tr>
<tr>
<td>2 Handicaps (pruritus, flushes)</td>
<td></td>
<td>38.8%</td>
</tr>
<tr>
<td>2 Handicaps (FIS/Hamilton)</td>
<td></td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Results from: Olivier Hermine & al. Masitinib for the treatment of severe systemic mastocytosis: Pooled phase 2 study simulation of phase 3 population and response criteria. EMBRN International Mast Cell and Basophil Meeting (21-23 October 2015, Marseille.

Furthermore, the relevance of pruritus and flushes symptoms was emphasized in the EMA scientific advice in June 2006 (EMEA/CHMP/H/SA/573/2/FU/1/2006/PA/II), the EMA concurred the following

“It is stated that virtually all patients would be suffering from flushes and pruritus. If a patient showed improvement in the Hamilton score and the Fatigue Scale score, it could be questioned whether AB1010 was effective in treating mastocytosis with handicap.”

Consequently, before unblinding, response 2 handicaps on pruritus and flushes were added in this SAP in the planned secondary analyses, to validate the efficacy of masitinib on symptoms recognized to be directly associated with the activity of Mast Cells.
The secondary analyses on Pruritus and Flush will be performed on the following populations:

<table>
<thead>
<tr>
<th>Secondary Analyses (except Tryptase)</th>
<th>Statistical population for the analysis</th>
<th>Replacement of missing data method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>mITT</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #1</td>
<td>PP</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #2</td>
<td>&gt;3M</td>
<td>Missing Data equal to Failure (MDF)</td>
</tr>
<tr>
<td>Sensitivity analysis #3</td>
<td>mITT</td>
<td>Observed Cases (OC) (missing data remain missing)</td>
</tr>
</tbody>
</table>

As described in section 6.4.2, the actual difference between ITT and mITT is in fact marginal. Therefore, the sensitivity analysis of ITT will be performed for the primary analysis only.

8.2.2. Pruritus score analysis

8.2.2.1. Protocol period analysis: pruritus response

Analyses will be performed as described in Section 8.1.1.

Description of the pruritus response

The pruritus score analysis will be done on the patients with handicap on pruritus at baseline.

- *The pruritus score analysis endpoint is the cumulative response on pruritus among patients with the handicap at Baseline.*

  With the response defined as: an improvement with respect to the baseline values ≥ 75% for pruritus.

  Handicap at baseline being defined as: pruritus score ≥ 9

For the patients presenting the handicap at Baseline (i.e. score ≥ 9), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above. So, 5 responses will be calculated by patient.

Description of the statistical model

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on the pruritus observed from week 8 to week 24: so 5 responses by patient (as described above). The correlation matrix to take into account the correlation between time points: week 8, week 12, week 16, week 20 and week 24 will be a exchangeable correlation structure matrix.
Beside the treatment, the visit variable will be included in the model. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is \( \leq 5\% \).

If GEE method fails to estimate treatment effect, for example, algorithm does not converge; Cochran-Mantel-Haenszel test will be used as backup method. The CMH test for repeated tests of independence will be used to test the difference between masitinib and placebo after controlling for visit variable. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is \( \leq 5\% \).

**Descriptive statistics:**
A summary table will be provided with cumulative response rate per visit.

### 8.2.2.2. Extension period analysis:

Other key analysis is the analysis of sustainability of response in extension. Therefore, the primary variable, response by patient*handicap, will be also analyzed on the extension period up to W96 (2 years).

**Statistical test:**
GEE model, or CMH test in case the first fails, as for cumulative response from W8 to W24.

**Descriptive statistics:**
A summary table will be provided with response rate per visit from W36 to W96.

### 8.2.3. Response 2 handicaps (pruritus + flushes) analysis

#### 8.2.3.1. Protocol period analysis: cumulative response

Analyses will be performed as described in Section 8.1.1.

**Description of the 2 handicaps response**

The analysis on response 2 handicaps (pruritus + flushes) will be done on the patients with handicap on pruritus and/or flushes at baseline.

- **The response 2 handicaps (pruritus + flushes) analysis endpoint is the cumulative response by patient*handicap on pruritus and flushes, among patients with the handicap at Baseline**

  With the response defined as: an improvement with respect to the baseline values \( \geq 75\% \) for pruritus and flushes.
  Handicap at baseline being defined as: pruritus score \( \geq 9 \) and flushes per week \( \geq 8 \)

  For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus and flushes) as defined above.

  So, from 5 to 10 responses will be calculated by patient: 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 10 if the patients presents the 2 handicaps at Baseline corresponding to the 2 handicaps * the 5 visits.

**Description of the statistical model**

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 8 to week 24; so from 5 to 10 responses by
patient (as described above). Correlations between measurements within a subject will be taken into account by using an exchangeable correlation matrix structure.

To account for a possible imbalance between treatment groups in the number patients with a given handicap (either pruritus, flushes), each observation will be weighted as described in Section 7.4.4.

Beside the treatment, the following factors and variables will be included in the model:
- handicap (pruritus, flushes)
- and visit (W8, W12, W16, W20, W24).

We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

If GEE method fails to estimate treatment effect, for example, algorithm does not converge; Cochran-Mantel-Haenszel test will be used as backup method. The CMH test for repeated tests of independence will be used to test the difference between masitinib and placebo after controlling for handicap and visit variables. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

Descriptive statistics:
A summary table will be provided with cumulative response rate.

8.2.3.2. Extension period analysis:
Other key analysis is the analysis of sustainability of response in extension. Therefore, cumulative response by patient*handicap on pruritus and flushes, will be also analysed according to Section 8.1.1 on the extension period up to W96 (2 years).

Statistical test:
GEE model, or CMH test in case the first fails, as for cumulative response from W8 to W24.

Descriptive statistics:
A summary table will be provided with cumulative response rate per visit from W36 to W96.

8.2.4. Tryptase level: short term measure (up to Week 24) of mast cell burden of disease activity
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 will be analysed for patients with a baseline level higher than 20 µg/L.
Absolute and percentage change from baseline in serum tryptase level to last visit ([W0-W24 period]) will be summarized for the mITT, PP and >3m populations.
Difference between treatment groups on relative and absolute change from Baseline will be tested with an analysis of covariance with the baseline value as covariate for the absolute change from baseline, and the Wilcoxon non-parametric exact test of ranks for relative change from baseline.
Response is defined as a diminution of 25% of tryptase level from baseline at last visit ([W0-W24 period]) will be analyzed for the mITT, PP and >3m populations using MDF.
Difference between treatment groups (masitinib versus placebo) will be tested using a logistic regression. If logistic regression fails to estimate treatment effect, for example, algorithm does not converge; Chi-square test or the Fisher Exact test, if the hypotheses of the Chi-square test are not fulfilled, will be used as backup method.

8.3. **Exploratory analyses**

Analyses will be performed on mITT, PP and >3M populations in MDF or LOCF, according to the type of data (qualitative or quantitative) and on mITT in OC.

8.3.1. **Other symptoms**

8.3.1.1. **Cumulative response on flushes among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (ie. number of flushes per week ≥ 8), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit.

These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

Same statistical test as for response on pruritus score will be performed on the cumulative response on flushes (i.e. GEE model using Logit as link function or CMH).

Response on flushes will be also analysed as at least one response from W8 to W24.

Same statistical test as for at least one response from W8 to W24 on pruritus score will be performed (i.e. Chi-square test or Fisher Exact test).

The response on flushes will be also analysed on the extension period up to W96 (2 years) in the same way than for pruritus score.

**Descriptive statistics:**

For flushes, response will be given at each time point between W0 and W96.

8.3.1.2. **Cumulative response on Hamilton score among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (ie. ≥ 19), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit.

These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

Same statistical test as for response on pruritus score will be performed on the cumulative response on Hamilton score (i.e. GEE model using Logit as link function or CMH).

Response on Hamilton score will be also analysed as at least one response from W8 to W24.

Same statistical test as for at least one response from W8 to W24 on pruritus score will be performed (i.e. Chi-square test or Fisher Exact test).
The response on flushes will be also analysed on the extension period up to W96 (2 years) in the same way than for pruritus score.

**Descriptive statistics:**
For Hamilton score, response will be given at each time point between W0 and W96.

**8.3.1.3. Cumulative response on FIS score among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (ie. ≥ 75), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit.

These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

Same statistical test as for response on pruritus score will be performed on the cumulative response on FIS score (i.e. GEE model using Logit as link function or CMH).

Response on FIS score will be also analysed as at least one response from W8 to W24.
Same statistical test as for at least one response from W8 to W24 on pruritus score will be performed (i.e. Chi-square test or Fisher Exact test).

The response on flushes will be also analysed on the extension period up to W96 (2 years) in the same way than for pruritus score.

**Descriptive statistics:**
For FIS score, response will be given at each time point between W0 and W96.

**8.3.1.4. Cumulative response on stools among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (i.e. ≥ 6), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit.

These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

Same statistical test as for response on pruritus score will be performed on the cumulative response on stools (i.e. GEE model using Logit as link function or CMH).

Response on stools will be also analysed as at least one response from W8 to W24.
Same statistical test as for at least one response from W8 to W24 on pruritus score will be performed (i.e. Chi-square test or Fisher Exact test).

The response on stools will be also analysed on the extension period up to W96 (2 years) in the same way as for pruritus score.

**Descriptive statistics:**
For stools, response will be given at each time point between W0 and W96.
8.3.1.5. **Cumulative response on micturitions among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (ie. ≥ 8), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit.

These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

Same statistical test as for response on pruritus score will be performed on the cumulative response on micturitions (i.e. GEE model using Logit as link function or CMH).

Response on micturitions will be also analysed as at least one response from W8 to W24.

Same statistical test as for at least one response from W8 to W24 on pruritus score will be performed (i.e. Chi-square test or Fisher Exact test).

The response on micturitions will be also analysed on the extension period up to W96 (2 years) in the same way than for pruritus score.

**Descriptive statistics:**

For micturitions, response will be given at each time point between W0 and W96.

8.3.2. **Mast Cells count and Urticaria pigmentosa evaluation: long term measures of mast cell absence of activity**

8.3.2.1. **Mast cells count in skin biopsy**

This measure is unlikely to detect a variation in the first 6 months as observed in phase II studies. We hypothesize that mast cells count could vary only after 1 or 2 years of treatment. Unfortunately mast cells count has only been done at Week 24.

For patients with available skin biopsy data (for all patients with skin lesions, skin biopsy should have been done) and available mast cells count. Absolute and percentage change from baseline to W24 and to last visit in mast cells count will be described when unit is the same at baseline and last visit. Absolute and percentage change from baseline will be also analyzed on mITT, PP and >3M populations using LOCF and on mITT in OC.

Difference between treatment groups on absolute and relative change from Baseline will be tested with an analysis of covariance with the baseline value as covariate for the absolute change from baseline, and the Wilcoxon non-parametric exact test of ranks for relative change from baseline.

8.3.2.2. **Urticaria Pigmentosa (UP) evaluation**

It is unlikely to detect a variation in UP in the first 6 months as observed in phase II studies. We hypothesize that UP could vary only after 1 or 2 years of treatment.

The analyses on Urticaria Pigmentosa (UP) will be performed on mITT, PP and >3M populations in LOCF for quantitative variable and in MDF for qualitative variables and on mITT in OC for:

- All the Systemic Severe patients (CDR)
- Systemic Severe patients for whom the Urticaria pigmentosa evaluations were performed prospectively (i.e. patients included following the amendment including the evaluation of the UP, protocol V6.0 of the 16th May 2013).

On patients with Urticaria Pigmentosa at baseline, the following parameter will be analysed:

- Relative change from baseline in the Body Surface Area (BSA) covered by the Urticaria Pigmentosa corrected with the Wallace formula (cf. section 8.7.4). Difference between treatment groups on relative change from Baseline will be tested with a repeated measurements analysis of covariance (GEE using Identity as link function) model from W8 to W24, from W8 to W96 and from W8 to final visit. Baseline value will be added in the model as covariate.

- “Darrier sign” disappearance (Yes/No) for patients with “Darrier sign” from W8 to W24, from W8 to W96 and from W8 to final visit. Difference between treatment groups will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the “Darrier sign” disappearance (Yes/No) observed at week 12 and week 24. Correlations between measurements within a subject will be taken into account by using an exchangeable correlation structure matrix. Beside the treatment, the visit variable will be included in the model. If GEE method fails to estimate treatment effect, for example, algorithm does not converge; Cochran-Mantel-Haenszel test will be used as backup method.

- Response from Investigator Assessment: define as an “Overall change” assessed by the investigator, as a “Great Improvement of urticaria pigmentosa (> 75%)”, from W8 to W24, from W8 to W96 and from W8 to final visit. Same statistical test as for “Darrier sign” disappearance will be performed on Response from Investigator Assessment (i.e. GEE model using Logit as link function or CMH).

The Urticaria evaluation will be also analysed on the extension period up to W96 (2 years).

8.3.2.3. Other: Mast Cells count in bone marrow biopsy and aspirate

As bone marrow biopsy or aspirate was not mandatory at baseline, except for patients without cutaneous lesion, few patients performed the exam. Therefore no formal statistical analysis will be provided. Individual data listing will be displayed for patients with available mast cell counts from bone marrow biopsy or aspirate.

8.3.3. Quality of Life

The response on the 4 handicaps and 2 handicaps, selected as primary and secondary analyses, are the best measures of quality of life since those handicaps have been selected to best represent the quality of life of patients suffering from mastocytosis and to have a validated measure. The other measures of QOL are purely exploratory.
In case the measures below are not consistent with 4H and 2H responses, it could mean those measures are not appropriate for the disease.

8.3.3.1. Performance status score

Performance status score corresponds to the 20th question of the AFIRMM questionnaire. These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

For the patients presenting the handicap at Baseline (i.e. performance status “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as a Performance status score “normal” or “light” at the visit.

Same statistical test as for response on pruritus score will be performed on the performance status score response (i.e. GEE model using Logit as link function or CMH).

The performance status score response will be also analysed on the extension period up to W96 (2 years).

8.3.3.2. OPA score

OPA score corresponds to the 53rd question of the AFIRMM questionnaire.

For the patients presenting the handicap at Baseline (i.e. OPA “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an OPA “normal” or “light” at the visit.

Same statistical test as for response on pruritus score will be performed on the OPA score response (i.e. GEE model using Logit as link function or CMH).

The OPA score response will be also analysed on the extension period up to W96 (2 years).

These analyses will be performed on mITT, PP and >3M populations in MDF and on mITT in OC.

8.3.3.3. AFIRMM questionnaire (V2.0) global score

Since the AFIRMM questionnaire has not been validated for prospective efficacy assessment, its results should be interpreted with caution.

This was emphasized in the EMA scientific advice in March 2005 (EMEA/CHMP/H/SA/573/2/2005/PA/III), where EMA stated: “The AFIRMM handicap score seems very complicated with 38 handicaps (in 11 categories) ...

Finally, the AFIRRM handicap score has not been validated in prospective clinical trials.”.

At the time of the scientific advice in March 2005, the AFIRMM questionnaire was in version 1 (38 questions). AFIRMM version 2 questionnaire (52 questions), used in the AB06006 study, was still not validated for prospective evaluation.

The AFIRMM questionnaire is validated for diagnosis, to assess of the burden of mastocytosis at baseline and the severity of patients at baseline. This validation has been performed through the AMERICAN STUDY (ref. Jennings S, et al. The Mastocytosis Society survey on mast cell disorders:...
patient experiences and perceptions. J Allergy Clin Immunol Pract. 2014 Jan-Feb;2(1):70-6). AFIRMM questionnaire was not created and has not been validated to measure change from baseline. All the following analyses will be performed on mITT, PP and >3M populations in LOCF, and on mITT in OC.

For the global score, value at time point, absolute and relative change from Baseline will be given. Difference between treatment groups on absolute and relative change from Baseline will be tested with a repeated measurements analysis of covariance (GEE using Identity as link function) model from W8 to W24. Baseline value will be added in the model as covariate.

The AFIRMM global score will be also analysed on the extension period up to W96 (2 years).

8.3.3.4. AFIRMM questionnaire (V2.0) - other items

As analysis of the AFIRMM questionnaire is an exploratory objective, its 52 items will not be assessed individually at this stage. It is also justified by the fact that only few patients would have some of these handicaps and that imbalance is expected between masitinib and placebo since the study does not stratify on these handicaps.

8.3.3.5. Quality of Life (QoL): QLQ-C30

Since the Quality of Life (QoL), QLQ-C30 questionnaire has not been validated for mastocytosis disease quality of life assessment, its results should be interpreted with caution.

Value at time point, absolute and relative change from Baseline for each of the following scores:

- Global Health Status score
- Functional Score (computed on physical, role, emotional, cognitive and social scales)
- Symptom score (computed on fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties scales)

Difference between treatment groups on absolute and relative change from Baseline will be tested with a repeated measurements analysis of covariance (GEE using Identity as link function) model from W8 to W24. Baseline value will be added in the model as covariate.

The QLQ-C30 scores will be also analysed on the extension period up to W96 (2 years).

All these analyses will be performed on mITT, PP and >3M populations in LOCF, and on mITT in OC.

8.3.3.6. Mastocytosis Symptoms rebound evaluation

This criterion, considered as highly exploratory because underlying data are mainly retrospective, will not be assessed at this stage.
8.4. **Subgroup analyses**

Efficacy subgroup analysis will be performed according patients c-kit mutation status, following the 3 categories presented below:

- Patients bearing D816V c-kit mutation:
  Define as patients bearing D816V c-kit mutation in all the organs in which was performed c-kit sequencing.
  Several sequencing could have been done for a patient for the same organ. If the D816V c-kit mutation has been found at least once, the patient will be considered as mutated for this organ.

- Patients Wild Type (WT)/unknown:
  Patients for whom the detection of kit816 is negative or unknown in all the organs in which was performed c-kit sequencing.

- Chimeric patients:
  Patients with D816V in one organ and WT/unknown in a second one.

As the randomization of the patients was not stratified on the c-kit mutation status, these analyses should be taken with high caution as it might be biased.

8.5. **MRI ancillary study (optional in France):**

Specific perfusion patterns measured by ASL-MRI has already suggest fundamental differences in the brain perfusion between patients suffering from cognitive troubles (Alzheimer disease, dementia,..) and cognitively healthy subjects.

Patients suffering from Mastocytosis could also suffer from cognitive disorders such as depression, memory losses, etc…

For the patients whom gave their consent to be evaluated for brain perfusion. Statistical analyses will be performed on MRI examination at Baseline and Week 24.

These statistical analyses will be performed by the team of Pr Boddaert (Service radiologie pédiatrique, Hôpital Necker Enfants Malades, 149 Rue de Sèvres, 75015 Paris), and will follow their internal procedures. A separated analysis report will be provided.

8.6. **Control of overall family-wise type I error rate**

To guard against spurious inflation of the Type I error rate, if primary analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>Cumulative response by patient*handicap on systemic severe according to CDR patients on mITT population, with MDF as replacement of missing data method.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If this analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.</td>
</tr>
<tr>
<td></td>
<td>A re-randomization test will be performed for the primary analysis, along with</td>
</tr>
</tbody>
</table>
a test without re-randomization as sensitivity analysis. No re-randomization test will be applied to any sensitivity or secondary analysis.

*Sensitivity analyses: analysis on PP with MDF and >3M with MDF, on ITT with MDF and on mITT with OC*

| Secondary analysis – Pruritus score analysis | Cumulative response on pruritus among patients with the handicap at Baseline (i.e. score ≥ 9), on systemic severe according to CDR patients on mITT population with MDF as replacement of missing data method). If this analysis is conclusive at a 5% level, analyses of efficacy will be continued with the analysis on pruritus and flushes (two handicaps).

*Sensitivity analyses: analysis on PP with MDF and >3M with MDF and on mITT with OC*

| Secondary analysis – Response 2 handicaps (pruritus+flushes) | Cumulative response by patient*handicap on pruritus and flushes among patients with the handicaps at Baseline, on systemic severe according to CDR patients on mITT population with MDF as replacement of missing data method). If this analysis is conclusive at a 5% level, analyses of efficacy will be continued with flushes analyses.

*Sensitivity analyses: analysis on PP with MDF and >3M with MDF and on mITT with OC*

| Secondary analysis – Tryptase level | Analyses on mITT, PP and >3M on systemic severe according to CDR patients with MDF for response and with OC for absolute and relative changes in patients with a baseline level higher than 20 µg/L.

| Exploratory analyses | Analyses on flushes, Hamilton score, FIS score, stools, micturitions, Mast Cells count in skin, Urticaria Pigmentosa, and Quality of Life: Performance status, OPA, AFIRMM, QLQ-C30 and mastocystosis symptoms rebound effect on systemic severe according to CDR patients.

These analyses are exploratory and will be performed on mITT, PP and >3M populations in MDF or LOCF, according to the type of data (qualitative or quantitative) and on mITT in OC.

### 8.7. Variables and derivations

#### 8.7.1. Main handicaps

**1) Pruritus score**

Pruritus score is equal to the sum of:

- Frequency of pruritus
  - Sporadically (1 point), Every second day (2 points), Every day (3 points)
Intensity of pruritus
- Mild (1 point), Moderate (2 points), Significant (3 points), Disabling (4 points)

Localization
- 0.5 point if pruritus on the head, 0 otherwise
- 0.5 point if pruritus on the back, 0 otherwise
- 0.5 point if pruritus on the anterior surface of the trunk, 0 otherwise
- 0.5 point if pruritus on one hand, 1 point if pruritus on both hands, 0 otherwise
- 0.5 point if pruritus on one leg, 1 point if pruritus on both legs, 0 otherwise

Influence on well-being
- Little (1 point), Moderate (2 points), Enormous (3 points)

Pruritus score is not calculated by the investigator (derivate variable to calculate).

If the response to the question “Presence of pruritus?” in the CRF is “No”, Score will be set to 0

If the response to the question “Presence of pruritus?” in the CRF is “Yes”, score will remain missing, if:
- Frequency is missing,
- Or intensity is missing,
- Or influence on well-being is missing,
- Or no localization is reported.

Response on pruritus is defined as follows:

If relative change from baseline in pruritus (%) ≤ -75% then Response on pruritus = 1 (Yes)

(2) Number of flushes per week

No derivate variable need to be calculated. The value reported in the CRF will be used.

Response of Number of flushes per week is defined as follows:

If relative change from baseline in Number of flushes per week (%) ≤ -75% then Response on Number of flushes per week = 1 (Yes)

(3) Hamilton score

Hamilton score is equal to the sum of the 17 items. Each item ranges from 0 to 4 according to the number of available responses (maximum score for the worse status).

Hamilton score is not calculated by the investigator (derivate variable to calculate).
Score will remain missing, if at least one item is not completed (!! For items 16A and 16B only one item need to be complete).

Response of Hamilton score is defines as follows:

If relative change form baseline in Hamilton score (%) ≤ -75% then Response on Hamilton score = 1 (Yes)

(4) Fatigue Impact Scale (FIS)

FIS main score is equal to the sum of the 40 items. Each item ranges from 0 to 4 according to the number of available responses (0 = no problem, 1 = small problem, 2 = moderate problem, 3 = big problem and 4 = extreme problem).

Three sub-scores can also be calculated: cognitive score (items 1, 5, 6, 11, 18, 21, 26, 30, 34 and 35), physical score (items 10, 13, 14, 17, 23, 24, 31, 32, 37 and 38) and social score (items 2, 3, 4, 7, 8, 9, 12, 15, 16, 19, 20, 22, 25, 27, 28, 29, 33, 36, 39 and 40).

FIS score is not calculated by the investigator (derivate variable to calculate).

When, for a same item, 2 responses have been ticked by the patient the following rule has been applied: minimum value has been retained for screening and Baseline visits, whereas maximum value has been retained for other visits. We made this choice as we are looking at the % change from Baseline for this parameter.

If more than 4 items are missing, overall score will be considered as missing. Otherwise, score will be calculated as follows : \([\text{sum of items filled} \times 40] / \text{(number of items filled)}\). This has been decided regarding a note from John Fisk who developed the questionnaire : “Missing data have been relatively rare in our experience with individual items omitted by less than 5% of respondents. The exception to this is item 29 (sexual function) and in some study samples item 28 (financial support). Given that the internal consistency of the scale and subscales has always been high, I have typically dealt with missing data by imputing such data and replacing the missing data with the median value for the total scale when necessary. It may also be prudent to drop subjects from the study analyses who omit more than 4 items (i.e. 10% of total) unless it can be determined from item-analyses of the study samples that missing items do not introduce a systematic bias to between-group comparisons.”

So, FIS score will remain missing if assessment was not done or at least 5 items are missing.

Be carefull, at the beginning of the study, a “non-copyright” version of the FIS has been used. In this version:

- Items were not reported in the same order than in the copyright version and they were not wording exactly as in the copyright version. A correspondence list has been established to reclass items as in the “copyright” version. This is done during the data management process.
Moreover a same item appeared twice in the questionnaire (item 24 from the ‘copyright’ version reported as items 23 and 40 in the ‘non copyright’ version) whereas another one was not present (item 23 from the ‘copyright’ version)

- For the item that appeared twice, the following rule has been applied: minimum value of item 23 and item 40 has been retained for screening and Baseline visits. Whereas maximum value has been retained for other visits. We made this choice as we are looking at the % change from Baseline for this parameter. This is done during the data management process.

- For the not present item (item 23), score will be calculated as follows: \[
\frac{(\text{sum of items filled}) \times 40}{\text{number of items filled}}
\]

As this item is missing for all the “non-copyright” questionnaires, global score is considered as missing if more than 5 items are missing (and not 4). Otherwise, as for the “copyright” version, score will be calculated as follows: \[
\frac{(\text{sum of items filled}) \times 40}{\text{number of items filled}}
\]
Response of FIS score is defined as follows:

If relative change form baseline in FIS score (%) ≤ -75% then Response on FIS score = 1 (Yes)

8.7.2. **AFIRMM questionnaire (V2.0)**

For each patient, the AFIRMM global score V2 is calculated as the addition for all handicaps weighed by the impact, the grade and the weight of the handicap according to the following formula:

\[
AFIRMM \text{ Score V2} = \sum_{1}^{38} (\text{Grade (handicap n)} \times \text{Weight (handicap n)}) = \sum_{1}^{38} (\text{Point (handicap n)})
\]

- Grade (0,1,2,3,4) = (0,1,2,3,4),
- Weight (0,1,2,3,4) = (1,2,3,4,5), defined severity of handicap
- Point (0,1,2,3,4) = (0,2,6,12,20)

The resulting AFIRMM Score V2 can range from 0 to 1040. The higher is the score, the more severe is the handicap of patient.

AFIRMM Score V2 is not calculated by the investigator (derivate variable to calculate). If more than 10 items are missing, score will be considered as missing. Otherwise, missing value to a specific item will be replaced by the value of the same item at the last available visit (LOCF considering all visits after Baseline), except if the visit is Baseline. In this case, missing value to a specific item will be replaced by 0 (best value) to minimize the score observed at Baseline.

8.7.3. **Quality of Life (QoL): QLQ-C30**

QLQ-C30 scores will be calculated according to the “EORTC QLQ-C30 Scoring Manual”*. The version used is the EORTC QLQ-C30 v3. Three main scores (Global Health Status score, Functional Score and Symptom score) and 14 sub-scores (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, Fatigue, Nausea and Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea, Financial Difficulties) will be calculated.

EORTC QLQ-C30 Scoring Manual scoring procedure:

**Scoring the EORTC QLQ-C30 version 3.0**

<table>
<thead>
<tr>
<th>Table 1: Scoring the QLQ-C30 version 3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scale</strong></td>
</tr>
<tr>
<td><strong>Global health status / QoL</strong></td>
</tr>
<tr>
<td>Global health status/QoL (revised)†</td>
</tr>
<tr>
<td><strong>Functional scales</strong></td>
</tr>
<tr>
<td>Physical functioning (revised)†</td>
</tr>
<tr>
<td>Role functioning (revised)†</td>
</tr>
<tr>
<td>Emotional functioning</td>
</tr>
<tr>
<td>Cognitive functioning</td>
</tr>
<tr>
<td>Social functioning</td>
</tr>
<tr>
<td><strong>Symptom scales / items</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Appetite loss</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Financial difficulties</td>
</tr>
</tbody>
</table>

* Item range is the difference between the possible minimum and the maximum response to individual items; most items take values from 1 to 4, giving range = 3. 
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in italics.

For all scales, the **RawScore**, RS, is the mean of the component items:

\[ \text{RawScore} = \frac{\sum (I_j)}{n} \]

Then for **Functional scales**:

\[ \text{Score} = \left(1 - \frac{(\text{RS} - 1)}{\text{range}}\right) \times 100 \]

and for **Symptom scales / items** and **Global health status / QoL**:

\[ \text{Score} = \left(\frac{(\text{RS} - 1)}{\text{range}}\right) \times 100 \]

**Examples:**

<table>
<thead>
<tr>
<th><strong>Emotional functioning</strong></th>
<th>RawScore = (Q10 + Q11 + Q12 + Q13) / 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF Score = (1 - (RawScore - 1)/3) × 100</td>
<td></td>
</tr>
</tbody>
</table>

**Fatigue**

| RawScore = (Q10 + Q11 + Q14) / 3 |
| FA Score = ((RawScore - 1)/3) × 100 |
8.7.4. **Urticaria Pigmentosa**

The percentage of body surface area entered in the CRF will be corrected by using the Wallace rule of nines, as follows:

<table>
<thead>
<tr>
<th>Body segment</th>
<th>CRF Score (%) / % of the body segment</th>
<th>Wallace % of the body segment</th>
<th>Corrected score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk (+Genital)</td>
<td>$X_{fC}/60$</td>
<td>36 (+1)</td>
<td>$X_{fC} = X_f \cdot 37/60$</td>
</tr>
<tr>
<td>Head</td>
<td>$X_{fH}/20$</td>
<td>9</td>
<td>$X_{fH} = X_f \cdot 9/20$</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>$X_{UL}/10$</td>
<td>18</td>
<td>$X_{UL}c = X_{UL} \cdot 18/10$</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>$X_{LL}/10$</td>
<td>36</td>
<td>$X_{LL}c = X_{LL} \cdot 36/10$</td>
</tr>
<tr>
<td>Total Score</td>
<td>$X_{Total}/100$</td>
<td>100</td>
<td>$X_{Totalc} /100$</td>
</tr>
</tbody>
</table>

The total score will be computed as follows:

\[
\text{Total score} = X_{fC} + X_{fH} + X_{UL}c + X_{LL}c
\]
9. **NUMBER OF PATIENTS (CF. PROTOCOL V7.0)**

*Primary analysis:*

A total of 142 patients (71 in masitinib group and 71 in placebo group) presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 will provide a 80% power with a two-sided 5% alpha in order to compare masitinib to placebo as primary analysis (GEE model for the cumulative response by patient*handicap: 4 handicaps / 5 visits), under the following hypotheses:

- Same response rate for all the 4 handicaps all along the study ie. 8.5% for placebo vs. 21% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 42.6% for the first study, 23.7% for the second and 30.6% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (24%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.
- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)
- 1:1 design ratio


Taking into account a percentage of non-evaluable patients around 5%, 150 patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 (75 in masitinib group and 75 in placebo group) will be randomized in the study.

*Secondary analysis:*

This sample size is sufficient to ensure a power ≥ 80% with an overall two-sided 5% alpha for the cumulative response on pruritus among patients with the handicap at Baseline.

- GEE model : 5 visits
- Same response rate all along the study ie. 6% for placebo vs. 24% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 25.0% for the first study, 38.5% for the second and 35.8% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (25%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.
- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)
- 1:1 design ratio
- With these hypotheses, 86 patients with handicap on pruritus at Baseline are needed. We expected that patients with handicap on pruritus at baseline will represent 65% of the patients included. Therefore, 132 patients are needed for this criterion.
10. DISPOSITION OF PATIENTS

In order to describe the population, the following analyses will be provided:

- Date of first patient screened, first patient included (baseline visit) and first patient randomized
- Date of last patient termination of [W0-W24] part of the study (or last patient last visit if any patient ongoing)
- Date of last patient termination of the study including extension part of the study (or last patient last visit if any patient ongoing)
- Population flow-chart will be completed (see figure 1)
  - Number of screened patients, randomized patients, screened and not randomized (screening failures) patients with reason for non-randomization.
  - Number of randomized patients by treatment group.
  - Number of ongoing patients by treatment group at the time of database lock. Reason for study termination will be described for patients who terminated the study (including listing of precision for reason “protocol deviation” or “other”).
  - Number of patients by treatment group in SAF, mITT, PP and >3M populations.
- Listing of protocol deviations (minor and major) per treatment group. Number of patients with major protocol deviation will be compared between treatment groups.
- Premature discontinuation will be defined as a study termination before week 24. Number and percentage of prematurely discontinued patients will be compared between treatment groups. Time and reason for premature termination will be described.
- Number and percentage of patients present at each visit by treatment group, on mITT, PP and >3M populations. Visits flow chart will be completed with main visits for each population.
- Number of patients by treatment group for each subgroup of interest in mITT, PP and >3M populations.
- Study duration (time between inclusion and study termination) will be described and compared between treatment groups.
- Number of patients randomized in each country and in each site will be described overall and by treatment groups.
11. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The initial description of the mITT, PP and >3M populations will be done per treatment group and for the total population for the following characteristics:

- Demographics: age (years, calculated between birth date and screening visit), sex, country, ethnicity, reproductive status

- Medical history:
  - Number of patients with at least one medical history, overall and per SOC and PTs

- Mastocytosis history, previous treatments and handicaps at baseline:
  - History: time since diagnostic calculated between date of diagnostic and screening visit, age at time of first diagnostic, mastocytosis classification (Smouldering Systemic/Indolent Systemic/Cutaneous)
    - Previous treatments for mastocytosis: description of previous treatments (ended before inclusion / ongoing at time of inclusion), time since last administration for treatments ended before inclusion, time since first administration for treatments ongoing at time of inclusion. A listing describing previous treatments will be edited.
    - Handicaps at baseline: descriptive statistics and number of patients with handicap (according to protocol v7.0) for pruritus score, number of flushes per day, number of stools per day, number of mictions per day, Hamilton score, FIS score, OPA score, AFIRMM score, mast cell infiltration and tryptase level

- Physical examination: presence/absence of abnormalities for each of the following systems: Skin and mucosae, Eyes, Ears/nose/throat, Heart/Cardiovascular system, Lung/Thorax, Abdomen, Musculo-skeletal system, Lymph nodes, Nervous system. A listing will be edited in order to describe abnormalities

- Vital signs: weight (kg), height (cm), body mass index (kg/m²) in quantitative, blood pressure (systolic and diastolic, in mm Hg), heart rate (bpm)

2. Laboratory data using raw value, low value/normal value/high value, and grading if available according to CTC-AE (Conversion in standardized unit and CTC-AE grading will be provided by Data Management):
   - Blood Hematology based on central laboratory: Erythrocytes, Hemoglobin, Hematocrit, Platelets, Leucocytes, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes
   - Blood Hematology based on local laboratory: PT, PTT, INR, BNP
   - Blood Biochemistry based on central laboratory: BUN, Creatinine, Creatinine clearance, Albumin, Total protein, Total bilirubin, Direct bilirubin, Phosphorus, Potassium, Sodium, Calcium, Glucose, LDH, Gamma GT, Cholesterol, Triglycerides, AST, ALT, Alkaline phosphatase, NT pro BNP, Troponin T
- Urine biochemistry using dipstick: Specific gravity, Blood, Leukocytes, Glucose, Proteins, pH, Bilirubin, Urobilinogen, Ketones, Nitrites, and 24h proteinuria in case of proteins on dipstick

- Hormonal work-up (listing): FSH, LH, estradiol/progesterone
- ECG normal/abnormal. Specifications for abnormal ECGs will be described.

- Quality of life assessment:
  - ECOG performance status
  - QLQ-C30 score (3 main scores + 14 sub scores)

- Concomitant treatments: Number of patients having at least one treatment ongoing at time of study drug first intake will be described overall and using Anatomical Therapeutic Chemical (ATC) Classification System (ATC1 and ATC2). Treatment ending before first intake will be described separately.
12. EXTENT OF EXPOSURE AND COMPLIANCE

Extent of exposure and compliance analyses will be performed, on the Central Document Review (CDR) SAF population.
The following data will be described by treatment group.

According the protocol, study drug (masitinib/placebo) should be administrated daily at 6 mg/kg/day.

12.1. **Exposure and treatment administration**

- Treatment exposure is calculated as:
  - Date of study drug last intake - date of first intake + 1.
  
  Date of first intake is based on the first administration documented.
  
  Date of last intake is based on the date of last intake reported in the last End of Study Form.
  
  For patients who are still treated with study drug in the study at the time of database lock, date of last intake will be replaced by the maximum of last administration reported, last study drug dispensation, and last visit confirming that patient is still treated.

- Patients not exposed to study drug will be described.

- Treatment duration is calculated taking into account potential treatment interruptions, i.e.:
  - Date of study drug last intake - first intake + 1 – number of days of interruption.

- In case this occurred during the study, exposure to the treatment the patient was not supposed to receive will also be described.

- Treatment start:
  - Description of delay between randomization and study drug first intake
  - Listings of individual data will be edited if necessary.

- In case this occurred during the study, exposure to the treatment the patient was not supposed to receive will also be described (e.g. patient randomised in placebo group taking masitinib, or patient randomised in masitinib group taking placebo).
12.2. **Dose at each visit**

At each study visit (every 4 weeks until W24 and then every 12 weeks) following dosages will be described:

- Daily dose (mg)
- Target dose regimen in mg/kg/day:
  - 6 mg/kg/day
  - 4.5 mg/kg/day
  - 3 mg/kg/day
  - 1.5 mg/kg/day
- Real dosage received in mg/kg/day, calculated as daily dose administrated at visit (mg/day) divided by patient’s weight at visit (kg), as continuous variable and using following classes: 0 (temporary interruption), ]0;2.25], ]0.25;3.75], ]3.75;5.25], ]5.25;6.75];>6.75 mg/kg/day.

12.3. **Compliance**

- Study drug compliance:

  Compliance will be calculated using count of returned tablets by the patient. The following formula is used:

  \[
  \text{Compliance} = \frac{\text{Quantity}_{\text{taken\_real}}}{\text{Quantity}_{\text{theoretical}}} \times 100
  \]

  With \( \text{Quantity}_{\text{taken\_real}} \) = Number of study drug tablets taken

  And \( \text{Quantity}_{\text{theoretical}} \) = theoretical number tablets that should have been taken per day x number of days of exposition to the study drug (Treatment exposure)

- Mean daily dose received during the study (mg/day) will be calculated using the following formula:

  \( \text{Cumulated dose received during the study (mg) / exposure duration (days)} \)

  - Cumulated received dose (mg) being calculated over all administration periods (accounting for periods of treatment interruptions with dose=0)

- Mean daily dose received during the study according to patient’s weight (mg/kg/day) will be also described, using following steps:

  - Definition of every administration period, starting each time the patient changes his weight or his daily dose.

    - Calculation of the real daily dose (mg/kg/day) of every administration period
• Calculation of the duration of each administration period
  o Mean of the doses across periods, weighted by each period duration:
    \[ \text{sum(realdose\_period1} \times \text{duration\_period1} + \text{realdose\_period1} \times \text{duration\_period1} + \ldots) / \text{Exposure duration (days)} \]
  o Mean daily dose received during the study according to patient’s weight (mg/kg/day) will be described as continuous variable and using following classes: \([0;2.25], [0.25;3.75], [3.75;5.25], [5.25;6.75]; >6.75 \text{ mg/kg/day}.\)

• Dose intensity (%) will be described per treatment group, defined as the ratio of total dose of treatment administered / total theoretical dose * 100. Dose intensity is calculated over the period from first intake until last intake, following the three steps below:
  o Cumulated received dose (mg) will be calculated over all administration periods (accounting for periods of treatment interruptions with dose=0) according to real dose taken by the patient (mg/day) and period duration (days)
  o Cumulated theoretical dose (mg) will be calculated over all visits from randomization until last intake, according to:
    ▪ Study drug regimen (6 mg/kg/day). Theoretical daily dose is based on weight at study visit and table provided in the protocol (mg/day).
    ▪ Period duration (days).
  o Then dose intensity will be calculated as the ratio of total dose of study treatment received / total theoretical dose * 100, and described as continuous variable. Patients having compliance lower than 80% will be described.

12.4. **Dose adjustments**

Dose reductions:
Dose reduction is defined as an intake of a daily dose lower than received dosage at baseline, during at least 2 days. Following analyses will be presented:

  o Number and percentage of patients with at least one dose reduction, overall and per reason (adverse event, patient omission, …)
  o Number of dose reductions per patient, overall and per reason
  o For dose reduction due to safety reasons (safety rules): Delay of occurrence of first dose reduction (days) calculated from study drug first intake
  o A listing will be provided for all dose reductions: delay of occurrence since study drug first intake, reason, etc.
Temporary interruptions:
Temporary interruption is defined as any absence of study drug intake during at least two days.

Following analyses will be presented:

- Number and percentage of patients with at least one temporary interruption, overall and per reason (adverse event, patient omission, …)
- Number of temporary interruptions per patient, overall and per reason
- For temporary interruption due to safety reasons (safety rules): Delay of occurrence of first temporary interruption (days) calculated from study drug first intake
- A listing will be provided for all temporary interruptions: delay of occurrence of since study drug first intake, duration, reason, etc.
13. SAFETY ANALYSIS

13.1. General rules

The safety analysis will be performed of systemic severe patients. It will be performed:

- first on the Central Document Review (CDR) SAF population
- then on the “SS+Others” SAF population.

The complete safety analysis will be also performed on the systemic severe patients pooled with the others mastocytosis patients of the SAF population.

The safety analysis will be performed using the following parameters:

- Exposure
- Adverse events
- Laboratory values (hematology, blood biochemistry and urinary biochemistry)
- Vitals signs (weight, blood pressure, heart rate), physical exams (normal/abnormal) and other safety parameters
- Concomitant treatments
- Specific safety parameter: Myocardial contractibility study

13.2. Exposure

Number of patients included in the SAF population (CDR) will be provided by treatment group.

Exposure duration will be described (in days and in months).

13.3. Adverse events

Period of analysis and global management:

All AEs starting between study drug first intake and 28 days after masitinib/placebo last intake will be taken into account for this analysis (except for development of cancers (SOC neoplasms), analyzed at any time).

For patients ongoing in the study at the time of data base lock, all adverse events occurring after treatment first intake will be taken into account.

AEs starting within the 7 days following the masitinib/placebo last intake will be supposed to occur at the last daily dose taken and not at a missing dose.

AE leading to dose reduction include AE with action taken in {dose reduction ; temporary interruption and dose reduction}. 
All listings will include following variables (a minima): treatment group, patient number, PT, SOC, intensity, seriousness, time of occurrence since first intake, outcome, duration of AE, relation with masitinib/placebo and action taken with masitinib/placebo.

A complete listing will be provided separately for following AEs:

- AEs starting before study drug first intake
- AEs starting after study drug last intake + 28 days.
- AE of patients who are not included in SAF population

Number of adverse events
Number of adverse events (all AEs) will be provided per treatment group.

Summary of adverse events (in number of patients)
Number and percentage of patients with at least one AE will be presented by treatment group, for the following types of AEs:

- AE (any)
- Non-fatal serious adverse events
- Deaths
- Severe adverse events
- Adverse events leading to
  - study drug permanent discontinuation (excluding deaths)
  - study drug temporary interruption
  - study drug dose reduction

This summary of AEs will be presented per period of occurrence, following this template:

<table>
<thead>
<tr>
<th></th>
<th>Protocol part</th>
<th>Extension period</th>
<th>All study period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[W0-W24]</td>
<td>masitinib</td>
<td>masitinib</td>
</tr>
<tr>
<td>Number (%) of patients</td>
<td>placebo</td>
<td>placebo</td>
<td>masitinib</td>
</tr>
<tr>
<td>with at least one AE</td>
<td></td>
<td>masitinib</td>
<td>placebo</td>
</tr>
<tr>
<td>AE</td>
<td></td>
<td>placebo</td>
<td>masitinib</td>
</tr>
<tr>
<td>Non-fatal SAE</td>
<td></td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td>placebo</td>
<td>masitinib</td>
</tr>
</tbody>
</table>

Table for summary of AEs occurring during protocol part [W0-W24] will be repeated in the following subgroups:

- Gender: male, female
- Age: ≤ 65 years old, > 65 years old
- Country
- Racial subgroup if less than 90% of patients belong to ethnicity “White or North African”

**Summary of adverse events (in incidence patient/month)**

Incidence (in patient/month) of AEs will be calculated using the following formula:

- Numerator: number of patients having presented an AE
- Denominator: sum of the exposure durations (in months) for patients in the concerned population.

This Incidence (in patient/month) of AEs will be presented by treatment group for the following types of AEs:

- AE (any)
- Non-fatal serious adverse events
- Deaths
- Severe adverse events
- Adverse events leading to
  - study drug permanent discontinuation (excluding deaths)
  - study drug temporary interruption
  - study drug dose reduction

This summary of incidence of AEs will be presented per period of occurrence, following this template:

<table>
<thead>
<tr>
<th>Number of patient/month</th>
<th>Protocol part [W0-W24]</th>
<th>Extension period</th>
<th>All study period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>masitinib p-m=</td>
<td>placebo p-m=</td>
<td>masitinib p-m=</td>
</tr>
<tr>
<td></td>
<td>placebo p-m=</td>
<td></td>
<td>placebo p-m=</td>
</tr>
<tr>
<td>AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Description of adverse events

Adverse events will be coded using MedDRA.

Number and percentage of patients with at least one adverse event will be presented by System Organ Class (by alphabetic order) and Preferred term (by descending frequency order among all patients), per treatment group and period of occurrence, according to following template:

<table>
<thead>
<tr>
<th>Number (%) of patients with at least one event</th>
<th>Protocol part [W0-W24]</th>
<th>Extension period</th>
<th>All study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>masitinib</td>
<td>placebo</td>
<td>masitinib</td>
<td>placebo</td>
</tr>
<tr>
<td>SOC1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table will be also presented for following categories of AEs:

- Adverse events
  - All
  - PTs presented by more than 5% of masitinib-treated patients, sorted by descending frequency in masitinib group
  - PTs presented by more than 10% of masitinib-treated patients, sorted by descending frequency in masitinib group
  - PTs presented by more than 20% of masitinib-treated patients, sorted by descending frequency in masitinib group
  - The 10 most frequent PTs reported in masitinib group, sorted by descending frequency in masitinib group
  - The 10 PTs having the higher positive difference of frequency between masitinib and placebo (delta % masitinib – % placebo), sorted by descending frequency in masitinib group

- Serious adverse events
  - Non-fatal SAE
    - All
    - The 10 most frequent PTs reported in masitinib group, sorted by descending frequency in masitinib group
  - Deaths
  - Adverse events leading to
    - study drug permanent discontinuation (excluding deaths)
- All
- The 10 most frequent PTs reported in masitinib group, sorted by descending frequency in masitinib group

➢ study drug temporary interruption
- All
- The 10 most frequent PTs reported in masitinib group, sorted by descending frequency in masitinib group

➢ study drug dose reduction
- All
- The 10 most frequent PTs reported in masitinib group, sorted by descending frequency in masitinib group

- Severe adverse events
- All
- The 10 most frequent PTs reported in masitinib group, sorted by descending frequency in masitinib group

Frequency of adverse events by masitinib dose of occurrence (mg/kg/day).
For each AE, dose of occurrence will be defined according to the masitinib real dose the patient was taking at time of AE occurrence (mg/kg/day). Period of analysis will include protocol part [W0-W24] pooled with extension period.
The doses will be classified according to following classes, in mg/kg/day:
- ≤6 ([0;5.25])
- (5.25;6.75])

Frequency of patients will be calculated among the number of patients treated at least once by the dosage.

<table>
<thead>
<tr>
<th>Number (%) of patients with at least one</th>
<th>≤6 (N=)</th>
<th>6 (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13.4. Deaths, other serious adverse events and other significant adverse events

“Other significant adverse events” includes in particular:

- AEs leading to study drug dose reduction
- AEs leading to study drug temporary interruption
- AEs leading to study drug permanent discontinuation (excl deaths)
Listing of deaths, other serious adverse events and other significant adverse events will be provided.

13.5. **AEs of interest**

AEs of interest will be defined from meddra terms by AB Science pharmacovigilance department. The list of System Organ Class/Preferred Term/Low level Term corresponding to each event is provided in section 16.4 as indicative list, and will be listed exhaustively in the output for each to AEs of interest.

- Rash
- Edema
- Gastrointestinal events of interest:
  - Nausea
  - Vomiting
  - Diarrhea
- Asthenia
- Potential Life Threatening Adverse Events
  - Severe Neutropenia
  - Most severe skin toxicities (SJS, DRESS, Hand and foot syndrome)
  - Severe Skin toxicities (SOC Skin and cutaneous disorders with intensity=severe)
  - Angioedema
- Specific risks
  - Cardiotoxicity
  - Hepatic disorders
  - Reproductive disorders
  - Renal disorders
  - Secondary malignancy
  - Infections

Each AE of interest will be analysed with the following:

- Number of patients of concerned AE of interest and by SOC/PT
- Action taken on study drug (in number of patients, each patient being analyzed with the worst action taken):
  1. None
  2. Temporary interruption
  3. Dose reduction
  4. Permanent discontinuation
- Severity (in number of patients, all severity begin taken into account)
- Time of occurrence of AEs, in days
- Duration of AEs, analyzing only AEs with outcome “Resolved (with or without sequelae)”, in days
13.6. **Laboratory evaluation**

Laboratory evaluation include: hematology, biochemistry, urinalysis, hormonal work-up.

For those 3 types of parameters, analysis will be performed on the following set of data:

- Baseline sample of each parameter will be the last valid value available before first intake.
- For patients who discontinued the study, samples performed more than 28 days after last intake will be excluded from analysis.
- In accordance with these two rules, all available results during study will be taken into account (incl. final visit). Retest samples (if any notified in the database) will be handled the following way:
  - If a retest result is available for a parameter already tested with the same sample date, the retest value will be kept.
  - If a retest result is available for a parameter already tested with a different sample date, cases will be discussed during data review. Otherwise decided at DRC, following solution will be applied:
    - If the retest is performed because of safety reason (e.g. confirmation of an abnormal value), the first available value at the visit will be used for the analysis.
    - If the retest is performed because of unreliability of the laboratory result, the first available reliable value at the visit will be used for the analysis.
    - Otherwise, the first available value at the visit will be used for the analysis.

**Hematology and biochemistry**

Following parameters will be analyzed:

- **Blood Hematology:**
  - Based on central lab: Erythrocytes, Hemoglobin, Hematocrit, Platelets, Leucocytes, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes,
  - Based on local lab only: PT, PTT, INR (baseline and end of study only)

- **Blood Biochemistry** based on central lab only: BUN, Creatinine, Albumin, Total protein, Total bilirubin, Direct bilirubin, Phosphorus, Potassium, Sodium, Calcium, Glucose, LDH, Gamma GT, Cholesterol, Triglycerides, AST, ALT, Alkaline phosphatase,

In the database, parameters will be available with standardized units. Besides, laboratory normal ranges will be used to define CTC-AE grading for each value, provided by the AB Science data-management department.
For each parameter, following analysis will be presented by group using descriptive statistics:

- Raw value at each time point
- Absolute change between baseline and time point
- For parameters graded with CTC-AE: Shift table (number and percentage) of worst grade during the study according to grade at baseline. For parameter having CTC-AE abnormalities as low and high values, both abnormalities will be graded and analyzed.

Urinalysis:

Urine biochemistry using dipstick include following parameter, collected with format negative, trace, +, ++, +++: Specific gravity, Blood, Leukocytes, Glucose, Proteins, pH, Bilirubin, Urobilinogen (using conversion 1mg/dL =17.1 µmol/L), Ketones, Nitrites.

In case of proteins >= 30 mg/dL (i.e. “+” or more), description of 24-hour proteinuria.

For each parameter, following analysis will be presented by group using descriptive statistics:

- Level at each time point
- For qualitative parameters, shift table (number and percentage) of worst level during the study according to level at baseline.

A listing of patients with positive proteins on dipstick will be edited. This listing will present all protein values for these patients as well as their 24-hours proteinuria results.

Hormonal work-up:

A listing of individual measurements (FSH, LH estradiol/progesterone) will be edited.
13.7. Vital signs, physical exam and other safety measurements

All other safety parameters will be analyzed on the following set of data:

- Baseline sample of each parameter will be the last valid value available before first intake.
- For patients who discontinued the study, exams performed more than 28 days after last intake will be excluded from analysis.
- In accordance with these two rules, all available results during study will be taken into account (incl. final visit).

Vital signs:

- Weight: Weight will be described using descriptive statistics, by visit.
- Blood pressure and Heart rate: Those parameter will be analyzed with:
  - Abnormality (high/normal/low) at each time point:
  - Systolic Blood Pressure (SBP) using [100;150] as normal ranges
  - Diastolic Blood Pressure (DBP) using [60;100] as normal ranges
  - Heart Rate (HR) using [60;100] as normal ranges
  - using a shift table (number and percentage) of worst level (high/normal/low) during the study according to level at baseline. NB: One patient having presented both high and low value during study will be accounted for both.

Physical exam:

Physical exam consists of appreciation of presence/absence of abnormalities for each of the following body systems: Skin and mucosae, Eyes, Ears/nose/throat, Heart/Cardiovascular system, Lung/Thorax, Abdomen, Musculo-skeletal system, Lymph nodes, Nervous system.

Each physical exam will be described by study visit using number and percentage of patients presenting abnormality.

A listing of abnormalities will be edited per body system, along with the abnormalities reported in body system “other”.

ECG:

ECG results will be described by study visit using number and percentage of patients presenting abnormality.

A listing of ECG abnormalities will be edited with specification of clinically significance.
Chest X-ray
Chest X-ray at baseline and at final visit will be described using a shift table. A listing will be edited in order to describe abnormalities.

Urinary cytology
Urinary cytology, if performed (as included in V6.0 of the protocol), is a specific search for transitional and/or malignant cells.

It is classified as “Unsatisfactory specimen”, “negative”, ”atypical”, ”suspicious”, “positive”.

A listing of results being “atypical”, “suspicious” or “positive” will be provided.

If the NMP22 test was performed (it was included in V7.0 of the protocol), its result will be provided in the same listing.

13.8. Concomitant treatments
Concomitant treatments will be classified according to the date of start:

• Before study drug first intake: those treatments will be excluded from safety analysis and will be listed only into the baseline description.

• For patients who discontinued study, treatments starting more than 28 days after last intake will be excluded, and listed separately.

Once selected the concomitant treatment for analysis, the number and percentage of patients with at least one concomitant treatment will be presented by Anatomic Group and ATC Class (ATC1 and ATC3).
13.9. **Myocardial contractibility study (for French patients)**

As part of the international study, French patients enrolled in this study entered a specific cardiac surveillance in order to study potential effect of masitinib on myocardial contractibility. Echocardiogram was performed for assessing myocardial contractibility features and especially the Left Ventricular Ejection Fraction.

The exam will allow collecting following parameters at week 0, week 24 and final visit:

- Left Ventricular Ejection Fraction (primary), in %
- Fractional shortening (midwall mFS), in absolute value
- Systolic and diastolic left ventricular diameters, in mm or cm
- Optionally, left ventricular contractility during Isovolumic Contraction, in %

A specific Statistical Analysis Plan is edited for analysis of those parameters.
14. CHANGES FROM PROTOCOL

1. Missing Data equal to Failure (MDF) method for patient present at visit but with data missing:
We applied in the SAP a modification of MDF protocol definition for patients who are present at visit and for whom data is missing. In this case, protocol says to consider the response as a failure, whereas the SAP will not replace the data, which is preferable, as non-observed values can be considered as Missing Completely At Random (MCAR).

2. The “corresponding interactions” between handicap and visit variables, planned to be included in the primary analysis statistical model in the protocol, will be no longer included in the model to prevent for non-convergence of it.
15. APPENDIX

APPENDIX 1 – INCLUSION CRITERIA IN PHASE 3 STUDY AB06006 (VERSION 6.0 DATED 09.08.2013 PAGE 3)

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient with one of the following documented mastocytosis as per WHO classification:</td>
</tr>
<tr>
<td>▪ Smouldering Systemic Mastocytosis</td>
</tr>
<tr>
<td>▪ Indolent Systemic Mastocytosis</td>
</tr>
<tr>
<td>2. Patient with documented mastocytosis and evaluable disease based upon histological criteria: typical infiltrates of mast cells in a multifocal or diffuse pattern in skin and/or bone marrow biopsy</td>
</tr>
</tbody>
</table>

APPENDIX 2 – INCLUSION CRITERIA IN PHASE 2 STUDY AB04010 (VERSION 1.0 DATED 28.04.2006 PAGE 3)

**Diagnosis and Main Criteria for Inclusion:**

1. Patients of both sex, aged ≥ 18 years, affiliated to the French social security regimen.
2. Patients with documented Indolent systemic mastocytosis with handicap (ISMwh) having at least 2 infiltrated* organs (skin and/or bone-marrow and/or internal organ).
   
   *Patients with mast cells infiltration in skin but with no evidence of mast cell infiltration in bone marrow and/or other organs may be enrolled if they have significant clinical symptom(s) other than skin symptoms. The enrolment of such patients must be approved by AB Science.*
3. Bone–marrow, or skin or internal biopsy–documented mastocytosis and evaluable disease.

APPENDIX 3 – INCLUSION CRITERIA IN PHASE 2 STUDY AB06013 (VERSION 6.1 DATED 29.09.2014 PAGE 3)

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients with one of the following documented mastocytosis:</td>
</tr>
<tr>
<td>▪ Smouldering systemic mastocytosis</td>
</tr>
<tr>
<td>▪ Indolent systemic mastocytosis with organomegaly</td>
</tr>
<tr>
<td>▪ Indolent Systemic Mastocytosis having 2 infiltrated organs (skin and bone-marrow)</td>
</tr>
<tr>
<td>▪ Any mastocytosis with in the last 6 months at least 3 anaphylactic shocks or syncrops requiring either use of adrenaline or medical assistance</td>
</tr>
<tr>
<td>▪ Cutaneous Mastocytosis (CM)</td>
</tr>
<tr>
<td>2. Skin biopsy–documented mastocytosis and evaluable disease based upon:</td>
</tr>
<tr>
<td>▪ Histological criteria: typical infiltrates of mast cells in a multifocal or diffuse pattern in skin biopsy</td>
</tr>
<tr>
<td>▪ Clinical criteria: typical skin lesions (maculopapular, urticaria pigmentosa, mastocytoma)</td>
</tr>
</tbody>
</table>

APPENDIX 4 – INCLUSION CRITERIA IN AFIRMM PROTOCOL (O. HERMINE et AL. PLoS ONE 2008)
Of the 363 patients that responded, 262 were part of an ongoing pathophysiological study started in November 2003 by AFIRM. The patients selected and enrolled in the pathophysiological study included (i) patients suffering CM as documented by a skin biopsy and without mast cells in other tissues and (ii) patients suffering from SM as documented by mast cell infiltration in a bone marrow and/ or another internal organ (i.e., liver or gastrointestinal tract) with or without skin involvement. In addition, all patients had to be affiliated with a social security regimen or covered by insurance. The patients


Background information on the disease to be treated

Cutaneous, Systemic Indolent and Smouldering mastocytosis with handicaps is a rare disease without well-established guidelines to assess handicaps and a treatment response.

There is a debate within the mastocytosis research community concerning the need to revise and expand the WHO classification for mast cell disease, its diagnostic and response criteria [1, 2, 3, 4, 5].

Whilst the publication of consensus statements on disease classification, diagnosis, response criteria and treatment have served the community well over the past decade, the cornerstone for which is the World Health Organization (WHO) classification system [6, 7], the underlying philosophy seems highly geared towards aggressive variants of mastocytosis and is of less relevance to the indolent, non-aggressive, forms of the disease; our targeted population in the ongoing phase 3 study. This latter group represents more than 90% of all mastocytosis cases and although the majority of these patients can expect a normal life expectancy [8], the associated mast cell mediator release symptoms they endure have a highly negative effect upon quality-of-life to the point of being disabling [9]. The current WHO classification system does not provide any recommendation about how to assess treatment response in indolent, non-aggressive, forms of the disease.

References
Clinical Study Protocol

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

Phase of development: Phase 3

Study design: Randomized, double-blind, placebo controlled, parallel group, multicentre study

Diagnosis: Patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap

Test product and dosage(s): AB1010 (masitinib) given orally at the dose of 6 mg/kg/day with possible dose adjustments / AB1010, 100 and 200 mg tablets, bid administration

Comparator product and dosage(s): Placebo

Duration of treatment: 24 weeks

Coordinating investigator: Pr. Olivier Lortholary MD, PhD– Necker Hospital – Paris

Sponsor: AB Science, 3 avenue George V, 75008 Paris, France
Tel: +33 1 47 20 00 14

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IND 68,317
EudraCT number: 2008-000972-25

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STUDY SYNOPSIS

NAME OF COMPANY: AB SCIENCE

NAME OF FINISHED PRODUCT: MASITINIB

NAME OF ACTIVE INGREDIENT: AB1003

Study Title:
A 24-week with possible extension, prospective, multicenter, 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.

Study Code Number: AB06006

Coordinating investigator: Olivier Lortholary MD, PhD – Necker Hospital - Paris

Clinical Study Centres: Up to 100 sites in Europe, United-States, India, Latin America, South Africa

Study periods: duration of treatment: 24 weeks

Phase of development: 3

Safety and efficacy objectives:
The objective is to compare the safety and efficacy of masitinib to placebo in patients with documented Smouldering or Indolent Systemic mastocytosis (recruitment of Cutaneous mastocytosis patients being interrupted according to protocol version 6.0) with severe handicap on the following endpoints:

Primary endpoint:
- Cumulative response by patient*handicap :

Secondary endpoints:
- Cumulative response on pruritus among patients with the handicap at Baseline
- Cumulative response on OPA score among patients with “severe” or “intolerable” handicap at Baseline
- Quality of Life (QoL) : QLQ-C30 global score, functional scores and symptom scores at each visit
- AFIRMM questionnaire :
  • global score
  • for each of the 52 items : cumulative response among patients with “severe” or “intolerable” handicap at Baseline
- Cumulative response on micturitions among patients with the handicap at Baseline
- Cumulative response on stools among patients with the handicap at Baseline
- Urticaria Pigmentosa (UP) evaluation at week 12, 24 and then every 12 weeks
- Mastocytosis symptoms rebound effect evaluation from 1 month after study/treatment discontinuation. Severity of symptom sand time of occurrence of the rebound effect after study/treatment discontinuation will be evaluated. Patient overall wellbeing from treatment period will be also evaluated.

Safety profile of masitinib: Occurrence of Adverse Events, vital signs, ECG, Chest X-Ray and biological parameters.

Efficacy endpoints will be analysed on the overall patient population and additionally on patients bearing activation point mutations in the phosphotransferase domain of c-Kit such as the main
Mutation Asp-816-Val (D816V) versus patients for whom the detection of kit816 is negative or unknown in the organ biopsied.

Methodology/Study Design:
This is a prospective, multicentre, randomized; double blinded, placebo-controlled, 2-parallel group with a randomization 1:1, phase 3 study comparing the efficacy and the safety of masitinib at 6 mg/kg/day versus placebo in the treatment of patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap (recruitment of Cutaneous mastocytosis patients being interrupted according to protocol version 6.0).

A total of 150 patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap will be randomized in two treatment groups:

- Group 1: 75 patients will receive masitinib at 6 mg/kg/day
- Group 2: 75 patients will receive placebo

Treatment allocation:
Because handicap/scores at baseline regarding pruritus, flushes, depression and fatigue might influence the study outcome, they must be equally balanced in the two treatment groups. Hence, randomization procedures include a minimization process aimed at reducing any difference in the distribution of the handicaps/scores at baseline and country in patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap.

Inclusion criteria:
1. Patient with one of the following documented mastocytosis as per WHO classification:
   - Smouldering Systemic Mastocytosis
   - Indolent Systemic Mastocytosis
2. Patient with documented mastocytosis and evaluable disease based upon histological criteria: typical infiltrates of mast cells in a multifocal or diffuse pattern in skin and/or bone marrow biopsy
3. Patient withdrawn documented treatment failure of his/her handicap(s) with at least one of the following therapy used at optimized dose:
   - Anti H1
   - Anti H2
   - Proton pump inhibitor
   - Osteoclast inhibitor
   - Cromoglycate Sodium
   - Antileukotriene
4. Handicapped status defined as at least two of the following handicaps, including at least one among pruritus, flushes, depression and fatigue:
   - Pruritus score ≥ 9
   - Number of flushes per week ≥ 8
   - Hamilton rating scale for depression(HAMD-17) score ≥ 19
   - Number of stools per day ≥ 4
   - Number of micturition per day ≥ 8
   - Fatigue Impact Scale total score (asthenia) ≥ 75
5. Patients with OPA ≥ 2 (moderate to intolerable general handicap)
6. ECOG ≤ 2
7. Patient with adequate organ function:
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NAME OF ACTIVE INGREDIENT: AB1003

- Absolute neutrophils count (ANC) $\geq 2.0 \times 10^9$/L,
- Haemoglobin $\geq 10$ g/dL
- Platelets (PTL) $\geq 100 \times 10^9$/L
- AST/ALT $\leq 3x$ ULN ($\leq 5$ x ULN in case of liver mast cell involvement),
- Bilirubin $\leq 1.5x$ ULN
- Creatinine clearance $>60$mL/min (Cockcroft and Gault formula)
- Albumin $>1$ x LLN
- Urea $\leq 1.5x$ ULN
- Proteinuria $< 30$mg/dL on the dipstick; in case of proteinuria $\geq 1+$ on dipstick, 24 hours proteinuria should be $\leq 1.5g/24$ hours

8. Male or female patient aged 18 to 75 years, weight $> 50$ kg, BMI between 18 and 35 kg/m²

9. Female patient of childbearing potential (entering the study after a menstrual period and who have a negative pregnancy test), who agrees to use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. Acceptable forms of contraception include:

- A documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository)
- Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) should also be used
- Double barrier method: Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Any other contraceptive method with a documented failure rate of $<1\%$ per year
- Abstinence when this is in line with the preferred and usual lifestyle of the patient.

10. Male patients must use medically acceptable methods of contraception if your female partner is pregnant, from the time of the first administration of the study drug until three months following administration of the last dose of study drug. Acceptable methods include:

- Condom;
- If you have undergone surgical sterilization (vasectomy with documentation of azoospermia) a condom should also be used.

Male patients must use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. The acceptable methods of contraception are as follows:

- Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Your female partner uses oral contraceptives (combination oestrogen/progesterone pills), injectable progesterone or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Your female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) should also be used;
Your female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);

Abstinence when this is in line with the preferred and usual lifestyle of the patient.

11. Patient must be able and willing to comply with study visits and procedures per protocol

12. Patient must understand, sign, and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures performed

13. Patient must understand the patient card and follow the patient card procedures in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity during the first 2 months of treatment

14. Patient affiliated to a social security regimen

Exclusion criteria:

1. Patient with one of the following mastocytosis:
   - Cutaneous Mastocytosis
   - Not documented Smouldering Systemic Mastocytosis or Indolent Systemic Mastocytosis
   - Systemic Mastocytosis with an Associated clonal Hematologic Non Mast cell lineage Disease (SM-AHNMD)
   - Mast cell leukaemia (MCL)
   - Aggressive systemic mastocytosis (ASM)

2. Previous treatment with any Tyrosine Kinase Inhibitor

3. 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 aetiology within 3 months
   - Uncontrolled severe hypertension, according to the judgment of the investigator, or symptomatic hypertension

4. Patient who had major surgery within 2 weeks prior to screening visit

5. Vulnerable population defined as:
   - Life expectancy < 6 months
   - Patient with < 5 years free of malignancy, except treated basal cell skin cancer or cervical carcinoma in situ
   - Patient with any severe and/or uncontrolled medical condition
   - Patient with known diagnosis of human immunodeficiency virus (HIV) infection

6. 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, or institutionalized by court decision

7. Patient with any condition that the physician judges could be detrimental to subjects participating in this study; including any clinically important deviations from normal clinical
Precautions and Contraindications

Previous treatment

8. Change in the symptomatic treatment of mastocytosis or administration of any new treatment of mastocytosis within 4 weeks prior to baseline
9. Treatment with any investigational agent within 4 weeks prior to baseline

Centralization of c-Kit sequencing and mast cell counting:

For all patients, skin biopsy will be performed at screening, except for patients without cutaneous lesion for whom a bone marrow aspirate or biopsy will be mandatory, in order to document potential c-kit mutation (only at screening) and mast cell counting. Additionally, skin biopsy (or bone marrow aspirate or biopsy) will be performed at week 24, or at end of visit for mast cell counting.

Optionally, a bone marrow aspirate or biopsy could be performed in addition to the skin biopsy at screening (and at week 24, or at end of study visit) to document mast cell counting.

The c-kit sequencing and mast cell counting will be performed centrally in order to ensure consistency in the study results. The procedure to follow for performing skin, optionally bone marrow aspirate and bone marrow biopsy is described in protocol appendix 14.8.

Myocardial contractibility study:

As part of the international study, French patients enrolled in this study, will enter a specific cardiac surveillance in order to study potential effect of masitinib on myocardial contractibility. Echocardiogram will be performed for assessing myocardial contractibility features and especially the Left Ventricular Ejection Fraction.

2D and M-mode echocardiography which provide qualitative and semi quantitative measurements of ventricular systolic function could be used. However, whenever it’s possible, three-dimensional echocardiography should be preferred. This technique has excellent correlation with radionuclide angiography for calculation of left ventricular ejection fraction in patients and has observer variability similar to that of radionuclide angiography (9).

As per study protocol, patients will have to perform at baseline and at week 24 a doppler echocardiography. This examination should be conducted in the supine position, with the same ultrasound system and preferably by the same physician. All patients should be haemodynamically stable. Tracings should be recorded during expiration. Para-sternal and apical views have to be obtained according to the recommendations of the American Society of Echocardiography. Values should be presented as means from three consecutive cardiac cycles. Left ventricular ejection fraction should be calculated according to the same integration method for the two measurements (i.e. baseline, week 24 and end of study visit).

The following echocardiogram endpoints should be measured:

- Left Ventricular Ejection Fraction at week 0, week 24 and end of study visit (primary)
- Fractional shortening (midwall mFS) at week 0, week 24 and end of study
- Systolic and diastolic left ventricular diameters at week 0, week 24 and end of study
- Optionally, left ventricular contractility during Isovolumic Contraction at week 0, week 24 and end of study

Background information and statistical considerations are provided in section 7.3 of the study protocol.

Duration of Treatment, extension phase and maximum exposure duration:

Eligible patients will be treated with masitinib or matching placebo for 24 weeks with possible extension. Patients who completed the Week 24 period, with regular assessments and evaluation can enter a double blind extension phase.
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- In case of positive clinical benefit/response established by investigator
- If required by the investigator and agreed by the patient.

The maximum exposure to treatment is 2 years.

Exposure to treatment for more than 2 years will be possible only if:
- A Substantial amendment is approved by Competent Authority
- The benefit/risk for the study is positive based on available data
- The individual benefit/risk is still assessed as positive by investigator and documented

The informed consent form has been resigned to remind patient about potential long term risks.

Treatment administration:
Subjects enrolled will receive a total daily dose of 6 mg/kg masitinib or a matching placebo, to be taken during meals as indicated in the table below:

Table 1: Dose of study treatment to be administered according to patient’s weight (randomization dose: 6 mg/kg/day)

<table>
<thead>
<tr>
<th>Patient’s weight in kg</th>
<th>Daily dose (mg)</th>
<th>Morning* (mg)</th>
<th>Evening** (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤41.6</td>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 41.6 &gt; 58.3</td>
<td>58.3</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 58.3 &gt; 74.9</td>
<td>74.9</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 74.9 &gt; 91.6</td>
<td>91.6</td>
<td>500</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 91.6 &gt; 116.6</td>
<td>116.6</td>
<td>600</td>
<td>200+100</td>
</tr>
</tbody>
</table>

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

Dose reduction

Should a dose reduction be necessary, the patient will receive 4.5 mg/kg/day. The daily dose and the administration of the study treatment, according to the patient’s weight, is displayed in the table below:

Table 2: Dose of study treatment to be administered according to patient’s weight, after a dose reduction to 4.5 mg/kg/day (randomization dose: 6 mg/kg/day)

<table>
<thead>
<tr>
<th>Patient’s weight in kg</th>
<th>Daily dose (mg)</th>
<th>Morning* (mg)</th>
<th>Evening** (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤41.6</td>
<td>STOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 41.6 &gt; 58.3</td>
<td>58.3</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 58.3 &gt; 77.7</td>
<td>77.7</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 77.7 &gt; 99.9</td>
<td>99.9</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 99.9 &gt; 116.6</td>
<td>116.6</td>
<td>500+100</td>
<td>200+100</td>
</tr>
</tbody>
</table>

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

No dose escalation will be authorized for patients who have had a dose reduction for safety reasons.

Procedure in case of missed or vomited doses of study treatment tablets:
- In case the morning dose has been missed, it can be taken until 2 pm. on the same day. Should it be later than 2 pm, the missed dose will not be made up and study treatment will be resumed at the evening dose on the same day.
- In case the evening dose is missed, it should not be made up the day after in addition to the morning dose. The study treatment will be resumed the day after as scheduled in the protocol.
- Should the patient vomit within 10 minutes after the last study treatment dose intake, another dose should be taken.
Procedures to manage potential adverse reaction:

Study treatment refers to masitinib or its matching placebo.

Surveillance:
- Complete blood count at screening, baseline, W1, W2, W3, W4, W5, W6, W7, W8, W10, and every 4 weeks until the end of study treatment.
- Hepatic work up (AST, ALT, gamma GT, total bilirubin, AP, LDH) at screening, baseline, W2, W4, W6, W8 and every 4 weeks until the end of study treatment.
- BNP at baseline and ECG at baseline then every 12 weeks.
- Chest X-ray (only Posterior-Anterior view) at baseline (not required if chest X-ray performed within 3 months prior to baseline) and at the end of the study.
- At each visit, cardiac symptoms are carefully checked by medical interview and clinical examination.
- At baseline and at each patient visit, the physical exam of the patient must include a careful thyroid palpation.
- Urinary cytology and NMP22 test at baseline and then every 12 weeks.
- BetaHCG at screening, baseline, at the end of the study and in case of suspicion of pregnancy.
- In non-menopausal women using non-hormonal contraceptive method, hormonal work-up at baseline then every 12 weeks.
- Optional spermogram at baseline then every 12 weeks.

Patient card and procedures to follow by the patient during the first 2 months

All patients will receive a card mentioning the risk of severe neutropenia and the risk of severe skin toxicity with masitinib and the procedures to follow in case of signs or symptoms suggesting the occurrence of those 2 risks.

Call from site to patient once a week for the first 2 months

During the two first months of treatment, the study staff should call the patient every week to verify with the patient the weekly workups (i.e. Absolute Neutrophils Count) and to enquire about all signs which might be due to an underlying infection and ensure the absence of skin detachment and/or ulcerations.

In case a patient experiences either a severe neutropenia or severe skin toxicity, a specific pharmacogenomic blood sample should be collected and sent to the central lab on the day of the collection. The tube to be used for pharmacogenomic analysis must be either an EDTA tube (4 mL) or 2 PaxGene RNA/DNA tube (2x2.5 mL), provided by AB Science.

- Neutropenia regardless of the causal relationship to study treatment:
  - In case of absolute neutrophils count between 0.5 and 1x10⁹/L
  - Study treatment will be interrupted until absolute neutrophils count has returned above 1.5 x10⁹/L, and then restarted at the same dose
  - If duration of neutropenia > 4 weeks, the dose of study treatment will be decreased by one step
  - In case of absolute neutrophils count < 0.5x10⁹/L
  - Study treatment will be definitely discontinued
  - The investigator must inform the sponsor immediately (within 24 hours by fax using a Serious Adverse Event form) even if he/she considers the neutropenia as non-serious
  - In case of associated fever, the patient must be hospitalized in a special unit
  - In case of fever, oral ulceration, sore throat or infection, a complete blood count should be performed in order to check the neutrophil count. In case of neutropenia, the above mentioned rules should be applied
  - The patient should be instructed to follow the procedures described in the patient card in case of
<table>
<thead>
<tr>
<th>NAME OF COMPANY: AB SCIENCE</th>
<th>NAME OF FINISHED PRODUCT: MASITINIB</th>
<th>NAME OF ACTIVE INGREDIENT: AB1003</th>
</tr>
</thead>
</table>

Signs or symptoms of severe neutropenia.
- In any case, all concomitant treatment potentially inducing neutropenia must be stopped.

Renal disorders regardless of the causal relationship to study treatment
- In case of one of the 4 following events occur:
  - proteinuria ≥ 30 mg/dL on dipstick confirmed by a 24 hours proteinuria > 1.5g/24 hours
  - creatinin clearance < 50 mL/min (Cockroft and Gault formula)
  - albumin < 0.75 x LLN
  - urea > 1.5 x ULN

Study treatment will be interrupted until return to baseline; then treatment will be restarted at the same dose.

- If one of the 4 events occurs a second time, study treatment will be interrupted until adverse event has returned to baseline, and then restarted with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day).
- If one of the 4 events occurs a third time: study treatment will be permanently discontinued. In case of severe renal disorders, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day). If severe renal disorders re-occurs after dose reduction, study treatment must be definitely discontinued.
- If renal disorders are disabling or life-threatening, study treatment must be definitely discontinued.

Hypoalbuminemia regardless of the causal relationship to study treatment
- In case of hypoalbuminemia between 0.75 and 1 LLN, the dose of study treatment should be reduced (new dose: 4.5 mg/kg/day).
- In case of hypoalbuminemia lower than 0.75 LLN, study treatment must be definitely discontinued.

Liver disorders regardless of the causal relationship to study treatment
- In case of grade 2 liver enzymes increase; i.e. transaminases (AST or ALT or both) ≤ 5 ULN, and/or in case of bilirubin increase ≤ 3 ULN, study treatment should be maintained.
- In case of grade 3 liver enzymes increase, i.e. transaminases (AST or ALT or both) increase > 5 ULN and < 20 ULN, and/or in case of bilirubin increase ≥ 3 ULN and < 10 ULN, study treatment should be interrupted until transaminases levels return to ≤ 3 ULN and bilirubin level returns ≤ 1.5 ULN. Hepatic surveillance tests will be performed every week. Then resume study treatment with a dose reduction (new dose: 4.5 mg/kg/day).
- In case of second grade 3 liver enzymes increase, i.e. transaminases (AST or ALT or both) increase higher than 5 ULN and < 20 ULN and/or a second bilirubin increase > 3 ULN and < 10 ULN occur when study treatment is resumed, study treatment must be definitely discontinued.
- In case of grade 4 transaminases increase (i.e. AST or ALT > 20 ULN and/or bilirubin > 10 ULN), study treatment must be definitely discontinued.

Cardiac disorders, regardless of the causal relationship to study treatment.
At each visit, cardiac symptoms are carefully checked by medical interview and clinical examination.
In the event of cardiac event:
- In the event of thoracic pain
  1. Perform an ECG: if there is any change compared to the previous ECG(s), a cardiologist should be consulted.
ii. Perform a dosage of troponin: if the result is higher to LLN, a cardiologist should be consulted
   If an acute coronary syndrome is confirmed, study treatment should be definitely discontinued

- In the event of dyspnoea or signs of cardiac failure
  i. Perform a clinical examination: if there is clinical signs of cardiac failure, study treatment should be definitely discontinued and a cardiologist should be consulted
  ii. Perform an ECG: if there is any change compared to the previous ECG(s), a cardiologist should be consulted
  iii. Perform a dosage of BNP (or NT proBNP):
   1. If BNP is between 100 and 400 pg/mL (NT proBNP between 400 and 2000 pg/mL) without clinical signs of cardiac failure, control the dosage one week later: if there is an increase higher than 30% when compared to baseline value, a cardiologist should be consulted and the discontinuation of study treatment should be discussed according to the benefit risk ratio for the patient
   2. If BNP is higher than 400 pg/mL (NT proBNP higher than 2000 pg/mL) without clinical signs of cardiac failure, study treatment should be interrupted and a cardiologist should be consulted with an ECG and an echocardiography for the discussion of discontinuation or not of study treatment, according to the benefit/risk ratio for the patient.
  iv. Perform a dosage of troponin: if the result is higher to LLN, a cardiologist should be consulted
  v. Perform an echocardiography:
   1. If LVEF < 50%: study treatment should be definitely discontinued and a cardiologist should be consulted
   2. If LVEF between 50 and 60%, without clinical signs of cardiac failure, maintain study treatment and control the LVEF two weeks later:
      a. If clinical signs of cardiac failure appear: discontinue study treatment and a cardiologist should be consulted
      b. If LVEF is still between 50 and 60%: control the LVEF one month later, maintain study treatment, control the LVEF every 3 months
      c. If LVEF is equal or higher than 60%: maintain study treatment, control the LVEF 3month later.
      d. If LVEF is lower than 50%: discontinue study treatment and a cardiologist should be consulted.

- In the event of isolated lower limbs oedema
  ▪ Check clinical signs of cardiac failure
  ▪ Perform a dosage of BNP (or NT proBNP)
  ▪ If there is any suspicion of a cardiac origin, a cardiologist should be consulted.

- In the event of blood pressure increased
  ▪ Adapt the anti-hypertensive medications
  ▪ If high blood pressure persists, a cardiologist should be consulted and the discontinuation of study treatment should be discussed according to the benefit risk ratio for the patient.

- In the event of other potential cardiac adverse events, like syncope without known aetiology, severe conduction disorders, persistent ventricular tachycardia, resuscitated sudden death, study treatment should be interrupted and a cardiologist should be consulted.
  ▪ In the event of severe conduction disorders, study treatment may be resumed after pacing
In the other cases, study treatment must be definitely discontinued.

- **Reproductive system disorders and pregnancy**
  - If pregnancy is suspected during the study, study treatment must be immediately withheld until the result of a laboratory pregnancy test is available. Should pregnancy be confirmed, the patient must be withdrawn from study. Thereafter, the patient (and/or partner, if applicable) must be asked to participate in the AB Science pregnancy surveillance program and the baby and patient’s health will be followed at least up to 3 months after birth.
  - Menstrual cycle of pre-menopausal women not using hormonal contraceptive should be recorded at each study visit. In case of irregular cycles without known cause after exploration (such as pre-menopausal or history of irregular cycles), study treatment must be definitely discontinued. In addition, FSH, LH, estradiol and progesterone level of all pre-menopausal women not using hormonal contraceptive will be assessed at baseline and every 12 weeks during the course of the study, in front of the date of last menstruations.
  - A pelvic ultrasound will be performed in women of childbearing potential at baseline and final visit
  - Regarding male patients enrolled in the present study, they will be asked to perform a semen analysis (i.e. sperm count, morphology and motility analysis) at baseline, every 12 weeks and final visit. This procedure will be optional depending on the patient consent.

- **Skin toxicity regardless of the causal relationship to study treatment**
  In case of mucous ulceration, and/or skin detachment and/or suspicion of erythema multiforme or Stevens-Johnson syndrome, Lyell syndrome or DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) regardless of the severity of the event:
  - Study medication must be interrupted and the patient must consult a dermatologist. Study treatment can be re-challenged after mandatory agreement of the dermatologist.
  - The investigator must inform the sponsor immediately (within 24 hours by fax using a Serious Adverse Event form), even if he/she considers the skin toxicity as non-serious. AB Science will contact the investigator and the dermatologist in order to document the case (specific questionnaire see Appendix, photography of the lesions, cutaneous biopsy, ...)
  - Should an epidermal necrolysis (erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome) be suspected, study treatment must be definitely discontinued.
  - Should a DRESS syndrome be suspected, study treatment must be definitely discontinued.

In case of Grade 1 (CTC-AE classification) maculo-papular rash or desquamation:
- Study treatment will be maintained and patient will be treated with hydroxyzine 100 mg/day for 8 days

In case of Grade 2 (CTC-AE classification) maculo-papular rash or desquamation:
- Study treatment will be interrupted, and patient will be treated with hydroxyzine 100 mg/day for 8 days combined with prednisone for 8 days (1 mg/kg for 2 days, 0.5 mg/kg for the next 2 days, then 20 mg/day for 2 days, and last 10 mg/day for 2 days). After return to baseline or grade ≤1, study treatment will be resumed at the same dose level as before interruption
- In case of reoccurrence of a Grade 2 maculo-papular rash or desquamation, study treatment must be interrupted and the same symptomatic treatment should be initiated. After return to baseline or grade ≤1, study treatment will be resumed with at the same dose reduction (new dose: 4.5 mg/kg/day).
- If grade 2 maculo-papular rash or desquamation re-occurs, study treatment must be interrupted and the same symptomatic treatment should be initiated. After return to baseline or grade ≤1, study treatment will be resumed with at a dose reduction (new dose: 4.5 mg/kg/day).
- If Grade 2 maculo-papular rash or desquamation re-occurs after dose reduction, study treatment must be definitely discontinued.
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<td>MASITINIB</td>
<td>AB1003</td>
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In case of Grade 3 skin toxicity, except mucous ulceration, and/or skin detachment and/or suspicion of erythema multiforme or Stevens-Johnson syndrome, Lyell syndrome or DRESS, study treatment should be interrupted and a dermatologist should be consulted to confirm the diagnosis, assess the risk and define the symptomatic treatment for the patient. The dermatologist will give his/her opinion on whether patient could resume study treatment depending on skin lesions and patient safety. If the dermatologist agrees that study treatment should resume, study treatment will be resumed with a dose reduction (new dose: 4.5 mg/kg/day).

- **Oedema regardless of the causal relationship to study treatment**
  - In the event of isolated lower limbs oedema:
    - Check clinical signs of cardiac failure
    - Perform a dosage of BNP (or NT proBNP)
    - If there is any suspicion of a cardiac origin, a cardiologist should be consulted.
  - In case of moderate oedema, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose
  - If moderate oedema re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If moderate oedema re-occurs after dose reduction, study treatment must be definitely discontinued.
  - In case of severe oedema, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If severe oedema re-occurs, discontinue definitely study treatment
  - In case of incapacitating or life-threatening oedema or angioedema, discontinue definitely study treatment.

- **Nausea or vomiting regardless of the causal relationship to study treatment**
  - In case of nausea or vomiting, anti-emetics are recommended according to the usual practice.
  - In case of moderate nausea or vomiting, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose
  - If moderate nausea or vomiting re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If moderate nausea or vomiting re-occurs after dose reduction, study treatment must be definitely discontinued.
  - In case of severe nausea or vomiting, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If severe nausea or vomiting re-occurs, discontinue definitely study treatment
  - In case of disabling or life-threatening nausea or vomiting, discontinue definitely study treatment

- **Diarrhoea regardless of the causal relationship to study treatment**
  - In case of diarrhoea, anti-diarrheal medications are recommended according to usual practice.
  - In case of moderate diarrhoea, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose
  - If moderate diarrhoea re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If moderate diarrhoea re-occurs after dose reduction, study treatment must be definitely discontinued.
  - In case of severe diarrhoea, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
  - If severe diarrhoea re-occurs, discontinue definitely study treatment
  - In case of incapacitating or life threatening diarrhoea, discontinue definitely study treatment.
- **Dehydration**
In case of dehydration, study treatment should be interrupted and symptomatic treatment should be initiated.

- **Pulmonary disorders**
In case of aggravation of pre-existing symptoms, or new pulmonary symptoms without known aetiology (cough, dyspnoea, fever), study treatment will be interrupted until results of the etiological work-up are received.

- **Ocular disorders**
In case of moderate ocular disorders lasting for more than 1 week, or in case of severe ocular disorders, an ophthalmologist should be consulted to decide about patient care.

- **Carcinogenicity**
  
  **Risk of bladder cancer**
  A carcinogenicity study in male mice has shown potential risk of bladder carcinogenicity. This risk was not evidenced in human experience. However, urinary cytology including a specific search for transitional and/or malignant cells and a NMP22 test will be performed at baseline visit, every 12 weeks and at the final visit.

  **Risk of thyroid cancer / adenoma**
  At baseline and at each patient visit, the physical exam of the patient must include a careful thyroid palpation. Should a thyroid nodule be detected, an endocrinologist must be consulted for further diagnosis and treatment, if applicable.

  **Risk of uterine carcinoma**
  At baseline and every 12 weeks, a hormonal work up including progesterone, estradiol, FSH and LH must be performed in non-menopausal female patients treated with masitinib and using a non-hormonal contraceptive method.

- **Risk management plan for adverse event not described above and suspected to be related to study treatment**
  Please note that the previous rules apply regardless of the causal relationship to study treatment, while this rule applies only for adverse events suspected to be related to study treatment.
  - At the first occurrence of moderate adverse event, study treatment will be interrupted until adverse event has returned to baseline value or mild intensity, then resumed at the same dose level.
  - If the same moderate adverse event re-occurs, study treatment will be interrupted until adverse event has returned to baseline or mild intensity, then resumed with a dose reduction (4.5 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 will be interrupted until adverse event has returned to baseline level or mild intensity, then resumed with a dose reduction (4.5 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.

In case of severe adverse event suspected to be related to study treatment, an evaluation of the benefit/risk ratio by the investigator and an agreement of the Pharmacovigilance Department of the
Sponsor will be necessary before resuming study treatment.

In case of serious, unexpected adverse event, the treatment will be interrupted. The treatment could only be resumed when the adverse event has returned to baseline value and after the Independent Data Monitoring Committee would have given his approval.

Concomitant treatments allowed during the study (at stable doses):

1. **Mandatory concomitant medication:**

   An oral antihistamine (cetirizine 10 mg/day) must be combined systematically with the study drug for 60 days. Cetirizine will be initiated at the same time as study treatment. To avoid the possible sedative effect of anti-histamine, the treatment will be taken in the evening, at bedtime.

2. **Other concomitant treatments:**

   All symptomatic treatments such as:
   - Anti H1
   - Anti H2
   - Proton pump inhibitor
   - Osteoclast inhibitor (biphosphonates)
   - Cromoglycate Sodium
   - Antileukotriene
   - Adrenaline in case of anaphylactic shocks
   - Other therapies used for the symptomatic care

   They should be maintained at the same dose during the study. No change in the symptomatic treatment of mastocytosis or administration of any new treatment of mastocytosis should occur.

**Prohibited concomitant treatments:**

- Anticancer agent (including chemotherapy, high dose of corticosteroids, biologics agent)
- 2CDA
- Interferon
- Any investigational treatment related or not related to mastocytosis
- Live attenuated vaccines
- Drugs known to be at high risk of Stevens-Johnson syndrome: allopurinol, lamotrigine, carbamazepine, phenytoin, phenobarbital, sulfasalazine, sulfamid, oxicam and nevirapine; or to be at high risk of DRESS syndrome: minocycline, nodafenil, dapsone.

**Treatments which should be given with high caution:**

- Drugs known to interact with the same CYP450 isoenzymes (2C9, 2D6 and 3A4) than masitinib whether inducers, inhibitors or substrates.
- Acetaminophen/paracetamol
- Any nephrotoxic drug

**Independent Data Monitoring Committee**

An Independent Data monitoring committee (IDMC) with expertise and experience in the diagnosis and management of mastocytosis, and without direct involvement in the conduct of the study will be set up specifically to monitor safety data throughout the duration of a study. All adverse events occurring during the trial will be forwarded to this Committee.

The Committee recommends a closer follow-up on the events occurring during the study with an evaluation of the data quarterly independently from the sponsor and reserves the possibility of alerting the Scientific Committee of AB Science in the event of observation of highly unexpected events compared to the initial assumptions in early term of lack of efficacy, limiting toxicity or early efficacy. In case of alert:
• AB SCIENCE should consider discussing an action with Competent Authority(ies) in advance.

• If this alert concerns early efficacy, Head of Biometry should develop appropriate stopping rules and adjustment of type I error before examining the data.

The IDMC will review analyses by treatment group twice during the study. The IDMC will recommend the discontinuation of the study due to lack of efficacy; lack of efficacy being defined as a conditional power < 10%. If needed, the sample size might be revisited further to IDMC analysis.

### Criteria for Evaluation:

#### Efficacy:

Handicaps are defined as:

- **Main handicaps**: pruritus score $\geq 9$, number of flushes per week $\geq 8$, HAMD-17 score $\geq 19$, Fatigue Impact Scale $\geq 75$

- **Other handicaps**: micturition $\geq 8$, stools $\geq 4$

Response on a handicap is defined as an improvement $\geq 75\%$ for pruritus, flushes, Hamilton and fatigue.

**Primary variable:**

- Cumulative response by patient*handicap

For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

Week 4 is not considered for the calculation of this response as:

- All patients take anti-histamines between Baseline and week 4 even if they didn’t take such treatment before study entry

- Based on phase II studies, first month of treatment is under efficient

So, from 5 to 20 responses will be calculated by patient: 5 if the patients present only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients present the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits.

**Sensitivity analysis:** same 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.

**Secondary variables**

- Cumulative response on pruritus among patients with the handicap at Baseline

Cumulative response is calculated for pruritus as pruritus is considered as the most objective and representative measure in mastocytosis benefiting from a validated measure.

For the patients presenting the handicap at Baseline (i.e. score $\geq 9$), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

**Sensitivity analysis:** same 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.
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**assessment at a visit because a patient left the study prematurely or had no measurement at the visit.**

- **OPA score**

OPA score corresponds to the 53rd question of the AFIRM questionnaire.

For the patients presenting the handicap at Baseline (ie. OPA “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an OPA “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.

- **Quality of Life (QoL) : QLQ-C30**

Value at time point, absolute and relative change from Baseline for each scale (functional scales i.e. physical, role, cognitive, emotional and social; symptom scales i.e. fatigue, nausea/vomiting, pain and global scale) and each individual items (8, 11, 13, 16, 17 and 28).

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

- **AFIRM questionnaire**

For the global score, value at time point, absolute and relative change from Baseline will be given. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

For each of the 52 items, cumulative response among patients with “severe” or “intolerable” handicap at Baseline will be given. For the patients presenting the handicap at Baseline (ie. answer “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an answer “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.

- **Cumulative response on micturition among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (ie. ≥ 8), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.

- **Cumulative response on stools among patients with the handicap at Baseline**

For the patients presenting the handicap at Baseline (ie. ≥ 6), the response at each study visit (5 visits...
from week 8 to week 24) will be calculated. Response being defined as an improvement $\geq 75\%$ at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

**Sensitivity analysis:** same 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.

- Urticaria Pigmentosa (UP) evaluation
  
  Percentage of patients with UP improvement at time point.

- Mastocytosis symptoms rebound effect evaluation
  
  Percentage of patients who experiencing a rebound effect on at least one symptom after study/treatment discontinuation. Mean number of symptoms showing a rebound per discontinued patients. Percentage of patients who experiencing a rebound effect per symptom. Mean time of the occurrence of the rebound effect after study/treatment discontinuation. Symptom severity will be described. Patient overall wellbeing from treatment period will be also described.

**Safety:**

Masitinib safety profile will be compared to placebo on the following parameters:

- Occurrence of Adverse Events (AEs)
- Changes in physical examination including vital signs (blood pressure, pulse rate) and weight
- Clinical laboratory tests (biochemistry, haematology, urinalysis, ECG).

**Follow-Up**

Patients who completed the Week 24 period, with regular assessments and evaluation can enter a double blind extension phase:

- In case of positive clinical benefit/response established by investigator
- If required by the investigator and agreed by the patient.

The maximum exposure to treatment is 2 years. Exposure to treatment for more than 2 years will be possible only if:

- A Substantial amendment is approved by Competent Authority
- The benefit/risk for the study is positive based on available data
- The individual benefit/risk is still assessed as positive by investigator and documented

The informed consent form has been resigned to remind patient about potential long term risks. In this case the follow-up of patients will be identical with assessments every 12 weeks.

- Patients with AEs or clinically significant abnormal laboratory test results at the final visit will be followed up by telephone calls, site visit, and/or additional evaluation until resolved or stabilized.

**Analysis datasets:**

Protocols v5.0 and v6.0 changed handicaps definition from mild to moderate to severe. Additionally protocol v6.0 restricted the inclusion of patients with documented Smouldering or Indolent Systemic mastocytosis. With previous versions of the protocol, patients with cutaneous mastocytosis could be included. Protocol v6.0 restricted the inclusion to documented Smouldering or Indolent Systemic mastocytosis as there was no or limited cutaneous mastocytosis in the 2 phase 2 studies and in an effort to improve the benefit/risk balance.

Thus, the objective of the study is to compare the safety and efficacy of masitinib to placebo in
patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap. Therefore patients including before protocol v6.0 and presenting a cutaneous mastocytosis, a non-documented Smouldering or Indolent Systemic mastocytosis or a documented Smouldering or Indolent Systemic mastocytosis with non-severe handicap will be supportive. Efficacy and safety analysis of these patients will be exploratory and will consist in the presentation of individual listing.

- Intention-To-Treat (ITT) dataset

The ITT population will be defined as all patients randomized presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0. Patients will be classified according to the treatment arm to which they have been randomized, irrespective of the actual treatment received. The documented lack of taking at least one dose of the study drug after randomization and patients with no efficacy measure after randomization will be discussed.

- Modified Intent-To-Treat (mITT) dataset

The mITT dataset will include all ITT patients but patients withdrawing prematurely from the study for a well-documented non-treatment-related cause will be excluded. Among these causes, we could list withdrawal of consent for other reason than lack of efficacy or toxicity related to treatment, death for reason not related to treatment or no treatment intake.

- Per Protocol (PP) dataset

The PP data set consists of all patients of the mITT data set without any major protocol deviation. This is the set of patients who participated in the study as intended. Patients terminating the study prematurely will be included in the PP data set provided that there is no protocol deviation. Before locking the data base, the precise reasons for excluding patients from the PP data set will be fully defined and documented by the Data Review Committee.

Protocol deviations will be defined as:
- inclusion and non-inclusion criteria were not met
- intake of forbidden medication
- non-respect of visit dates
- missing value for main criterion without premature termination
- non-respect of protocol design
- any other deviations during the course of the study

Data Review Committee will classify as “minor” or “major” all the deviations of the study. This classification should be done prior to the unblinding the data.

- Safety population

The safety population consists of all patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 who took at least one dose of study medication (masitinib or placebo).

Sample Size:

*Primary analysis:* A total of 142 patients (71 in masitinib group and 71 in placebo group) presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 will provide a 80% power with a two-sided 5% alpha in order to compare masitinib to placebo as primary analysis (GEE model for the cumulative response by patient*handicap : 4 handicaps / 5 visits), under the following hypotheses:

- Same response rate for all the 4 handicaps all along the study ie. 8.5% for placebo vs. 21% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 42.6% for the first study, 23.7% for the second and 30.6% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (24%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.
- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)
- 1:1 design ratio


Taking into account a percentage of non-evaluable patients around 5%, 150 patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 (75 in masitinib group and 75 in placebo group) will be randomized in the study.

Secondary analysis: This sample size is sufficient to ensure a power $\geq 80\%$ with an overall two-sided 5% alpha for the cumulative response on pruritus among patients with the handicap at Baseline.

- GEE model : 5 visits
- Same response rate all along the study ie. 6% for placebo vs. 24% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 25.0% for the first study, 38.5% for the second and 35.8% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (25%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.
- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)
- 1:1 design ratio
- With these hypotheses, 86 patients with handicap on pruritus at Baseline are needed. We expected that patients with handicap on pruritus at baseline will represent 65% of the patients included. Therefore, 132 patients are needed for this criterion.

Statistical Methods:

For analysis on pruritus, flushes, Hamilton and FIS :

- Handicaps are defined as : pruritus score $\geq 9$, number of flushes per week $\geq 8$, HAMD-17 score $\geq 19$, Fatigue Impact Scale $\geq 75$
- Response on a handicap is defined as an improvement $\geq 75\%$ for pruritus, flushes, Hamilton and fatigue.

Primary analysis:

The primary analysis will be done on the mITT population. It is based on the cumulative response by patient*handicap:

- For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above
- So, from 5 to 20 responses will be calculated by patient : 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients presents the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).
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Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 4 to week 24: so from 5 to 20 responses by patient (as described above). Beside the treatment, the following factors and covariables will be included in the model: handicap, visit and corresponding interactions. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

Sensitivity analysis will be provided with Last Observation Carried Forward (LOCF) and Observed Cases (data remain missing) instead of missing=failure. Sensitivity analyses will also be provided on ITT and PP populations.

**Secondary analysis :**
The secondary analysis will be done on the mITT population. It is based on the cumulative response on pruritus among patients with the handicap at Baseline:

- For the patients presenting the handicap at Baseline (ie. score ≥ 9), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above.
- So, 5 responses will be calculated by patient.

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 4 to week 24; so from 5 by patient (as described above). Beside the treatment, the following factors and covariables will be included in the model: handicap, visit and corresponding interactions. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

Sensitivity analysis will be provided with Last Observation Carried Forward (LOCF) and Observed Cases (data remain missing) instead of missing=failure. Sensitivity analyses will also be provided on ITT and PP populations.

**Control of overall family-wise type I error rate:**

To guard against spurious inflation of the Type I error rate, if primary analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

**Primary analysis**
Cumulative response by patient*handicap on mITT population. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

If this analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

*Sensitivity analysis :*
- same 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
- same analysis on ITT and PP populations instead of mITT

**Secondary analysis**
Cumulative response on pruritus among patients with the handicap at Baseline (i.e. score ≥ 9). If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).
data will be considered as failure (missing = failure as primary analysis). If this analysis is conclusive at a 5% level, analyses of efficacy will be continued with exploratory analyses.

**Sensitivity analysis:**
- same 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.
- same analysis on ITT and PP populations instead of mITT

**Exploratory analyses**
Analyses on OPA, QLQ, AFIRMM, micturition, stools, Urticaria Pigmentosa and mastocytosis symptoms rebound effect. These analyses are exploratory.

**Subgroup analysis:**
Subgroup analysis is planned for studying the efficacy of the study treatment in patients bearing activation point mutations in the phosphotransferase domain of c-Kit such as the main mutation Asp-816-Val (D816V) in at least one organ versus patients for whom the detection of kit816 is negative in the organ biopsied or unknown. This subgroup analysis will be conducted on all variables. Potential chimeric patients (D816V in one tissue and WT in a second one) will be considered as patient bearing c-kit mutation.

**Table 3: Response definition for Mast Cell Infiltration and Tryptase level**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Pathological if at baseline</th>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
<th>Stable Disease (SD)</th>
<th>Progressive Disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>5% or more pathological mast cells (PMC) on bone marrow biopsy, assessed either on morphological ground or by immunohistochemistry or by immunocytology (c-Kit+ and CD25+)</td>
<td>PMC &lt; 5%</td>
<td>PMC &gt; 5% and decrease ≥ 25% from baseline</td>
<td>PMC &gt; 5% and stable number (baseline number ±25%)</td>
<td>Increase ≥ 25% from baseline</td>
</tr>
</tbody>
</table>
| Skin         | Skin lesions (extension % body surface or tumor size)  
Symptoms* (Darier’s sign, flushing, itching, blistering) | All skin lesions and related symptoms disappeared (=0) | Reduction >25% of skin lesions and related symptoms (decrease by at least 1 pt of the scale score) | All others cases | Progression >25% of skin lesions and/or related symptoms (Increase by at least 1 pt of the scale score) |
| Tryptase level | Serum level ≥ 20 µg/ml | Level ≤ 20 µg/ml | Level ≥ 20 µg/ml and decrease ≥ 25% | Level ≥ 20 µg/ml, and -25% < change ≤ +25% | Increase > 25% |

*0 (no symptoms), 1 (mild, infrequent, no therapy required), 2 (mild/moderate and frequent, may be successfully managed by standard therapy), 3 (severe and frequent, requiring extensive local and systemic therapy), and 4 (requiring immediate therapy and hospitalization, severe adverse event, SAE).
### Table 4: Definition of Symptomatic treatment failure with respect to patient enrolment

A failure is, for one handicap, a failure to at least one treatment

<table>
<thead>
<tr>
<th>Handicap</th>
<th>Anti H1 Dose</th>
<th>Anti H1 Duration</th>
<th>Anti H2 Dose</th>
<th>Anti H2 Duration</th>
<th>Proton Pump Inhibitor Dose</th>
<th>Proton Pump Inhibitor Duration</th>
<th>Cromoglycate Dose</th>
<th>Cromoglycate Duration</th>
<th>Antileukotriene Dose</th>
<th>Antileukotriene Duration</th>
<th>Other Dose</th>
<th>Other Duration</th>
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<td>Pruritus</td>
<td>RUD</td>
<td>1 month</td>
<td></td>
<td></td>
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<td></td>
<td>Local corticosteroid</td>
<td>6 weeks</td>
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<tr>
<td>flushes</td>
<td>RUD</td>
<td>3 months</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hamilton score</td>
<td>RUD</td>
<td>3 month</td>
<td>RUD</td>
<td>6 weeks</td>
<td>RUD</td>
<td>6 weeks</td>
<td>RUD</td>
<td>6 weeks</td>
<td>Anti depressive drug</td>
<td>3 months</td>
<td></td>
<td></td>
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<tr>
<td>Nbr stools</td>
<td>RUD</td>
<td>6 weeks</td>
<td>RUD</td>
<td>6 weeks</td>
<td>RUD</td>
<td>6 weeks</td>
<td>RUD</td>
<td>6 weeks</td>
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<tr>
<td>Nbr micturitions</td>
<td>RUD</td>
<td>1 month</td>
<td></td>
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<td></td>
<td>RUD</td>
<td>6 weeks</td>
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RUD: Recommended Usual Dose.
## STUDY FLOW-CHART

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<th>Treatment period</th>
<th>Extension period</th>
<th>End of study</th>
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<td>Screenin g Baseline</td>
<td>W1, W2, W3, W5,</td>
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<td>W24 Every 4 weeks Every 12 weeks Final visit(1)(3)</td>
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</table>

(1) If the final visit is performed on week 24, all assessment will not be repeated.
(2) In case of proteinuria >1+ (30 mg/dL) on the dipstick, 24-H protein will be measured.
(3) In non-menopausal women using non-hormonal contraceptive method.
(4) Additionally, at any time in case of suspicion of pregnancy.
(5) In case a chest X-ray has been performed within 3 months prior to baseline, it might be used as baseline chest X-ray. For chest X-ray only Posterior-Anterior view is required.
(6) Mastocytosis symptoms rebound effect assessment should be performed by telephone call or during site visit starting from one month after treatment discontinuation (for any reason/end of the study; appropriate pages in CRF should be completed.
(7) In women of childbearing potential.
### Localisation of the blood and urinary tests (C: Central Lab / L: Local lab):

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<th>Extension period</th>
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</table>

(1) If the final visit is performed on week 24, all assessment will not be repeated.
(2) If proteinuria ≥ 1+ (30 mg/dL) on the dipstick, 24-hour proteinuria should be performed
(3) Only at week 2 and week 6
(4) Only for pre-menopausal women not using hormonal contraceptive
# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

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<th>Definition</th>
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<tr>
<td>(A)sMAHNMD</td>
<td>(Aggressive) Systemic Mastocytosis Associated clonal Hematologic Non-MC-lineage Disease</td>
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<td>IGF1R</td>
<td>Insulin-like Growth Factor 1 Receptor</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISM</td>
<td>Indolent Systemic Mastocytosis</td>
</tr>
<tr>
<td>ISM+wH</td>
<td>Indolent Systemic Mastocytosis with Handicap</td>
</tr>
<tr>
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<td>Janus Kinase 2</td>
</tr>
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<td>Kit Ligand</td>
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<td>LH</td>
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<tr>
<td>MCGF</td>
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<tr>
<td>MCL</td>
<td>Mast Cell Leukemia</td>
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<tr>
<td>MTD</td>
<td>Maximum Tolerated Dose</td>
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<tr>
<td>NOAEL</td>
<td>No Observed Adverse Effect Level</td>
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<td>OPA</td>
<td>Overall Patient Assessment</td>
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<tr>
<td>PDGF</td>
<td>Platelet-Derived Growth Factor</td>
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<tr>
<td>PIM1</td>
<td>Provilal Integration Site 1</td>
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<tr>
<td>PKC</td>
<td>Protein Kinase C</td>
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<tr>
<td>p.o.</td>
<td>per os/ by mouth/orally</td>
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<tr>
<td>RTK</td>
<td>Receptor Tyrosine Kinase</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SCF</td>
<td>Stem Cell Factor</td>
</tr>
<tr>
<td>SL</td>
<td>Stem Factor</td>
</tr>
<tr>
<td>SM</td>
<td>Systemic Mastocytosis</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>SRC</td>
<td>Steroid Receptor Coactivator</td>
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<tr>
<td>SSM</td>
<td>Smouldering Systemic Mastocytosis</td>
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<td>UP</td>
<td>Urticaria Pigmentosa</td>
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<td>Vascular Endothelial Growth Factor Receptor</td>
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<td>WBC</td>
<td>White Blood Cell Count</td>
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<td>World Health Organization</td>
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<tr>
<td>WT</td>
<td>Wild Type</td>
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INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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2 INTRODUCTION AND STUDY RATIONALE

2.1 Masitinib (AB1010) non-clinical experience

Masitinib (AB1010) is a New Chemical Entity actually under development as an anti-cancer and an anti-inflammatory agent.

All AB1010 doses used for non-clinical studies in animals are expressed as the amount of AB1010, the monomesylate salt, whereas in clinical studies doses are expressed as the amount of free base, named AB1003. The relationship between AB1010 and AB1003 is the ratio of their molecular weights (594.76 for the monomesylate salt and 498.66 for the free base) which is 1.19.

2.1.1 Pharmacology

The pharmacological properties of AB1010 have been thoroughly investigated in vitro and in vivo, mainly in mice.

AB1010 is a protein-tyrosine kinase inhibitor which, in vitro, potently and selectively inhibits the mutated form, in the juxtamembrane (JM) region, of the c-Kit receptor and the c-Kit wild-type (WT) receptor. It also inhibits the PDGF receptor and the mutated Fibroblast Growth Factor (FGF) Receptor (FGFR3).

At the cellular level, AB1010 is a selective inhibitor of JM c-Kit dependent cell proliferation in the nanomolar range (IC\textsubscript{50} 5 nM) and c-Kit WT dependent cell proliferation in the 0.1 micromolar range (IC\textsubscript{50} between 0.1 and 0.3µM). AB1010 is able to block PDGF-dependent cell proliferation at nanomolar concentrations (IC\textsubscript{50} between 0.25-10 nM) and FGFR3-dependent cell proliferation in the micromolar range (IC\textsubscript{50} between 1 and 2 µM). These concentrations are attainable in vivo.

AB3280, the main plasmatic metabolite of AB1010 produced in human, retains the activity and selectivity profiles of the parent compound AB1010.

In vivo, AB1010 shows significant anti-tumor activity after oral administration at well tolerated doses in a murine model, a Balb/c Nude mouse model with a subcutaneous graft of a transgenic murine hematopoietic cell line, transfected with the gene encoding c-Kit JM \Delta27. AB1010, given orally twice a day for ten consecutive days, resulted in strong inhibition of tumor growth in a range of doses between 30 mg/kg and 200 mg/kg. In addition, AB1010 given orally at either 100 or 200 mg/kg resulted in complete resorption of the tumor following a 10 day treatment. AB1010 has therefore demonstrated anti-tumor activity regardless of the tumor volume at the beginning of the treatment.

Safety pharmacology studies revealed no significant effects of single administration of AB1010 on the central nervous and respiratory system in rats, and no modification of cardiovascular function or electrophysiological parameters in telemetered dogs.

2.1.2 ADME and Pharmacokinetics in animals

The toxicokinetic profile was determined during the repeat-dose toxicity studies, in rats and dogs.

AB1010 plasma levels in rats and dogs were measured by LC-MS/MS using a fully validated method. Only in one preliminary, non GLP study in dogs, the determination of AB1010 plasma level was performed by HPLC/UV.

In addition to the toxicokinetic data available, 2 ADME studies investigated the blood and plasma pharmacokinetics, tissue distribution and mass balance of total radioactivity in rats and dogs following single administration of [\textsuperscript{14}C]-AB1010 by intravenous injection and oral gavage.

The main PK characteristics of AB1010 obtained from the ADME studies are the following:

- AB1010 is well absorbed after oral administration: 83\% of absorption of the administered radioactivity in dogs and 72.5\% of the administered radioactivity in rats.
• Tissue distribution revealed extensive distribution throughout the body in rats, with highest levels seen in the intestines, liver, kidneys and spleen. At 24 hours post-dose, trace amounts (<2.2%) of the administered radioactivity were measured in most organs and tissues, indicating that AB1010 is rapidly eliminated from these tissues.

• Up to 3 metabolites in addition to the parent drug were found in urine in both species. The major metabolite observed, respectively in rats and dogs up to 52.4% and 26.0% of total sample radioactivity, is a carboxylic acid metabolite of AB1010, resulting from the cleavage of the amide bond. In the feces, parent \[^{14}C\]-AB1010 was the major radioactive component present, representing, respectively in rats and dogs, up to 57.0% and 41.1% of total sample radioactivity. The major metabolite detected in rats and dogs feces, at around 20-25% of total sample radioactivity, was confirmed to be the N-desmethyl AB1010 (AB3280).

• Excretion occurred predominantly in the feces and was almost complete within seven days, regardless of administration route, dose and species.

• After oral administration of non radiolabelled AB1010 to rats, mice and dogs, the desmethylated metabolite AB3280 was found in significant quantities (6 to 24.9% in rats, 28.2 to 64.3% in mice and 6 to 8% in dogs) in the plasma.

• From in vitro study using hepatic microsomes from different species, it can be concluded that the phase I metabolism of AB1010 is rather similar in human, rat, mouse, Cynomolgus monkey and rabbit with all species forming three metabolites in addition to AB3280 as major metabolites.

It is worth noting here, that AB3280 has also been found as the major plasmatic metabolite in humans.

A pharmacokinetic study comparing the tablet formulation used in human clinical trials with the aqueous solution formulation used in preclinical studies was conducted in dogs and concluded of similar pharmacokinetics parameters of AB1010.

When tested in vitro, AB1010 appeared to be an inhibitor of CYP2C9, CYP2D6 and CYP3A4 in human liver microsomes and a weak inducer of CYP1A2 which suggests that AB1010 could alter CYP (1A2, 2C9, 2D6- and /or 3A4)-mediated metabolic-dependent clearance of co-administered drugs.

Whatever the species including humans, AB1010 is highly bound to plasma proteins (86 to 97%).

2.1.3 Toxicology

Acute toxicity of AB1010 was investigated in rats after oral and iv administration. The results obtained indicate that AB1010 is a product with low acute toxicity as its LD50 was not reached at 2000 mg/kg per os and at 100 mg/kg iv.

Oral repeated-dose toxicity studies were performed in rats and dogs, with duration of 2 weeks, 4 weeks and 13 weeks in both species, then 26 weeks in rats and 39 weeks in dogs.

Bone marrow toxicity
The bone marrow toxicity observed in dogs and rats was characterized by hypopcellularity at microscopic examination, modified hematology parameters (decreased red and white blood cell parameters) and clinical signs (palor of the nose, oral and ocular regions). These effects were observed at 50 mg/kg and above. At 15 mg/kg, these effects were not observed in dogs and were considered marginal in rats. In addition, these effects were reversible at 150 mg/kg in both species. They are not unexpected according to the mechanism of action of the test compound and its expected activity on hematopoiesis resulting from c-Kit inhibition.

Liver toxicity
Liver toxicity observed in dogs and rats at 50 mg/kg was characterized by a modest increase of hepatic enzyme activities and decreased plasma concentrations of protein and albumin and by microscopic changes such as bile canalicular plugs and vacuolated Kupffer cells. At 150 mg/kg, the severity of
these effects was increased; liver enlargement was recorded at necropsy of the dogs. The effects on the liver were partially reversible after the end of the recovery period in dogs.

**Gastro-intestinal toxicity**

Gastro-intestinal toxicity was observed in dogs and was mostly characterized by clinical signs. At 15 mg/kg, these clinical signs included vomiting, regurgitation and soft feces but were observed with low frequency and severity. At higher doses, the frequency and severity of these signs were increased.

**Renal events**

*In the 26-week toxicity study*, rats given 100mg/kg/day, showed increased urea and creatinine blood levels that correlated with slight to moderate degenerative/necrotic tubular nephropathy.

*Preclinical toxicity studies in dogs* (4, 13 and 39-weeks repeated dose) showed renal toxicity (*ie* significant presence of blood, bilirubin and proteins) only in dogs exposed to 150mg/kg/day and in the 4 weeks study. One female treated at 30mg/kg/day in the 39 weeks study was sacrificed close to the end of the study for poor conditions. Renal toxicity was highlighted and consisted in proteinuria, haematuria, bilirubinuria, anemia, hypoprotidemia and hypoalbuminemia, but without any macro nor microscopic renal lesions at histopathological analysis. The edema in the pericardium was considered to be a contributing factor for the moribund condition of the animal, but was probably the result of hypoalbuminemia and hypoprotidemia detected in this dog.

**Cardiac events**

*The 26-weeks toxicity study in rats* showed slight myocardial degeneration and fibrosis in 6/20 males given 30mg/kg/day and in 7/20 males given 100 mg/kg/day, with slightly increased ASAT activity levels (<2ULN).

**Biological disorders**

Additional untoward effects, such changes in APTT and fibrinogen values (both were reduced in rats and increased in dogs), increased blood urea levels and decreased blood triglycerides levels (in rats) were observed at 50 and 100 mg/kg/day.

**Reprotoxicity and teratogenicity**

AB1010 is teratogenic and presented few reprotoxicities in animal as developed below.

*In all toxicity studies in rats*, female genital organs showed morphological changes indicative of disturbance of the estrous cycle in females given 100mg/kg/day or more. The ovaries showed a moderate to large number of luteal and/or follicular hematocysts, no or few corpora lutea, and very few or few follicular developments. Pending the ovarian status, this was associated with endometrial epithelial cell atrophy or hypertrophy together with hyalinosis of endometrial stroma and the vagina showed epithelial cell atrophy, hyperplasia or mucification. Partial reversibility was noted for the female genital organs in the 4-week toxicity in rats, whereas no evidence of reversibility was noted at necropsy in the 13-week toxicity in rats.

*In the 39-week toxicity study in dogs*, microscopic post-mortem examination showed vacuolation of the epithelium in the seminiferous tubules of the testes and related oligospermia in the epididymes of two males given 30 mg/kg/day.

Studies for effects on embryo-fetal development (segment 2) showed that AB1010 is devoid of developmental toxicity *in rabbits*, but displays some developmental toxicity in rats (*ie* reduced mean fetal body weight, unossified or incompletely ossified fetuses in the skull and sternebrae) at doses above 30 mg/kg/day.

A study of fertility and early embryonic development until implantation, by oral route in rats did not show any effects of treatment on seminology.

The study of fertility *in rats* (segment 1) showed that the fertility of females given 100mg/kg was affected, as indicated by the number of low number of corpora lutea and implantation sites and the high pre-implantation loss.
The return to fertility study in rats female, given AB1010 for 28 days at 0, 15 and 50 mg/kg, showed that after a 14 day washout period female fertility was back to normal function.

Genotoxicity and carcinogenicity

The negative results obtained in all the genotoxicity tests performed on AB1010 and AB3280 provide good evidence supporting the lack of mutagenicity of AB1010 and of the major circulating (N-desmethylated) metabolite AB3280. The main circulating metabolite, AB3280 is also negative in a bacterial reversion test as well as in a chromosome aberration study.

Carcinogenicity studies are ongoing in rats and in mice. The antiproliferative and anti-inflammatory profile of AB1010 argues against a carcinogenic potential effect related to its pharmacological activity.

No hyperplasia or pre-neoplastic lesion was observed in the 26-week rat or 39-week dog toxicity studies.

It is relevant to note that one of AB1010 metabolite, the aromatic amine AB2436 is suspected to be genotoxic. However although potent analytical methods such as LC-MS/MS have been used, the presence of this metabolite has never been detected in urines of rats and dogs.

Conclusion:

Many of the findings observed in toxicity studies may be attributed to the pharmacological activity of the compound and to prolonged suppression of cell division in various organs.

The NOAEL after oral repeated-doses for 4-week was established at 15 mg/kg in dogs and rats. This NOAEL was confirmed in the 13-week toxicity study in dogs. The NOAEL of the 13-week toxicity study in rats was established at 30 mg/kg.

The NOAEL of the 2 long-term toxicity studies (26 week in rats and 39 week in dogs) was established at 10 mg/kg.

AB3280 has been found as the major plasmatic metabolite in humans receiving AB1010 by oral route. This justified the evaluation of this compound in a 2-week toxicity study by oral route (gavage) in rats. Its NOAEL is considered to be 250 mg/kg/day.

2.2 AB1010 Current Safety Profile

2.3 Overview

Four-hundred and thirty-one subjects/patients were part of this safety review, 95 healthy volunteers, 40 end-stage cancer patients and 296 patients with various medical conditions (86 patients with oncology disease, including 29 patients receiving study drug in combination with chemotherapy, and 210 patients with inflammatory disease).

Among the 431 subjects/patients included in this report, there were 32 known placebo subjects/patients, and 399 subjects/patients either receiving AB1010 or unblinded treatment (AB1010 or placebo). Among them, only 16 were estimated to be treated by placebo. Therefore, the safety profile of the 399 subjects/patients is likely to be very similar to the one of the estimated 383.

In the overall subjects/patients population, 230 serious adverse events regardless the relationship the study drug were reported in 96 patients (24.1% - 42.5% in phase I Solid Tumors patients, 40.7% in phase II oncology patients, 21.9% in phase II non-oncology patients).

Thirteen deaths occurred during the studies, all reported in the oncology studies, and due to progressive disease in 10/13 cases. For the 3 remaining ones, the causality of study treatment was questionable, but cannot be demonstrated, according to sponsor.

12.8% of the patient population treated with AB1010 at least once, presented at least one non fatal suspected/not assessable SAE (17.5% in phase I Solid Tumors patients, 19.8% in phase II oncology patients, 13.3% in phase II non-oncology patients).
Seventy subjects/patients (17.5% - 20.0% in phase I Solid Tumors patients, 16.3% in phase II oncology patients, 22.4% in phase II non-oncology patients) discontinued permanently study drug for suspected/not assessable AE.

Severe adverse events suspected (or not assessable) to be related to study drug, occurred more frequently in Phase I Solid Tumors patients and in Phase II oncology patients (40.0 and 39.5%, respectively), than in Phase II non-oncology patients (25.5%).

Overall, 1914 suspected/not assessable adverse events (AE) were reported in 314 subjects/patients (72.8% - 100.0% in phase I Solid Tumors patients, 97.7% in phase II oncology patients, 83.2% in phase II non-oncology patients), while 31.3% of subjects/patients receiving placebo reported at least one AE.

In the overall subject/patient population treated with AB1010 at least once, most frequent suspected/not assessable AE with an incidence greater than 20% were:

- nausea and/or vomiting (32.8%) - nausea (28.6%), vomiting (17.0%),
- edema 27.3% regardless their MedDRA coding,
- diarrhea (22.6%),
- rash 20.8% regardless their MedDRA coding.

Frequent suspected/not assessable AE with an incidence comprised between 5 and 20% were asthenia (19.0%) mostly related to oncology indications, abdominal pains (12.0%), decreased appetite (8.3%), anemia (8.0%), pruritus (7.8%), headache (7.0%), neutropenia (6.3%), and muscle spasm (6.3%).

### 2.3.1 Healthy volunteers

In the Healthy Volunteer studies, the most common reported AE were abdominal pain, nausea and diarrhea in about 10% of the subjects followed by headache, vomiting and dizziness. Gastrointestinal disorders occurring at the dose of 800mg/day were considered as limiting toxicities, and the maximal recommended dose was established at 400 mg/day, which corresponds to 6mg/kg/day, the recommended dose for non-oncology indications.

### 2.3.2 Phase I Solid Tumors study

In the phase I in solid tumors, the safety profile of AB1010 appeared acceptable, with mainly mild to moderate adverse events. Drug-related moderate gastrointestinal disorders (nausea, vomiting, diarrhea) were considered dose limiting. Their intensity increased with daily dose, with no significant toxicity reported up to 12 mg/kg/day and an increased number of limiting toxicity above this dose.

Even though the MTD was not formally achieved in this trial where doses up to 15mg/kg/day were tested, the dose of 12 mg/kg was thus considered as the maximal recommended dose, compatible with a long term administration of this drug.

Other information coming from Phase I Solid Tumors is that for chronic use, AB1010 should be dosed according to weight (in mg/kg/day) to minimize over dosing and that administering AB1010 twice daily instead of once daily will help limit the gastrointestinal toxicity.

### 2.3.3 Phase II studies

*Most frequent suspected/not assessable adverse events (occurring in more than 20% of patients)*

Most frequent, suspected/not assessable AE reported in at least 20% of the Phase II population patients treated with AB1010 at least once, were:

- nausea/vomiting (34.4%) - nausea (30.1%), vomiting (15.2%),
- edema 32.6% regardless their MedDRA coding,
- rash 27.0% regardless their MedDRA coding,
- diarrhea (22.0%).

No obvious drug relationship was observed for any AE except possibly for edema in non-oncology patients. It seems that there is a threshold of dose at 7.5mg/kg/day beyond which main AEs increase in terms of frequency, as shown in Table 5 below.

Table 5: All studies – Number of patients (%) with one of the suspected/not assessable adverse event of interest by dose

<table>
<thead>
<tr>
<th>Dose at AE onset (mg/kg/day)</th>
<th>Placebo (N=32)</th>
<th>All patients (N=399)</th>
<th>&lt;3.0 (N=49)</th>
<th>3.0 (N=113)</th>
<th>4.5 (N=93)</th>
<th>6.0 (N=138)</th>
<th>7.5 (N=93)</th>
<th>9.0 (N=68)</th>
<th>10.5-12.0 (N=37)</th>
<th>&gt;12.0 (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or Vomiting</td>
<td>0 (0.0%)</td>
<td>131 (32.8%)</td>
<td>7 (14.3%)</td>
<td>16 (14.2%)</td>
<td>20 (21.5%)</td>
<td>22 (15.9%)</td>
<td>29 (31.2%)</td>
<td>26 (38.2%)</td>
<td>15 (40.5%)</td>
<td>9 (90.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>114 (28.6%)</td>
<td>4 (8.2%)</td>
<td>13 (11.5%)</td>
<td>16 (17.2%)</td>
<td>21 (15.2%)</td>
<td>23 (24.7%)</td>
<td>23 (33.8%)</td>
<td>12 (32.4%)</td>
<td>9 (90.0%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>68 (17.0%)</td>
<td>5 (10.2%)</td>
<td>5 (4.4%)</td>
<td>8 (8.6%)</td>
<td>7 (5.1%)</td>
<td>16 (17.2%)</td>
<td>16 (23.5%)</td>
<td>9 (24.3%)</td>
<td>7 (70.0%)</td>
<td></td>
</tr>
<tr>
<td>Edema - All</td>
<td>1 (3.1%)</td>
<td>109 (27.3%)</td>
<td>2 (4.1%)</td>
<td>7 (14.3%)</td>
<td>10 (10.7%)</td>
<td>26 (18.8%)</td>
<td>39 (41.9%)</td>
<td>20 (29.4%)</td>
<td>12 (32.4%)</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (3.1%)</td>
<td>90 (22.6%)</td>
<td>5 (10.2%)</td>
<td>8 (7.1%)</td>
<td>8 (8.6%)</td>
<td>14 (10.1%)</td>
<td>21 (22.6%)</td>
<td>19 (27.9%)</td>
<td>16 (43.2%)</td>
<td>5 (50.0%)</td>
</tr>
<tr>
<td>Rash - All</td>
<td>1 (0.0%)</td>
<td>83 (20.8%)</td>
<td>1 (2.0%)</td>
<td>12 (10.6%)</td>
<td>10 (10.7%)</td>
<td>23 (16.7%)</td>
<td>29 (31.2%)</td>
<td>14 (20.6%)</td>
<td>7 (18.9%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Incidence of suspected/not assessable gastrointestinal disorders, rashes, and edema in each subpopulation is presented in Table 6 below.

Table 6: Phase II studies – Most frequent suspected/not assessable AEs

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (N=32)</th>
<th>P II (N=282)</th>
<th>Oncology (N=86)</th>
<th>Oncology - Monotherapy (N=57)</th>
<th>Oncology - Combination (N=29)</th>
<th>Non-Oncology (N=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or Vomiting</td>
<td>0 (0.0%)</td>
<td>97 (34.4%)</td>
<td>46 (53.5%)</td>
<td>31 (54.4%)</td>
<td>15 (51.7%)</td>
<td>51 (26.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0%)</td>
<td>85 (30.1%)</td>
<td>41 (47.7%)</td>
<td>28 (49.1%)</td>
<td>13 (44.8%)</td>
<td>44 (22.4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0%)</td>
<td>43 (15.2%)</td>
<td>25 (29.1%)</td>
<td>15 (26.3%)</td>
<td>10 (34.5%)</td>
<td>18 (9.2%)</td>
</tr>
<tr>
<td>Edema - All</td>
<td>1 (3.1%)</td>
<td>92 (32.6%)</td>
<td>47 (54.7%)</td>
<td>36 (63.2%)</td>
<td>11 (37.9%)</td>
<td>45 (23.0%)</td>
</tr>
<tr>
<td>Rash - All</td>
<td>1 (3.1%)</td>
<td>76 (27.0%)</td>
<td>31 (36.0%)</td>
<td>17 (29.8%)</td>
<td>14 (48.3%)</td>
<td>45 (23.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (3.1%)</td>
<td>62 (22.0%)</td>
<td>32 (37.2%)</td>
<td>21 (36.8%)</td>
<td>11 (37.9%)</td>
<td>30 (15.3%)</td>
</tr>
</tbody>
</table>

P II, Phase II studies

Table 6 shows that the incidence of main AE seems to be higher in oncology indication, what could be explained by the fact that oncology patients received doses above or equal to the threshold of 7.5mg/kg/day.

The majority of AE were mild or moderate in intensity. About 24.4% and 12.7% of the oncology and non-oncology patients population, respectively, experienced at least one severe gastrointestinal disorders, rashes, or edema.

Most of AE (77.5% of nausea/vomiting, 68.3% of edema, 79.4% of rash, and 76.9% of diarrhea) resolved either under treatment, without interruption.

Table 7 below presents the global occurrence of main AEs for patients included in phase II studies (excluding patients receiving placebo) during the first 3 months of treatment, and during the extension period.
63.8% of patients suffered from nausea/vomiting, diarrhea, rash, and edema within the first 3 months of treatment, versus 33.6% after month 3, including 17 patients (18.9%) treated with doses up to 6mg/kg/day; suggesting a transitory pattern for these main side effects.

There might be a possible explanation of some of these AE by the mechanism of action of AB1010. Diarrhea and rash might be explained by the release of the mediators due to the mast cell apoptosis triggered by c-kit inhibition. Edema might be explained by the inhibition of PDGFR, a receptor tyrosine-kinase involved in the interstitial pressure of the tissues.

To conclude, most frequent AEs (gastrointestinal disorders, rashes, and edema) which were, in their vast majority, mild to moderate, which mostly resolved under treatment; and which are related to the mechanism of action of the product, are therefore manageable.

**Frequent suspected/not assessable adverse events (occurring in more 5-20% of patients)**

Frequent, suspected/not assessable AE occurring in 5 to less than 20% of the Phase II population patients treated with AB1010 at least once, were:

- asthenia (18.8%),
- abdominal pains (11.3% - abdominal pain 6.7%, abdominal pain upper 6.4%),
- pruritus (10.6%),
- headache (7.4%),
- neutropenia (6.7%),
- muscle spasms (6.7%),
- pyrexia (5.7%).

Incidence of frequent suspected/not assessable AE in each subpopulation is presented in Table 8 below.
Table 8: Phase II studies – Frequent suspected/not assessable AEs

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (N=32)</th>
<th>P II (N=282)</th>
<th>Oncology (N=86)</th>
<th>Oncology - Monotherapy (N=57)</th>
<th>Oncology - Combination (N=29)</th>
<th>Non-Oncology (N=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>2 (6.3%)</td>
<td>53 (18.8%)</td>
<td>31 (36.0%)</td>
<td>26 (45.6%)</td>
<td>5 (17.2%)</td>
<td>22 (11.2%)</td>
</tr>
<tr>
<td>Abdominal pains</td>
<td>1 (3.1%)</td>
<td>32 (11.3%)</td>
<td>14 (16.3%)</td>
<td>12 (21.0%)</td>
<td>2 (6.9%)</td>
<td>18 (9.1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (3.1%)</td>
<td>19 (6.7%)</td>
<td>9 (10.5%)</td>
<td>7 (12.3%)</td>
<td>2 (6.9%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>0 (0.0%)</td>
<td>18 (6.4%)</td>
<td>9 (10.5%)</td>
<td>9 (15.8%)</td>
<td>0 (0.0%)</td>
<td>9 (4.6%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0.0%)</td>
<td>30 (10.6%)</td>
<td>12 (14.0%)</td>
<td>11 (19.3%)</td>
<td>1 (3.4%)</td>
<td>18 (9.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3.1%)</td>
<td>21 (7.4%)</td>
<td>4 (4.7%)</td>
<td>4 (7.0%)</td>
<td>0 (0.0%)</td>
<td>17 (8.7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0 (0.0%)</td>
<td>19 (6.7%)</td>
<td>14 (16.3%)</td>
<td>7 (12.3%)</td>
<td>7 (24.1%)</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0 (0.0%)</td>
<td>19 (6.7%)</td>
<td>10 (11.6%)</td>
<td>10 (17.5%)</td>
<td>0 (0.0%)</td>
<td>9 (4.6%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0 (0.0%)</td>
<td>16 (5.7%)</td>
<td>7 (8.1%)</td>
<td>2 (3.5%)</td>
<td>5 (17.2%)</td>
<td>9 (4.6%)</td>
</tr>
</tbody>
</table>

As for most frequent AE, the incidence of main AE seems to be higher in oncology indication, where patients received higher doses of treatment. However, asthenia seems to be more specific to oncology studies.

The majority of AE was of mild and moderate intensity (11.4% were severe AE). Most of AE resolved either under treatment or after temporary interruption of treatment.

Rare suspected/not assessable adverse events

Five patients (1.3% in the overall population) presented severe neutropenia, definitely suspected to be related to study drug according to the sponsor,

Four other cases of severe suspected/not assessable neutropenia, were reported, but remained questionable by sponsor, since they might be accounted for intercurrent viral infection (1 patient), they occurred in combination with chemotherapy (2 patients), or they resolved under treatment (1 patient).

All neutropenia occurred within the first 35 days of treatment, leading to the hypothesis that neutropenia might be due to hypersensitivity of neutrophils to c-Kit inhibition.

All patients recovered within one to three weeks after the AE onset. AB1010 treatment was maintained in one patient, and restarted in three other ones, without reoccurrence of neutropenia.

A risk management plan has been implemented, for early detection of such cases, and consists in repeated blood work-ups during the first 3 months of treatment (every week during the first two months, then every two weeks up to the month 3, then every month during treatment).

Other adverse events

No significant cardiac events, no renal disorders, and no secondary malignancies were reported.

Laboratory events

Mild to moderate increase in ALT, AST and lymphopenia, anemia and leucopenia were reported in the order of 40% in oncology indications and 10% in non-oncology indication.

These results support the observations reported in the “adverse events” section, and highlight no unexpected abnormalities with a mild to moderate increase in ALT, AST and lymphopenia, anemia and leucopenia.

Vital signs

No cardiac abnormality was reported in patients with normal values at baseline. In particular, there was no abnormality in ECG and no difference in frequency of occurrence was observed with placebo on hypertension and tachycardia.

Around 10% of patient had either Grade I or Grade II proteinuria detected by dipstick analysis.
There might be a possible explanation of some of these AE by the mechanism of action of AB1010 which may induce some permeability dysfunctions through inhibition of PDGFR or other kinase involved in podocyte function and renal leakage.

**Conclusion**

These safety data suggest that AB1010 is globally well-tolerated at the doses of 7.5-12mg/kg/day in oncology indications, and up to 6mg/kg/day in non-oncology indications.

Most frequent AEs, nausea/vomiting, edema, rash and diarrhea, are manageable, since they are in the vast majority, mild to moderate, mostly resolve under treatment; and are related to the mechanism of action of the product.

1.3% of patients experienced severe neutropenia that might be due to hypersensitivity of neutrophils to c-Kit inhibition. A risk management plan was implemented to early detect these patients.

### 2.4 Pathology under investigation

#### 2.4.1 Indication

Mastocytosis is a disease characterized by mast cell invasion in various organs. Mast cells are bone marrow derived cells which produce histamine and other substances causing allergic and anaphylactic reactions. Accumulation of mast cells in body organs can inhibit the functionality of the organ and eventually cause degeneration.

Mastocytosis usually involves the skin and bone marrow, but may also involve other internal organs. Severe mastocytosis may make life miserable for patients, causing symptoms of itching, difficulty in concentrating, peptic ulcers, and diarrhea. It can also lead to life-threatening anaphylactoid reactions and be associated with fatal hematologic disorders. Systemic mastocytosis (SM) is a clonal disease of myelomastocytic progenitors. The clinical picture of SM is variable, ranging from an asymptomatic (indolent) course to highly aggressive courses with a short survival.

Mutations of the mast cell growth factor receptor (also known as KIT protein, the product of the c-Kit proto-oncogene) are found in patients with mastocytosis but not in all. Patients display either activating point mutations in the phosphotransferase domain of c-Kit such as the mutation Asp-816-Val or the c-Kit wild type (WT) receptor.

In order to assess the frequency of c-Kit mutation in patients with mastocytosis, AFIRMM, Association Francaise pour les Initiatives et la Recherche sur le Mastocyte et les Mastocytoses, has identified in the last five years in France, 1297 patients with mastocytosis. Among them, 593 have been enrolled in a study to define the status of c-kit and the correlations with clinical presentations of the disease.

Preliminary results demonstrate that 30% of the patients do not present the classical D$_{816}$V mutation on skin biopsy in our panel (Table 3, unpublished data). The detection of mutation at the position 816 was less frequent in the bone-marrow biopsy. A different quality of RNA extraction on skin and bone-marrow biopsies might explain the difference in the results obtained.

<table>
<thead>
<tr>
<th>SKIN</th>
<th>Number of patients</th>
<th>frequency (% patients)</th>
<th>BONE MARROW</th>
<th>Number of patients</th>
<th>frequency (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested</td>
<td>533</td>
<td>-</td>
<td>342</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>D816</td>
<td>338</td>
<td>70%</td>
<td>89</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>147</td>
<td>30%</td>
<td>98</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

Based on clinical findings and symptoms, six major categories of patients with mastocytosis have been identified (Table 4).
Table 10: Official WHO classification

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>WHO terms</th>
<th>Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-AHNMD</td>
<td>Systemic Mastocytosis with an Associated clonal Hematologic Non Mast cell lineage Disease</td>
<td>Associated with myelodysplasia and myeloproliferative syndrome and sometimes with an acute leukemia or lymphoma</td>
</tr>
<tr>
<td>MCL</td>
<td>Mast Cell Leukemia</td>
<td>Large numbers of atypical mast cells in the peripheral blood MCs in bone marrow smears (≥20%)</td>
</tr>
<tr>
<td>ASM</td>
<td>Aggressive Systemic Mastocytosis</td>
<td>At least one C-Finding</td>
</tr>
<tr>
<td>SSM</td>
<td>Smouldering Systemic Mastocytosis</td>
<td>MCs in bone marrow &gt; 5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At least two B- Findings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No C-Finding</td>
</tr>
<tr>
<td>ISM</td>
<td>Indolent Systemic Mastocytosis</td>
<td>MC infiltration in at least 1 extracutaneous tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No B and C Findings</td>
</tr>
<tr>
<td>CM</td>
<td>Cutaneous Mastocytosis</td>
<td>Typical skin lesions: either maculopapular, urticaria pigmentosa, mastocytoma. Typical infiltrate of mast cell in skin (no other tissue involvement)</td>
</tr>
</tbody>
</table>

Table 11: Biological and Clinical Findings as per WHO definition

<table>
<thead>
<tr>
<th>B findings</th>
<th>C findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High Mast Cell (MC) burden:</td>
<td>Organopathies</td>
</tr>
<tr>
<td>• Infiltration grade in bone marrow (bm) &gt; 30%</td>
<td>• Bone Marrow: cytopenia</td>
</tr>
<tr>
<td>by histology and/plus serum tryptase &gt; 200 ng/ml</td>
<td>ANC &lt; 1 000/µL</td>
</tr>
<tr>
<td>• Dysmyelopoiesis:</td>
<td>Hb &lt; 10 g/dl</td>
</tr>
<tr>
<td>• Hypercellular marrow with loss of fat cells</td>
<td>Plt &lt; 100 000/µL</td>
</tr>
<tr>
<td>or discrete signs of Myelodysplasia or Myeloproliferation, normal blood counts or slight persisting deviation without progression</td>
<td>(one or more found)</td>
</tr>
<tr>
<td>• Organomegaly:</td>
<td>• Liver: palpable Hepatomegaly with ascites,</td>
</tr>
<tr>
<td>• Palpable Hepatomegaly without ascites or</td>
<td>abnormal liver function tests and/or portal</td>
</tr>
<tr>
<td>other signs of organ impairment or/and</td>
<td>hypertension.</td>
</tr>
<tr>
<td>Lymphadenopathy palpable or visceral LN-</td>
<td>• Spleen: palpable splenomegaly with</td>
</tr>
<tr>
<td>enlargement found in US or CT (&gt;2 cm)</td>
<td>hypersplenism</td>
</tr>
<tr>
<td>and/or Palpable Splenomegaly without</td>
<td>• GI tract: malabsorption with hypoalbuminemia</td>
</tr>
<tr>
<td>hypersplenism</td>
<td>and weight loss</td>
</tr>
<tr>
<td></td>
<td>• Skeleton: bone lesions with large-sized</td>
</tr>
<tr>
<td></td>
<td>osteolyses or/and severe osteoporosis with</td>
</tr>
<tr>
<td></td>
<td>consecutive pathologic fractures</td>
</tr>
</tbody>
</table>

Cutaneous mastocytosis (CM)

Cutaneous mastocytosis occurs normally in children and usually presents as a typical rash in the skin with minimal or no systemic and organ involvement. It causes patients to experience flushing, swelling and blister formation as well as itching of the lesions which may occur spontaneously.

Types of cutaneous mastocytosis include solitary mastocytoma and urticaria pigmentosa (UP). UP is the most common type and represents about 65% of all paediatric cases. The typical lesions consist of red-brown to yellowish macules or papules that may vary in size from millimetres to centimetres in diameter. Patients with CM have normal peripheral blood cell counts and serum tryptase <20 ng/ml.

Systemic Mastocytosis (SM)

Systemic mastocytosis (SM) is a clonal disease of myelomastocytic progenitors, characterized by an abnormal proliferation of mast cells in the tissues. The clinical picture in SM is variable ranging from an asymptomatic (indolent) course to highly aggressive courses with a short survival. Survival is actually of approximately 2 years in males with systemic mast cell disease, and >10 years in females (extrapolated from 50% survival point in Kaplan-Meier curves).
Based on the level of severity and organ involvement further major categories of systemic mastocytosis have been identified and are described below. Other descriptions for the categories are used in the literature though all are based on similar clinical and pathogenic events:

1. patients with **indolent systemic mastocytosis without handicap** (ISM) who have a favorable prognosis and may suffer from mediator-related symptoms but do not suffer from significant organopathy caused by mast-cell infiltration. Typical cases present with maculopapular skin lesions of mastocytosis.

2. patients with **indolent systemic mastocytosis with handicap** (ISMwH) who do not suffer from organopathy caused by mast-cell infiltration but suffer considerably from mediator-related symptoms.

3. patients with **smouldering systemic mastocytosis** (SSM) for whom the clinical course is not aggressive but clinical and laboratory findings are indicative of slow progression leading to a huge burden of neoplastic cells (mast cells and/or other myelopoietic cells) over time. These patients present with hypercellular marrow and organomegaly and have clear signs of an increase in mast cell burden, i.e. increase in serum tryptase and increased sizes of bone marrow cell infiltrates OR have recurrent life-threatening hypotensive episodes that did not resolve or improve in response to previous anti-mediator-type drugs or 2CDA or IFNalpha

4. patients with **aggressive systemic mastocytosis** (ASM) who present significant organopathy due to MC-infiltration (C-Findings). Almost any organ can be involved. The organ-systems most frequently affected are the bone marrow, skeletal system, liver, spleen, and the gastrointestinal tract. Respective C-findings include cytopenias, osteolysis (or osteoporosis) with pathologic fractures, hepatosplenomegaly with impaired liver function and ascites, and malabsorption. In some cases, eosinophilia and lymphadenopathy are prominent clinical features. In contrast to ISM, patients with ASM often present without maculopapular skin lesions. Patients with ASM can show a slowly progressing or a rapid clinical course. Rapidly progressing ASM may also shift into another category of SM, i.e. MCL or (A)SMAHNMD within short time. Irrespective of the clinical course, no curative therapy for ASM and MCL has become available to date. Survival in aggressive systemic mast cell disease is of 2-3 years.

5. patients with an **associated clonal hematologic non-MC-lineage disease** (AHNMD) develop an associated clonal hematologic non-mast cell lineage disease such as myeloproliferative disorder, myelodysplasic syndrome or acute myeloid leukemia.

6. patients with **mast cell leukemia** (MCL). MCL is a rare systemic MC disease characterized by (rapidly) progressive C-Findings, a high proportion of MCs in bone marrow smears (≥20%), circulating MCs, and a short survival in most cases (<6 months).

The ASM/MCL/AHNMD/SSM forms represent less than 10% of the population and the other forms account for 90% of systemic mastocytosis.

There is no known therapy which effectively destroys the mast cells that cause mastocytosis. We have determined that almost all cases of adult mastocytosis are caused, at least in part, by mutations which cause the mast cell growth factor receptor c-kit to be constantly stimulating mast cell growth. Constitutive activation of c-Kit may also increase mast cell survival and the release of mediators. Furthermore, it may increase the risk of the development of other genetic alterations, which could lead to a switch from indolent to aggressive disease. KIT protein is a tyrosine kinase, and its activity can be blocked by a new class of drugs called tyrosine kinase inhibitors. Tyrosine kinase inhibitors which inhibit the activated c-kit found in mast cell tumor lines effectively kill those cells in laboratory tests. Thus, theoretically a large group of patients may benefit of c-kit tyrosine kinase inhibitors therapy. The first registered kinase inhibitor able to block c-kit is Imatinib. Beside its activity against the kinase activity of Bcr-Abl (Chronic myelogenous leukemia), PDGFR, Imatinib blocks kinase activity of wt c-kit and juxtamembrane mutation of c-kit, but not the D816V kinase activity. Surprisingly, although not yet fully understood few cases report and a recent pilot study showed that Imatinib may improve symptoms associated with mastocytosis as well as mast cell infiltration. This effect might be due to the SCF synthesis by pathological mast cells, which in turn may recruit normal mast cells and
melanocytes. Furthermore the fibrosis associated to mastocytosis could be due to PDGF synthesis by abnormal mast cells (bearing the D816V C-kit mutation). In such cases blocking wild type c-kit and PDGFR may reduce symptoms, mast cell infiltration, and pigmentation and fibrosis associated with mastocytosis.

Taken together these findings and hypothesis provide a rationale to use a PDGFR and c-kit kinase inhibitor in the treatment of mastocytosis.

In order to confirm these results, the study purposes to evaluate the activity of masitinib in a larger group of patients with smouldering systemic, indolent systemic and cutaneous mastocytosis.

2.4.2 Current therapies

In addition to symptomatic therapies such as anti-histaminic (H1/H2), osteoclast inhibitors, antileukotrienes, or proton pump inhibitors which are often ineffective in patients with cutaneous or systemic mastocytosis, following alternative therapies exist but have major drawbacks.

Interferon therapy

Interferon therapy has been used in mastocytosis because of its activity in myeloproliferative disorders.

Few reports based on small series have demonstrated that interferon therapy may induce some responses in the disease, even in some cases complete response. However, prospective larger study shows that in fact in most cases interferon therapy cannot reduce mast cell infiltration. Furthermore in mastocytosis interferon therapy is associated with a high rate of side effects and particularly with depression. As a consequence the dropout rate is very high and only few patients (>25%) can maintain therapy for a long period of time. A few cases suggest that corticosteroids and interferon together may improve response rate. However, once again corticosteroids are associated with side effects.

Due to its high rate of side effects and its poor efficacy, particularly in reducing tumor burden, interferon is now rarely used. It may be used in mastocytosis with symptoms to reduce mediators release but its benefit must be weighed against its high rate of side effects.

Cladribine

Cladribine is a purine analogue that is efficient to induce apoptosis in resting cells. It has been used successfully in hairy cell leukemia and in Langerhans histiocytosis. Recent publications showed that cladribine shows an efficacy to decrease symptoms associated with mediators release, but also to reduce mast cell tumor burden in up to 50% of cases with few complete responses. However, relapses occur and maintenance therapy is probably needed in the majority of cases.

Although well tolerated, cladribine administration induces an immunosuppressive state and although not yet fully demonstrated is potentially carcinogenic. Therefore repetition of cures in maintenance therapy might be not recommended particularly in indolent mastocytosis with handicap.

Imatinib

Imatinib is a kinase inhibitor designed to block bcr-abl and abl. Subsequently, it has been shown that Imatinib is also able to block the kinase activity of wild type c-kit and juxtamembrane mutated c-kit but not of phosphotransferase domain mutation. As a consequence it has been used successfully in tumor in which juxtamembrane c-kit mutations, such as gastro-intestinal stromal tumors, are found.

In mastocytosis the proof of concept of blocking c-kit has been demonstrated in a patient with an aggressive mastocytosis bearing a juxtamembrane c-kit mutation. In this patient, Imatinib was able to induce a very good regression of the tumor burden.

A recent pilot study showed that in mastocytosis with no phosphotransferase domain mutations, imatinib was able to reduce mast cell infiltration. In this study, 12 adults with symptomatic systemic mast-cell disease were prospectively treated at a dose of either 100 mg or 400mg per day. Out of the ten patients assessed for response, five (50%) had a measurable response, four of whom had important mast-cell cytoreduction and two who had complete clinical and histological remission. In the five
patients with eosinophilia, three had complete clinical and haematological remission. However, in all of these studies the efficacy of the drug on various symptoms associated with mast cell mediators release was not assessed systematically.

2.5 Rationale for the development of AB1010 in mastocytosis

2.5.1 Study rationale

There is currently no effective and/or well tolerated therapy able to down regulate the mast cells that cause mastocytosis, but encouraging results obtained with imatinib provide rationale to investigate further the effect of c-kit inhibitors in mastocytosis.

AB1010 is a new potent inhibitor of c-Kit a tyrosine kinase receptor. As detailed below, its selective and potent effect is probably multifactorial and may include inhibition of cell proliferation, inhibition of cell cycle progression and the induction of apoptosis. All of these outcomes reduce the number of accumulating mast cells in body tissues. The drug is thereby specific to mastocytosis and active in slowing or reducing the number of mast cells particularly in aggressive forms of disease.

Inhibition of enzymatic activity of purified c-kit encoded tyrosine kinase by AB1010

The action of AB1010 in inhibiting c-kit tyrosine kinase activity has been demonstrated in an ELISA assay using the purified intracellular soluble domain (567-976) of c-kit expressed in baculovirus measuring phosphorylation of a peptide target containing a tyrosine group. AB1010 potently inhibited enzymatic activity with an IC50 of 0.01 µM.

Inhibition of mast cell proliferation by AB1010

The specific anti-proliferative activity of AB1010 was exhibited in a selection of mammalian cell lines suitable for testing the specific activity of c-kit tyrosine kinase. These included:

- Ba/F3 (immortalised murine pro-B cell line, transfected with c-kit)
- HMC-1 (human mast cell leukemia cell line expressing constitutively activated c-kit)
- TF1 (human cell line expressing endogenous c-kit)
Table 12 - Anti-Proliferative Activity of AB1010

<table>
<thead>
<tr>
<th>Cell line</th>
<th>AB1010 IC50 [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ba/F3;</td>
<td></td>
</tr>
<tr>
<td>Ba/F3 h c-Kit WT IL3</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Ba/F3 m Kit Δ27 (JM domain)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Ba/F3 m c-Kit WT</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Ba/F3 m Kit V558D (JM domain)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Ba/F3 m c-Kit D814V</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Ba/F3 h c-Kit WT</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Ba/F3 h c-Kit D816V</td>
<td>&gt;5</td>
</tr>
<tr>
<td>HMC-1</td>
<td></td>
</tr>
<tr>
<td>HMC-1 α155 (Kit V560G – JM domain)</td>
<td>0.08</td>
</tr>
<tr>
<td>HMC-1 5C6 (Kit D816V)</td>
<td>&gt;5</td>
</tr>
<tr>
<td>TF1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

AB1010 inhibited the proliferation of cells that express wild type c-kit with an IC50 of less than 0.3 µM.

AB1010 was also tested on ex vivo primary murine mast cells expressing endogenous WT c-kit, and was shown to inhibit proliferation of bone marrow mast cells and autophosphorylation of c-kit upon stimulation with SCF at a dose of 1 µM.

Figure 2 - AB1010 inhibits Bone Marrow Mast Cells (BMMC) proliferation

Induction of mast cell apoptosis by AB1010

As shown in Table 13 below, incubation with submicromolar concentrations of AB1010 selectively induced apoptosis in cells that express WT or JM-mutated c-kit.

Table 13 - Induction of Apoptosis by AB1010

<table>
<thead>
<tr>
<th>Cell line</th>
<th>AB1010 IC50 [µM] after 48h treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ba/F3</td>
<td></td>
</tr>
<tr>
<td>Ba/F3 m Kit Δ27 (JM domain)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Ba/F3 m Kit D814V</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Ba/F3 h c-Kit WT</td>
<td>0.2</td>
</tr>
<tr>
<td>Ba/F3 h c-Kit D816V</td>
<td>&gt;5</td>
</tr>
<tr>
<td>HMC-1</td>
<td></td>
</tr>
<tr>
<td>HMC-1 α155 (V560G – JM domain)</td>
<td>0.1</td>
</tr>
<tr>
<td>HMC-1 5C6 (Kit D816V)</td>
<td>&gt;5</td>
</tr>
<tr>
<td>TF1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

m: murine; h: human

The ability of AB1010 to induce apoptosis was further demonstrated in a Ba/F3-derived cell line expressing the WT c-kit gene, and in TF1 cell line. In this experiment apoptosis was induced to a level of approximately 80% versus control cells in which 10% of cells were apoptotic.
AB1010 in vitro potency on blocking WT c-kit compared to Imatinib

At the cellular level, AB1010 is a more selective inhibitor of c-Kit WT dependent cell proliferation (IC50 of 0.2 μM), than imatinib mesilate (IC50 of 0.6 μM).

Figure 4 - Activity of AB1010 on Ba/F3 cell lines expressing c-Kit WT and c-Kit JM Δ27

Conclusion

In conclusion, Mastocytosis is a rare disease for which there is no treatment and no possibility of spontaneous remission. Overall, blocking wild type c-kit may reduce symptoms, mast cell infiltration, pigmentation and fibrosis associated with mastocytosis. As AB1010 is a potent and selective inhibitor of the c-Kit receptor, it should be good candidate for the treatment of Mastocytosis.

2.5.2 Current clinical experience in mastocytosis

Preliminary data from the two phases IIa performed in patients with Indolent Systemic or Cutaneous Mastocytosis with handicap and respectively bearing and not bearing the activating point mutations in the phosphotransferase domain of c-kit (such as D816V), show encouraging results.

Clinical experience in patients not bearing the activating point mutations in the phosphotransferase domain of c-kit (such as D816V) – Wild Type –

The first open label study (AB04010) was conducted in patients systemic indolent or cutaneous mastocytosis with handicap not bearing the activating point mutations in the phosphotransferase
domain of c-kit (such as D816V).

25 patients have been enrolled in the open label study. Handicaps were defined as a number of flushes per day $\geq 1$, a pruritus score $\geq 6$, a number of stools per day $\geq 4$ (i.e. diarrhoea), a number of micturition $\geq 8$ (i.e. pollakiuria) and a Hamilton rating scale for depression score $\geq 10$. Most frequent handicaps observed at baseline were: flush (80% of patients), pruritus (76% of patients), depression (60% of patients), diarrhoea (40% of the patients) and pollakiuria (40% of the patients).

At week 12, the most important improvement observed was a mean reduction of -60.2% of flush frequency. Consistently, pruritus and Hamilton rating scale for depression scores were improved respectively of 43.8% and 40.3% compared to baseline. Furthermore, significant reduction of the daily number of stools and micturitions was observed in patients suffering from diarrhea and pollakiuria, respectively -44.3% and -39.3%.

Overall Patient Assessment and Quality of Life assessed by the QLQ C-30 improved consistently. The AFIRMM questionnaire, encompassing 38 mastocytosis related symptoms, improved at week 12 with mean reduction of the score of -42.6%.

Six eligible patients presented a chimeric c-kit status at baseline. Surprisingly, efficacy results showed no difference between WT/WT patients and the chimeric ones on the clinical response. Further investigation on patients bearing c-kit mutation would be of value.

Faster time to response of action and better clinical responses were often observed in patients who were initially treated with the 6mg/kg/day. Increments of dose were needed in 54% of patients treated at initial dose of 3 mg/kg/day to get clinical response. Thus, initial dose of 6 mg/kg/day seems to be more efficient.

The overall response rate was 65.0% in the PP population. This clinical response at week 12 does not seem to be correlated to the haematological response (infiltration of mast cells or tryptase level).

The few pharmacokinetic parameters obtained from this study showed that they were roughly comparable in patients with mastocytosis and in healthy volunteers.

16 patients (64%) entered in the extension phase. 12 patients were still treated at clinical report’s cut-off date with for some of them treatment exposure greater than two years. Among the four patients who exited the extension phase due to a lack of efficacy, three of them were considered non responder at week 12. The efficacy response observed at week 12 was for the others maintained and even further improved during the extension phase, demonstrating the sustainability of the efficacy of AB1010.

Clinical experience in patients bearing the activating point mutations in the phosphotransferase domain of c-kit (such as D816V) – Wild Type –

To further demonstrate the efficacy of masitinib in patients with systemic or cutaneous mastocytosis bearing the D816V c-kit mutation, AB Science has conducted a second phase II study (study AB06013).

21 patients were enrolled in the open label study. All patients were c-kit D816V in at least one organ. Two patients were chimeric according the localization. Handicaps were defined as a number of flushes per day $\geq 1$, a pruritus score $\geq 6$, a number of stools per day $\geq 4$ (i.e. diarrhoea), a number of micturition $\geq 8$ (i.e. pollakiuria), a Hamilton rating scale for depression score $\geq 10$ and asthenia assessed by a Fatigue Impact Scale score $\geq 40$. Most frequent handicaps observed at baseline were: pruritus (95.2 %), flushes (85.7 %), depression (71.4 %), asthenia (61.9 %), pollakiuria (47.6 %) and diarrhea (42.8 %).

The week 12 efficacy results in patients with handicaps at baseline, irrespective of the dose taken, are summarized hereafter (ITT analysis). The most important improvement observed was a mean reduction of -59.4% of flush frequency. Consistently, stools frequency, pruritus and Hamilton scores were improved respectively of -54.9%, -46.3% and -45.9% compared to baseline. Furthermore, significant reduction of the FIS score and micturitions was observed in patients suffering from asthenia and pollakiuria, respectively -39.4% and -34.7%.
Overall Patient Assessment and Quality of Life assessed by the QLQC-30 improved consistently. The AFIRMM V2 questionnaire, encompassing 52 mastocytosis related symptoms, improved at week 12 with mean reduction of the score of -26.3%. With respect to patients impaired at baseline (AFIRMM score ≥140) the improvement of the AFIRMM total score reached -32.7% at week 12.

As per Clinical Response definition, 68.4% of the patients were responders at week 12.

The 6 mg/kg/day dose seems to be more potent on flush and micturition frequency, Hamilton and AFIRMM V2 scores. This finding supports the previous results obtained in patients suffering from mastocytosis demonstrating that the 6mg/kg/day was the most potent dose and the one that should be used in forthcoming clinical phase III studies. 13 patients (68.4%) entered in the extension phase. 10 patients were still treated at the cut-off date. The few clinical data available at week 24 tend to further demonstrate the sustainability of the efficacy of AB1010. Previous results in Wild Type patients and these results of the second phase IIa study support further development of AB1010 in patients suffering from cutaneous or systemic mastocytosis irrespective of their mutational status of c-kit.
3 STUDY OBJECTIVES

The objective of this study is to compare the efficacy and safety of masitinib at 6 mg/kg/day to placebo in the treatment of patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap based on treatment effect on the pruritus score, the number of flushes per week, the HAMD-17 score, and the Fatigue Impact Scale score.

Primary endpoint:
- Cumulative response by patient*handicap

Secondary endpoints:
- Cumulative response on pruritus among patients with the handicap at Baseline
- Cumulative response on OPA score among patients with “severe” or “intolerable” handicap at Baseline
- Quality of Life (QoL) : QLQ-C30 global score, functional scores and symptom scores at each visit
- AFIRMM questionnaire :
  • global score
  • for each of the 52 items : cumulative response among patients with “severe” or “intolerable” handicap at Baseline
- Cumulative response on micturitions among patients with the handicap at Baseline
- Cumulative response on stools among patients with the handicap at Baseline
- Urticaria Pigmentosa (UP) evaluation at week 12, 24 and then every 12 weeks

Clinical and biological safety profile (including occurrence of Adverse Events, the potential changes in vital signs, ECG, Chest X-Ray and biological parameters)
4 INVESTIGATIONAL PLAN

4.1 Overall study design and plan
This is a prospective, randomized, double-blinded, placebo-controlled, 2-parallel group, multicentre Phase 3 study comparing the efficacy and safety of oral masitinib at the dose of 6mg/kg/day to placebo in patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap.

Patients will be randomly allocated to one of the two following groups:
- group 1: masitinib (6 mg/kg/day)
- group 2: matching placebo

Treatment allocation:
Because handicaps/scores at baseline regarding pruritus, flushes, depression and fatigue might influence the study outcome, they must be equally represented in the two treatment groups. Hence, randomization includes a minimization procedure aimed at reducing any difference in the distribution of the handicaps/scores at baseline and country.

As patients will be randomized 1:1, it is planned to include 75 patients in masitinib group and 75 patients in the placebo group that is to say, 150 patients in total will be enrolled.

The patients will be treated for at least 24 weeks with possible treatment extension phase if judged medically appropriate by the investigator, with a maximum treatment exposure of 2 years. After 2 years, patients will be allowed to continue the treatment on a case by case basis only if a documented favourable benefit/risk ratio is established by the investigator. In this case, an additional informed consent form will have to be signed by the patient to remind him about potential long term risks.

In this case the follow-up of patients will be every 12 weeks.

4.2 Study flow-chart
The duration of the study will be 24 months, with each patient being treated for 24 weeks (6 months). Patient enrolment is expected to be completed within 48 months after the start of the study.

Patient must be followed at the study centre according to the flow chart and assessments outlined described hereafter.
Table 14: Study flow-chart

<table>
<thead>
<tr>
<th>Pre-treatment period</th>
<th>Treatment period</th>
<th>Extension period</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>Baseline Week 0</td>
<td>W1, W2, W3, W5, W6, W7, W10</td>
<td>W4, W8, W12, W16, W20</td>
</tr>
<tr>
<td>Patient Visit</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Written Informed Consent</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Call to patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Patient able to follow the patient card procedures</td>
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<tr>
<td>Mast cell infiltration assessment:</td>
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<td></td>
</tr>
<tr>
<td>- Skin biopsy</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>- And/or Bone marrow aspirate/biopsy (optional)</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>- Tryptase level</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Decision to randomize the patient</td>
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<tr>
<td>Handicap assessment:</td>
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<td></td>
</tr>
<tr>
<td>- Pruritus score</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Flashes/week</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- HAMD-17</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Fatigue Impact Scale</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Stools/day</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Micturitions/day</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Anaphylactic shock</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>- QLQ-C30 scores</td>
<td>x</td>
<td>x</td>
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<tr>
<td>- Overall Patient Assessment</td>
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<tr>
<td>- AFIRM Score V2</td>
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<td>- UP evaluation</td>
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<td>Safety assessment:</td>
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<tr>
<td>- Adverse event</td>
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<tr>
<td>- Concomitant treatment</td>
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<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Physical examination including vital signs and weight</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- ECG</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Doppler echocardiography</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>- NT pro BNP (or BNP)</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>- Chest X-ray</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Haematology</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Liver enzymes</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
<td>- Biochemistry</td>
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<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Urinalysis (dipstick)(2)</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>- Urinary Cytology and NMP22 test</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Spermogram (optional procedure)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Menstrual cycle</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>- FSH/LH/Estriadol/progesterone assessments(3)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pregnancy test (serum)(4)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pelvis ultrasound</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Treatment dispensation</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Treatment compliance</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

(1) If the final visit is performed on week 24, all assessment will not be repeated.

(2) In case of proteinuria>1+ (30 mg/dL) on the dipstick, 24-H protein will be measured.

(3) In non-menopausal women using non-hormonal contraceptive method.

(4) Additionally, at any time in case of suspicion of pregnancy.

(5) In women of childbearing potential.
5 STUDY POPULATION

The patient population will be patients with following mastocytosis as per WHO classification:
- Smouldering Systemic Mastocytosis
- Indolent Systemic Mastocytosis

Up to 150 patients will be randomized in the study (75 patients in masitinib group and 75 patients in placebo group) and treated at least for 24 weeks.

5.1 Inclusion criteria

1. Patient with one of the following documented mastocytosis as per WHO classification:
   - Smouldering Systemic Mastocytosis
   - Indolent Systemic Mastocytosis

2. Patient with documented mastocytosis and evaluable disease based upon histological criteria: typical infiltrates of mast cells in a multifocal or diffuse pattern in skin and/or bone marrow biopsy

3. Patient with documented treatment failure of his/her handicap(s) with at least one of the following therapy used at optimized dose:
   - Anti H1
   - Anti H2
   - Proton pump inhibitor
   - Osteoclast inhibitor
   - Cromoglycate Sodium
   - Antileukotriene

4. Handicapped status defined as at least two of the following handicaps, including at least one among pruritus, flushes, depression and fatigue:
   - Pruritus score ≥ 9
   - Number of flushes per week ≥ 8
   - Hamilton rating scale for depression(HAMD-17) score ≥ 19
   - Number of stools per day ≥ 4
   - Number of micturition per day ≥ 8
   - Fatigue Impact Scale total score (asthenia) ≥ 75

5. Patients with OPA ≥ 2 (moderate to intolerable general handicap)

6. ECOG ≤ 2

7. Patient with adequate organ function:
   - Absolute neutrophils count (ANC) ≥ 2.0 x 10⁹/L,
   - Haemoglobin ≥ 10 g/dL
   - Platelets (PTL) ≥ 100 x 10⁹/L
   - AST/ALT ≤ 3x ULN (≤ 5 x ULN in case of liver mast cell involvement),
   - Bilirubin ≤ 1.5x ULN
   - Creatinine clearance >60mL/min (Cockcroft and Gault formula)
   - Albumin >1 x LLN
   - Urea ≤ 1.5x ULN
   - Proteinuria < 30mg/dL on the dipstick; in case of proteinuria ≥ 1+ on dipstick, 24 hours proteinuria should be ≤1.5g/24 hours

8. Male or female patient aged 18 to 75 years, weight > 50 kg, BMI between 18 and 35 kg/m²

9. Female patient of childbearing potential (entering the study after a menstrual period and who have a negative pregnancy test), who agrees to use two highly effective methods (one for the
patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. Acceptable forms of contraception include:

- A documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository)
- Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) should also be used
- Double barrier method: Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Any other contraceptive method with a documented failure rate of <1% per year
- Abstinence when this is in line with the preferred and usual lifestyle of the patient.

10. Male patients must use medically acceptable methods of contraception if your female partner is pregnant, from the time of the first administration of the study drug until three months following administration of the last dose of study drug. Acceptable methods include:

- Condom;
- If you have undergone surgical sterilization (vasectomy with documentation of azoospermia) a condom should also be used.

Male patients must use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. The acceptable methods of contraception are as follows:

- Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Your female partner uses oral contraceptives (combination oestrogen/progesterone pills), injectable progesterone or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Your female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository) should also be used;
- Your female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository);
- Abstinence when this is in line with the preferred and usual lifestyle of the patient.

11. Male or female patient of child bearing potential must agree to use two methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for three months after the last treatment intake. Female patients must have a negative result in the pregnancy tests at screening and baseline.

12. Patient must be able and willing to comply with study visits and procedures per protocol

13. Patient must understand, sign, and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures performed
14. Patient must understand the patient card and follow the patient card procedures in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity during the first 2 months of treatment.

15. Patient affiliated to a social security regimen

5.2 Exclusion criteria

1. Patient with one of the following mastocytosis:
   - Cutaneous Mastocytosis
   - Not documented Smouldering Systemic Mastocytosis or Indolent Systemic Mastocytosis
   - Systemic Mastocytosis with an Associated clonal Hematologic Non Mast cell lineage Disease (SM-AHNMD)
   - Mast cell leukaemia (MCL)
   - Aggressive systemic mastocytosis (ASM)

2. Previous treatment with any Tyrosine Kinase Inhibitor

3. 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 aetiology within 3 months
   - Uncontrolled severe hypertension, according to the judgment of the investigator, or symptomatic hypertension

4. Patient who had major surgery within 2 weeks prior to screening visit

5. Vulnerable population defined as:
   - Life expectancy < 6 months
   - Patient with < 5 years free of malignancy, except treated basal cell skin cancer or cervical carcinoma in situ
   - Patient with any severe and/or uncontrolled medical condition
   - Patient with known diagnosis of human immunodeficiency virus (HIV) infection

6. 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, or institutionalized by court decision

7. Patient with any condition that the physician judges could be detrimental to subjects participating in this study; including any clinically important deviations from normal clinical laboratory values or concurrent medical events

Previous treatment

8. Change in the symptomatic treatment of mastocytosis or administration of any new treatment of mastocytosis within 4 weeks prior to baseline

9. Treatment with any investigational agent within 4 weeks prior to baseline

5.3 Discontinuation criteria

All interruptions, reductions, or any changes in study drug administration must be entered on the case report form (CRF).
Interruptions of study treatment will be based on clinical judgment of the investigator. The investigator should record the main reason and the exact time of premature discontinuation of treatment in the case report form and single out the primary reason if more than one is involved.

The patient may discontinue treatment for one of the following reason:

- Adverse event, including clinical adverse event, clinically significant biological or physical exam abnormality. Death is to be considered as an adverse event.
- Unsatisfactory therapeutic effect
- Major protocol violation
- Withdrawal of consent
- Reason not related to treatment or trial

All patients withdrawn from the study for any reason must undergo a complete final study termination visit.

If the patient discontinues the study due to a study drug-related adverse event, he/she must be followed weekly until resolution or stabilization of the event, whichever occurs first.

Complete end of study visit data must be collected for any patient discontinuing study treatment and within 2 weeks after the last drug intake. End of study evaluations will include adverse events, concomitant medications and therapies, physical examination, vital signs, ECG, chest X-Ray, pregnancy test (serum), skin biopsy (mast cell infiltration), measurement of tryptase level, handicap assessment, quality of life, biochemistry and haematology (as per protocol). All relevant information that related to the reason for treatment discontinuation including contributory factors must be included on the CRF.

5.4 Patients identification

Patients will be identified by a numeric code including the centre number followed by a chronological inclusion number for that centre (X-Y) and depending on the country the two first letters of the last name and first name and the birth date.
6 TREATMENTS

6.1 Treatment Definitions

Investigational Medicinal Product (IMP)

The IMP is defined as “a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.” In the present study, the IMP consists of masitinib and its matching placebo. IMP can be also referred as study treatment.

Cetirizine (mandatory concomitant medication for rash prophylaxis) does not comply with this definition and thus is not considered as IMP.

Concomitant treatments:

All medications being taken by the patients at study start and all medication given in addition to the IMP during the study are regarded as concomitant medications

6.2 Investigational Medicinal Product (IMP)

6.2.1 Packaging and labelling

All medications supplied by the sponsor to be used in this study will have been manufactured, tested, and released according to current GMP guidelines.

Masitinib is supplied as 100 mg and 200 mg non-divisible capsule-shaped orange coated tablets, packaged in polyethylene bottles. Inactive ingredients are microcrystalline cellulose, povidone, crospovidone, magnesium stearate, and Opadry orange coating agent. Placebo is supplied in tablets identical to the masitinib ones, with the same composition except for active ingredient.

The tablets are packaged by 30 units, in HPED bottles closed with a childproof cork.

The IMP will be packed and labelled according to current GMP guidelines, GCP guidelines, and national legal requirements. The package given to the patient will have a tear-off part. When the IMP is provided to the patient, the investigator or pharmacist (if applicable) will remove the tear-off part of the label and attach it to the respective section of the CRFs.

6.2.2 Shipment, Storage conditions, and Accountability

The investigator or pharmacist (if applicable) will received numbered treatments. Investigator/Pharmacist is responsible for safe and proper handling and storage of the IMP at the investigational site. The IMP must be stored in a locked facility with restricted access to the investigator and authorized personnel. The investigator must ensure that the IMP is administered only to the patients enrolled in this study. The IMP has to be stored at room temperature (between 15°C/59°F and 25°C/77°F). Temperature logs should be kept updated by the investigator or the pharmacist to document adequate storage during the course of the trial.

The IMP must not be used outside the context of this study protocol. The investigator or authorized staff is obliged to document the receipt, dispensation, and return of all IMPs received during this study.

At the end of each patient's participation in the study, all remaining IMPs must be returned to the sponsor for an accurate accounting of delivered and returned IMPs.

Records on receipt, use, return, loss, or other disposition of IMPs must be maintained. The investigator or, if applicable, pharmacist must sign the receipt forms. Records on IMP delivery to the site, the inventory at the site, the use by each patient, and the return to the sponsor must be maintained by the investigator and/or a pharmacist or another appropriately trained individual at the investigational site.
These records will include dates, quantities, batch numbers, and the unique code numbers assigned to the IMP and patients. The investigators must maintain records documenting that the patients were provided with the doses specified in the protocol. Furthermore, they should reconcile all IMPs received from the sponsor. It is the responsibility of the investigator to give reasons for any discrepancies in IMP accountability. Forms will be provided to enhance drug accountability.

All remaining IMPs shall be collected and returned to the sponsor for destruction at the end of the study.

6.2.3 Patient compliance

Patients will be instructed to bring their unused IMP at each visit. Compliance will be assessed by the investigator by counting the remaining tablets returned by the patient. The compliance at each visit should neither be lower than 90% nor higher than 105%. In the case of poor compliance, the reason for the discrepancy will be documented in the case report form. The investigator will decide on a clinical basis whether or not to keep the patient in the study.

6.2.4 Randomization and blinding procedures

A randomization list will be generated for packaging and labelling by Cardinal System (Vendor).

Handicaps/scores at baseline regarding pruritus, flushes, depression and fatigue might influence the study outcome, thus they must be equally represented in the two treatment groups. Randomization procedures include a minimization process aimed at reducing any difference in the distribution of the handicaps/scores at baseline and country.

The minimization will be performed according to the following covariates: pruritus score, number of flushes per week, Hamilton rating scale for depression, Fatigue Impact Scale score and country. Number of patients with handicaps and the mean will be balanced for each of these covariates.

Subjects will be assigned to one of the 2 treatment groups:

- Group 1: masitinib 6 mg/kg/day
- Group 2: matching Placebo

Eligible patients will be randomized by means of a computerized central randomization system called IVRS (interactive voice response system). The automated system will assign the appropriate IMP for each patient. Interaction with the automated system will be initiated by AB Science. AB Science will supply the investigators with user guides for the automated system in the national language.

This study is a double-blind study. The investigator will be provided with technical options and password information to selectively break the code for an individual patient by telephone, facsimile transmission, or through electronic message transfers.

The premature breaking of the code should be confined to emergency cases in which knowledge of the administered drug is necessary for adequate treatment. Whenever possible, the sponsor should be contacted before breaking the blinded emergency code. Should any code be broken, the respective patient will be withdrawn from further participation in the study and a written explanation must be given by the investigator; the sponsor must be notified immediately.

Procedures after allocation of treatment are as follows:

- Record randomization number and package numbers on CRFs.
- Dispense IMP to patient.
- The first dose of the treatment will be taken orally under supervision of site personnel. Record date and time of treatment dose taken at the study site on CRF.
- Instruct the patient to take the IMP as indicated in the section “5.1 Treatments Administration”.
Instruct patients to store IMP at room temperature. Instruct that both used and unused HDPE bottles must be returned at the next and subsequent visits for treatment accountability.

### 6.2.5 Treatment administration

Subjects enrolled will orally receive daily doses of masitinib at the dose of 6 mg/kg/day or a placebo for 24 weeks.

The study treatments will be supplied as 100 mg and 200 mg tablets of masitinib or a matching placebo. At randomization patients will be allocated to one of the following groups:

- group 1: masitinib 6 mg/kg/day
- group 2: matching placebo

Irrespective of the treatment allocated, active or placebo, the adaptation of the total dose to the weight will follow the same procedure. The following table helps to determine the number of tablets to take at each administration and their dosage.

#### Table 15: Direct indication of the dosage to be given (in mg)

<table>
<thead>
<tr>
<th>Patient’s weight in kg</th>
<th>6 mg/kg/day</th>
<th>Morning* (mg)</th>
<th>Evening** (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤41.6</td>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 41.6</td>
<td>300</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 58.3</td>
<td>400</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 74.9</td>
<td>500</td>
<td>200</td>
<td>200+100</td>
</tr>
<tr>
<td>&gt; 91.6</td>
<td>600</td>
<td>200+100</td>
<td>200+100</td>
</tr>
</tbody>
</table>

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

Masitinib or placebo must be taken in a sitting position with a large glass of water (250 ml, or 8 oz). If vomiting occurs, no additional trial medication should be taken that day. Patients will be treated in outpatient clinic. Patients with a past history of drug allergy or anaphylactic shock should be closely monitored during the initial week of therapy.

Patients will be administered with the initial starting daily dose of masitinib 6 mg/kg/day or placebo.

At baseline visit (Day 1), patients will take the first dose of treatment orally at the study site in the morning. Patients will be instructed to take the treatment once daily (morning) or twice daily (morning/evening) if indicated, during 24 weeks. During the study, patients must maintain full compliance with respect the study drug intake.

### 6.3 Concomitant treatments

All concomitant treatments will be recorded on the patient’s CRF, including name of the drug, total daily dose, route of administration, start and stop dates, and the reason for administration.

Patients are not allowed to enter the study if they receive any prohibited concomitant medication or medication in a dosage not allowed and which cannot be discontinued or reduced.

#### 6.3.1 Allowed concomitant treatments

##### 6.3.1.1 Mandatory concomitant medication

An oral antihistamine (cetirizine 10 mg/day) must be combined systematically with the study drug for 60 days. Cetirizine will be initiated at the same time as study treatment. To avoid the possible sedative effect of anti-histamine, the treatment will be taken in the evening, at bedtime.

##### 6.3.1.2 Others concomitant treatments

- All symptomatic treatments such as: Anti-H1, Anti-H2, proton pump inhibitor, osteoclast inhibitor, cromoglycate sodium, antileukotriene, adrenaline in case of anaphylactic shocks or
other therapies used for the symptomatic care should be maintained at the same dose during the study.

- Prophylactic anti-emetics should be withheld until the patient has experienced mild nausea or vomiting.
- Prophylactic use of loperamide (e.g. Imodium®, with suggested dosing as start: 4 mg p.o. x 1 than 2 mg p.o. after each loose stool, max 16 mg/day) is recommended for patients experiencing mild or moderate diarrhoea.
- Treatment of cutaneous rash:
  - If rash involved less than 50% of skin surface, study treatment will be maintained and patient will be treated with hydroxyzine 100mg/day for 8 days. If the patient is currently treated with cetirizine (60 first days of the study treatment period), cetirizine will be stopped.
  - If rash involves more than 50% of skin surface, study treatment will be interrupted, and patient will be treated with hydroxyzine 100mg/day for 8 days combined with prednisone for 8 days (1 mg/kg for 2 days, 0.5 mg/kg for the next 2 days, then 20 mg/day for 2 days, and last 10 mg/day for 2 days). After abatement, study treatment will be resumed at the same dose level as before interruption. If the patient is currently treated with cetirizine (60 first days of the study treatment period), cetirizine will be stopped.

6.3.1.3 Prohibited concomitant treatments

- Anticancer agent
  (including chemotherapy, high dose of corticosteroids, biologic agents)
- 2CDA
- Interferon
- Live attenuated vaccines
- Any investigational treatment related or not related to mastocytosis
- Drugs known to be at high risk of Stevens-Johnson syndrome: allopurinol, lamotrigine, carbamazepine, phenytoin, phenobarbital, sulfasalazine, sulfamide, oxicam and nevirapine; or to be at high risk of DRESS syndrome: minocycline, nodafenil, dapsone.

6.3.1.4 Treatments to be given with high caution

- Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or masitinib, drugs known to interact with the same cytochrome P450 (CYP450) isoenzymes (2C9, 2D6 and 3A4) as masitinib should be used with caution. Patients using concomitant medications known to be metabolized by these CYP450 enzymes will not be excluded from the study. However, the patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication. Should an event occur please obtain a blood sample for analysis of this medication whenever feasible.
  - Acetaminophen/paracetamol
  - Any nephrotoxic drug

A non-exhaustive list is provided in appendix # 14.15

6.4 Dose adjustment/Safety Procedures

Study treatment refers to masitinib or its matching placebo.

Surveillance
Complete blood count at screening, baseline, W1, W2, W3, W4, W5, W6, W7, W8, W10, and every 4 weeks until the end of study treatment.

Hepatic work up (AST, ALT, gamma GT, total bilirubin, AP, LDH) at screening, baseline, W2, W4, W6, W8 and every 4 weeks until the end of study treatment.

BNP at baseline and ECG at baseline then every 12 weeks.

Chest X-ray (only Posterior-Anterior view) at baseline (not required if chest X-ray performed within 3 months prior to baseline) and at the end of the study checked by medical interview and clinical examination.

At baseline and at each patient visit, the physical exam of the patient must include a careful thyroid palpation.

Urinary cytology and NMP22 test at baseline and then every 12 weeks.

βHCG at screening, baseline, at the end of the study and in case of suspicion of pregnancy.

In non-menopausal women using non-hormonal contraceptive method, hormonal work-up at baseline then every 12 weeks.

Optional spermogram at baseline then every 12 weeks.

Patient card and procedures to follow by the patient during the first 2 months

All patients will receive a card mentioning the risk of severe neutropenia and the risk of severe skin toxicity with masitinib and the procedures to follow in case of signs or symptoms suggesting the occurrence of those 2 risks.

Call from site to patient once a week for the first 2 months

During the two first months of treatment, the study staff should call the patient every week to verify with the patient the weekly workups (i.e. Absolute Neutrophils Count) and to enquiry about all signs which might be due to an underlying infection and ensure the absence of skin detachment and/or ulcerations.

In case a patient experiences either a severe neutropenia or severe skin toxicity, a specific pharmacogenomic blood sample should be collected and sent to the central lab on the day of the collection. The tube to be used for Pharmacogenomic analysis must be either an EDTA tube (4 mL) or 2 PaxGene RNA/DNA tube (2x2.5 mL), provided by AB Science.

6.4.1 Neutropenia regardless of the causal relationship to study treatment:

- In case of absolute neutrophils count between 0.5 and 1x10⁹/L
  - Study treatment will be interrupted until absolute neutrophils count has returned above 1.5x10⁹/L, and then restarted at the same dose
  - If duration of neutropenia > 4 weeks, the dose of study treatment will be decreased by one step
- In case of absolute neutrophils count < 0.5x10⁹/L
  - Study treatment will be definitely discontinued
  - The investigator must inform the sponsor immediately (within 24 hours by fax using a Serious Adverse Event form) even if he/she considers the neutropenia as non-serious
  - In case of associated fever, the patient must be hospitalized in a special unit
• In case of fever, oral ulceration, sore throat or infection, a complete blood count should be performed in order to check the neutrophil count. In case of neutropenia, the above mentioned rules should be applied.
• The patient should be instructed to follow the procedures described in the patient card in case of signs or symptoms of severe neutropenia.
• In any case, all concomitant treatment potentially inducing neutropenia must be stopped

6.4.2 Renal disorders regardless of the causal relationship to study treatment

• In case of one of the 4 following events occur:
  o proteinuria ≥ 30 mg/dL on dipstick confirmed by a 24 hours proteinuria > 1.5g/24 hours
  o creatinin clearance < 50 mL/min (Cockroft and Gault formula)
  o albumin < 0.75 x LLN
  o urea > 1.5 x ULN

Study treatment will be interrupted until return to baseline, then treatment will be restarted at the same dose.
• If one of the 4 events occurs a second time, study treatment will be interrupted until adverse event has returned to baseline, and then restarted with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day).
• If one of the 4 events occurs a third time: study treatment will be permanently discontinued. In case of severe renal disorders, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day). If severe renal disorders re-occurs after dose reduction, study treatment must be definitely discontinued.
• If renal disorders are disabling or life-threatening, study treatment must be definitely discontinued.

6.4.3 Hypoalbuminemia regardless of the causal relationship to study treatment

• In case of hypoalbuminemia between 0.75 and 1 LLN, the dose of study treatment should be reduced of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day).
• In case of hypoalbuminemia lower than 0.75 LLN, study treatment must be definitely discontinued.

6.4.4 Liver disorders regardless of the causal relationship to study treatment

• In case of grade 2 liver enzymes increase; i.e. transaminases (AST or ALT or both) ≤5 ULN, and/or in case of bilirubin increase ≤3 ULN, study treatment should be maintained.
• In case of grade 3 liver enzymes increase, i.e. transaminases (AST or ALT or both) increase > 5 ULN and < 20 ULN and/or in case of bilirubin increase ≥ 3 ULN and < 10 ULN, study treatment should be interrupted until transaminases levels return to ≤ 3 ULN and bilirubin level returns ≤ 1.5 ULN. Hepatic surveillance tests will be performed every week. Then resume study treatment with a dose reduction of 1.5 mg/kg/day (new dose: 4.5 mg/kg/day).
• In case of second grade 3 liver enzymes increase, i.e. transaminases (AST or ALT or both) increase higher than 5 ULN and < 20 ULN and/or a second bilirubin increase >3 ULN and < 10 ULN occur when study treatment is resumed, study treatment must be definitely discontinued.
• In case of grade 4 transaminases increase (i.e. AST or ALT > 20 ULN and/or bilirubine> 10 ULN), study treatment must be definitely discontinued.

6.4.5 Cardiac disorders, regardless of the causal relationship to study treatment

At each visit, cardiac symptoms are carefully checked by medical interview and clinical examination.
In the event of cardiac event:

- **In the event of thoracic pain**
  - Perform an ECG: if there is any change compared to the previous ECG(s), a cardiologist should be consulted
  - Perform a dosage of troponin: if the result is higher to LLN, a cardiologist should be consulted

If an acute coronary syndrome is confirmed, study treatment should be definitely discontinued.

- **In the event of dyspnoea or signs of cardiac failure**
  - Perform a clinical examination: if there is clinical signs of cardiac failure, study treatment should be definitely discontinued and a cardiologist should be consulted
  - Perform an ECG: if there is any change compared to the previous ECG(s), a cardiologist should be consulted
  - Perform a dosage of BNP (or NT proBNP):
    - If BNP is between 100 and 400 pg/mL (NT proBNP between 400 and 2000 pg/mL) without clinical signs of cardiac failure, control the dosage one week later: if there is an increase higher than 30% when compared to baseline value, a cardiologist should be consulted and the discontinuation of study treatment should be discussed according to the benefit risk ratio for the patient
    - If BNP is higher than 400 pg/mL (NT proBNP higher than 2000 pg/mL) without clinical signs of cardiac failure, study treatment should be interrupted and a cardiologist should be consulted with an ECG and an echocardiography for the discussion of discontinuation or not of study treatment, according to the benefit/risk ratio for the patient.
  - Perform a dosage of troponin: if the result is higher to LLN, a cardiologist should be consulted
  - Perform an echocardiography:
    - If LVEF < 50%: study treatment should be definitely discontinued and a cardiologist should be consulted
    - If LVEF between 50 and 60%, without clinical signs of cardiac failure, maintain study treatment and control the LVEF two weeks later:
      - If clinical signs of cardiac failure appear: discontinue study treatment and a cardiologist should be consulted
      - If LVEF is still between 50 and 60%: control the LVEF one month later, maintain study treatment, control the LVEF every 3 months
      - If LVEF is equal or higher than 60%: maintain study treatment, control the LVEF 3month later.
      - If LVEF is lower than 50%: discontinue study treatment and a cardiologist should be consulted.

- **In the event of isolated lower limbs oedema**
  - Check clinical signs of cardiac failure
  - Perform a dosage of BNP (or NT proBNP)
  - If there is any suspicion of a cardiac origin, a cardiologist should be consulted.

- **In the event of blood pressure increased**
  - Adapt the anti-hypertensive medications
  - If high blood pressure persists, a cardiologist should be consulted and the discontinuation of study treatment should be discussed according to the benefit risk ratio for the patient.

- **In the event of other potential cardiac adverse events, like syncope without known aetiology, severe conduction disorders, persistent ventricular tachycardia, resuscitated sudden death, study treatment should be interrupted and a cardiologist should be consulted.**
In the event of severe conduction disorders, study treatment may be resumed after pacing.
In the other cases, study treatment must be definitely discontinued.

6.4.6 Reproductive system disorders and pregnancy

- If pregnancy is suspected during the study, study treatment must be immediately withheld until the result of a laboratory pregnancy test is available. Should pregnancy be confirmed, the patient must be withdrawn from study. Thereafter, the patient (and/or partner, if applicable) must be asked to participate in the AB Science pregnancy surveillance program and the baby and patient’s health will be followed at least up to 3 months after birth.
- Menstrual cycle of pre-menopausal women not using hormonal contraceptive should be recorded at each study visit. In case of irregular cycles without known cause after exploration (such as pre-menopausal or history of irregular cycles), study treatment must be definitively discontinued. In addition, FSH, LH, estradiol and progesterone level of all pre-menopausal women not using hormonal contraceptive will be assessed at baseline and every 12 weeks during the course of the study, in front of the date of last menstruations.
- A pelvic ultrasound will be performed in women of childbearing potential at baseline and final visit.
- Regarding male patients enrolled in the present study, they will be asked to perform a semen analysis (i.e. sperm count, morphology and motility analysis) at baseline, every 12 weeks and final visit. This procedure will be optional depending on the patient consent.

6.4.7 Skin toxicity regardless of the causal relationship to study treatment

In case of mucous ulceration, and/or skin detachment and/or suspicion of erythema multiforme or Stevens-Johnson syndrome, Lyell syndrome or DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) regardless of the severity of the event:

- Study medication must be interrupted and the patient must consult a dermatologist. Study treatment can be re-challenged after mandatory agreement of the dermatologist.
- The investigator must inform the sponsor immediately (within 24 hours by fax using a Serious Adverse Event form), even if he/she considers the skin toxicity as non-serious. AB Science will contact the investigator and the dermatologist in order to document the case (specific questionnaire see Appendix, photography of the lesions, cutaneous biopsy, ...)
- Should an epidermal necrolysis (erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome) be suspected, study treatment must be definitely discontinued.
- Should a DRESS syndrome be suspected, study treatment must be definitely discontinued.

In case of Grade 1 (CTC-AE classification) maculo-papular rash or desquamation:

- Study treatment will be maintained and patient will be treated with hydroxyzine 100 mg/day for 8 days.

In case of Grade 2 (CTC-AE classification) maculo-papular rash or desquamation:

- Study treatment will be interrupted, and patient will be treated with hydroxyzine 100 mg/day for 8 days combined with prednisone for 8 days (1 mg/kg for 2 days, 0.5 mg/kg for the next 2 days, then 20 mg/day for 2 days, and last 10 mg/day for 2 days). After return to baseline or grade ≤ 1, study treatment will be resumed at the same dose level as before interruption.
- In case of reoccurrence of a Grade 2 maculo-papular rash or desquamation, study treatment must be interrupted and the same symptomatic treatment should be initiated. After return to baseline or grade ≤ 1, study treatment will be resumed with a dose reduction (new dose: 4.5 mg/kg/day).
- If grade 2 maculo-papular rash or desquamation re-occurs after dose reduction, study treatment must be definitely discontinued.
In case of Grade 3 skin toxicity, except mucous ulceration, and/or skin detachment and/or suspicion of erythema multiforme or Stevens-Johnson syndrome, Lyell syndrome or DRESS, study treatment should be interrupted and a dermatologist should be consulted to confirm the diagnosis, assess the risk and define the symptomatic treatment for the patient. The dermatologist will give his/her opinion on whether patient could resume study treatment depending on skin lesions and patient safety. If the dermatologist agrees that study treatment should resume, study treatment will be resumed with a dose reduction (new dose: 4.5 mg/kg/day).

If grade 3 skin toxicity re-occurs after dose reduction, study treatment must be definitely discontinued.

In case of Grade 4 skin toxicity, study treatment must be definitely discontinued and a dermatologist should be consulted.

6.4.8 Oedema regardless of the causal relationship to study treatment

- In the event of isolated lower limbs oedema:
  - Check clinical signs of cardiac failure
  - Perform a dosage of BNP (or NT proBNP)
    - If there is any suspicion of a cardiac origin, a cardiologist should be consulted.
- In case of moderate oedema, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose.
- If moderate oedema re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (4.5 mg/kg/day).
- If moderate oedema re-occurs after dose reduction, study treatment must be definitely discontinued.
- In case of severe oedema, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
- If severe oedema re-occurs, discontinue definitely study treatment.
- In case of incapacitating or life-threatening oedema or angioedema, discontinue definitely study treatment.

6.4.9 Nausea or vomiting regardless of the causal relationship to study treatment

- In case of nausea or vomiting, anti-emetics are recommended according to the usual practice.
- In case of moderate nausea or vomiting, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose.
- If moderate nausea or vomiting re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
- If moderate nausea or vomiting re-occurs after dose reduction, study treatment must be definitely discontinued.
- In case of severe nausea or vomiting, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).
- If severe nausea or vomiting re-occurs, discontinue definitely study treatment.
- In case of incapacitating or life-threatening nausea or vomiting, discontinue definitely study treatment.

6.4.10 Diarrhoea regardless of the causal relationship to study treatment

- Diarrhoea regardless of the causal relationship to study treatment
  In case of diarrhoea, anti-diarrheal medications are recommended according to usual practice.
  In case of moderate diarrhoea, interrupt study treatment until return to baseline or mild intensity, then resume at the same dose.
If moderate diarrhoea re-occurs, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).

O If moderate diarrhoea re-occurs after dose reduction, study treatment must be definitely discontinued.

In case of severe diarrhoea, interrupt study treatment until return to baseline or mild intensity, then resume with a dose reduction (new dose: 4.5 mg/kg/day).

O In case of severe diarrhoea re-occurs, discontinue definitely study treatment

In case of incapacitating or life threatening diarrhoea, discontinue definitely study treatment.

6.4.11 Dehydration

In case of dehydration, study treatment should be interrupted and symptomatic treatment should be initiated.

6.4.12 Pulmonary disorders

In case of aggravation of pre-existing symptoms, or new pulmonary symptoms without known aetiology (cough, dyspnoea and fever), study treatment will be interrupted until results of the etiological work-up are received.

6.4.13 Ocular disorders

In case of moderate ocular disorders lasting for more than 1 week, or in case of severe ocular disorders, an ophthalmologist should be consulted to decide about patient care.

6.4.14 Carcinogenicity

Risk of bladder cancer

A carcinogenicity study in male mice has shown potential risk of bladder carcinogenicity. This risk was not evidenced in human experience. However, urinary cytology including a specific search for transitional and/or malignant cells and NMP22 test will be performed at baseline visit, every 12 weeks and at the final visit.

Risk of thyroid cancer / adenoma

At baseline and at each patient visit, the physical exam of the patient must include a careful thyroid palpation. Should a thyroid nodule be detected, an endocrinologist must be consulted for further diagnosis and treatment, if applicable.

Risk of uterine carcinoma

At baseline and every 12 weeks, a hormonal work up including progesterone, estradiol, FSH and LH must be performed in non-menopausal female patients treated with masitinib and using a non-hormonal contraceptive method.

6.4.15 Risk management plan for adverse event not described above and suspected to be related to study treatment

Please note that the previous rules apply regardless of the causal relationship to study treatment, while this rule applies only for adverse events suspected to be related to study treatment.

- Risk management plan for adverse event not described above and suspected to be related to study treatment

Please note that the previous rules apply regardless of the causal relationship to study treatment, while this rule applies only for adverse events suspected to be related to study treatment.

- At the first occurrence of moderate adverse event, study treatment will be interrupted until adverse event has returned to baseline value or mild intensity, then resumed at the same dose level.
- If the same moderate adverse event re-occurs, study treatment will be interrupted until adverse event has returned to baseline or mild intensity, then resumed with a dose reduction (4.5 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 will be interrupted until adverse event has returned to baseline level or mild intensity, then resumed with a dose reduction (4.5 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.

In case of severe adverse event suspected to be related to study treatment, an evaluation of the benefit/risk ratio by the investigator and an agreement of the Pharmacovigilance Department of the Sponsor will be necessary before resuming study treatment.

In case of serious, unexpected adverse event, the treatment will be interrupted. The treatment could only be resumed when the adverse event has returned to baseline value and after the Independent Data Monitoring Committee would have given his approval.

### 6.4.16 Dose reduction

In case of reduction, the patient will received 4.5 mg/kg/day. The daily dose and the administration of the study treatment, according to the patient’s weight, is displayed in the following table:

Table 16: Dose of study treatment to be administered according to patient’s weight, after a dose reduction to 4.5 mg/kg/day (randomization dose: 6 mg/kg/day)

<table>
<thead>
<tr>
<th>Patient’s weight in kg</th>
<th>Daily dose (mg)</th>
<th>Morning* (mg)</th>
<th>Evening** (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 41.6</td>
<td>STOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 41.6</td>
<td>58.3</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 58.3</td>
<td>77.7</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 77.7</td>
<td>99.9</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>&gt; 99.9</td>
<td>500</td>
<td>200</td>
<td>200+100</td>
</tr>
</tbody>
</table>

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

No dose escalation will be authorized for patients who have had a dose reduction for safety reasons.

Procedure in case of missed or vomited doses of study treatment tablets:
- In case the morning dose has been missed, it can be taken until 2 pm on the same day. Should it be later than 2 pm, the missed dose will not be made up and study treatment will be resumed at the evening dose on the same day.
- In case the evening dose is missed, it should not be made up the day after in addition to the morning dose. The study treatment will be resumed the day after as scheduled in the protocol.
- Should the patient vomit within 10 minutes after the last study treatment dose intake, another dose should be taken.

Should the patient vomit later than 10 minutes following the last study treatment dose intake, study treatment will be resumed at the next theoretical dose intake, but the last dose will not be replaced.
7 EVALUATION CRITERIA

7.1 Efficacy variables

Handicaps are defined as:
- Main handicaps : pruritus score ≥ 9, number of flushes per week ≥ 8, HAMD-17 score ≥ 19, Fatigue Impact Scale ≥ 75
- Other handicaps : micturitions ≥ 8, stools ≥ 4

Response on a handicap is defined as an improvement ≥ 75% for pruritus, flushes, Hamilton and fatigue.

7.1.1 Primary efficacy variable

The primary efficacy criterion is the cumulative response by patient*handicap. For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

Week 4 is not considered for the calculation of this response as:
- All patients take anti-histamines between Baseline and week 4 even if they didn’t take such treatment before study entry
- Based on phase II studies, first month of treatment is under efficient

So, from 5 to 20 responses will be calculated by patient : 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients presents the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits.

Sensitivity analysis: same 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.

7.1.2 Secondary variables

- Cumulative response on pruritus among patients with the handicap at Baseline

For the patients presenting the handicap at Baseline (ie. score ≥ 9), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Cumulative response is calculated for pruritus as it seems that pruritus is the most objective measure between pruritus, flushes, Hamilton and FIS.

Sensitivity analysis: same 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.

- OPA score

OPA score corresponds to the 53rd question of the AFIRMM questionnaire.

For the patients presenting the handicap at Baseline (i.e. OPA “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an OPA “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient
left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.

- Quality of Life (QoL) : QLQ-C30

Value at time point, absolute and relative change from Baseline for each scale (functional scales i.e. physical, role, cognitive, emotional and social; symptom scales i.e. fatigue, nausea/vomiting, pain and global scale ) and each individual items (8, 11, 13, 16, 17 and 28).

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

- AFIRMM questionnaire

For the global score, value at time point, absolute and relative change from Baseline will be given. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

For each of the 52 items, cumulative response among patients with “severe” or “intolerable” handicap at Baseline will be given. For the patients presenting the handicap at Baseline (ie. answer “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an answer “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.

- Cumulative response on micturitions among patients with the handicap at Baseline

For the patients presenting the handicap at Baseline (ie. ≥ 8), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.

- Cumulative response on stools among patients with the handicap at Baseline

For the patients presenting the handicap at Baseline (ie. ≥ 6), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Sensitivity analysis: same 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.
- Urticaria Pigmentosa (UP) evaluation

Percentage of patients with UP improvement at time point.

## 7.2 Safety parameters

### 7.2.1 Laboratory test

The central laboratory will provide the investigational sites with the appropriate material prior to study start.

The following parameters will be assessed:

**Haematology**

Haematology includes assessment of Red blood Cells, haemoglobin, total WBC count, platelet count, and a differential count including neutrophils, lymphocytes, monocytes, eosinophils, and basophils, heparin, PT and PTT and will be performed according to the Visit Schedules (see Table 7).

**Biochemistry**

Biochemistry includes urea, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), gamma GT, LDH, cholesterol, phosphorus, sodium, potassium, calcium, glucose will be performed according to the Visit Schedules (see Table 7).

**Urinary analysis**

Urinary analysis includes blood, WBC, sugar, proteinuria, pH assessed by means of commercial urine dipsticks.

The sponsor-defined alert limits for routine laboratory parameters are shown in Appendix 14.13.

All blood samples must be collected, prepared, and arranged for transport according to the instructions provided by the central laboratory.

Beside these central laboratory procedures performed at baseline, W4, W8, W12, W16, W20 and W24/final visits, the patients will have to perform locally some routine blood cell counts every week during the first two month of treatment, at week 10 and then at least every 4 weeks. In case of clinically significant abnormal values detected through routine blood cell counts, the sponsor must be provided with a copy of the laboratory’s certification, and a tabulation of the normal ranges for each parameter required. All lab reports of laboratory workups performed outside the investigational site must be forwarded immediately by fax to the investigational site.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate CRF page. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF page.

### 7.2.2 Other safety parameters

**Physical examinations/vital signs**

A physical examination including vital signs will be performed according to the Visit Schedule. Information about the physical examination and vital signs must be present in the source documentation at the study site. Significant findings present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF page. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event CRF page.
There are no case report forms to capture routine normal findings from physical examinations and vital signs assessments. The physical examination will include the modified mini-mental status and a quality of life questionnaire.

**Body weight**

Measurements of body weight will be performed according to the Visit Schedule. Except for the body weight measurements performed during visits physical examination, other body weight measurements will not be captured on CRFs nor entered into clinical database but must be present in the source documentation at the study site. In addition, patients are encouraged to report to the study investigator any body weight change of more than 5% as compared to their pre-study body weight.

**Electrocardiogram**

A 12-lead ECG has to be done in a resting position. Prior to the recording the patient should be at rest for at least 5 min. All ECG measurements should be performed with a pace of 50 mm/s. The ECG printout will be reviewed by the investigator. A signed (by the investigator) and dated copy (no originals) will be attached to the CRF.

**Chest X-ray**

A Chest X-ray (only Posterior-Anterior view) has to be performed at baseline (not required if chest X-ray performed within 3 months prior to baseline) and at final visit. Potential abnormalities will be documented in the CRF.

**Urinary cytology**

A urinary cytology including a specific search for transitional and/or malignant cells will be performed at baseline, every 12 weeks, and at final visit.

**NMP22 test**

A NMP22 test will be performed at baseline, every 12 weeks, and at final visit.

**Pelvic ultrasound**

A pelvic ultrasound will be performed in women of childbearing potential at baseline and final visit.

### 7.3 Myocardial contractibility study

As part of the international study, French patients enrolled in this study will enter a specific cardiac surveillance in order to study potential effect of masitinib on myocardial contractibility. Echocardiogram will be performed for assessing myocardial contractibility features and especially the Left Ventricular Ejection Fraction.

2D and M-mode echocardiography which provide qualitative and semi quantitative measurements of ventricular systolic function could be used. However, whenever it’s possible, three-dimensional echocardiography should be preferred. This technique has excellent correlation with radionuclide angiography for calculation of left ventricular ejection fraction in patients and has observer variability similar to that of radionuclide angiography (9).

As per study protocol, patients will have to perform at baseline and at week 24 adoppler echocardiography. This examination should be conducted in the supine position, with the same ultrasound system and preferably by the same physician. All patients should be haemodynamically stable. Tracings should be recorded during expiration. Para-sternal and apical views have to be obtained according to the recommendations of the American Society of Echocardiography. Values should be presented as means from three consecutive cardiac cycles. Left ventricular ejection fraction should be calculated according to the same integration method for the measurements (i.e. baseline and week 24 and/or end of study visit).

Besides, such data are generated from the ejection phase which is load dependent and therefore not ideal for the determination of ventricular contractility. However, the load independent state of
ventricular contractility can only be assessed by high temporal resolution techniques timed to record during the isovolumic contraction (IVC) period which normally occurs over a brief time interval (approximately 80 ms). Furthermore, wall motion during IVC shows a biphasic pattern in normal patients but this may be altered when ventricular contractility is impaired. Currently, tissue Doppler imaging (TDI) provides information regarding regional myocardial function with high spatial and temporal resolution. Vogel et al. (10) showed that myocardial acceleration during IVC was a sensitive marker of the global state of contractility and was not particularly dependent on pre- or after load. A number of other studies support this assertion (11, 12, 13).

Hence optionally depending of the same ultrasound system available peak myocardial velocities could be recorded using the pulsed Doppler tissue imaging technique with a sample volume was 6 mm. The acoustic power and filter frequencies should be adjusted.

The following echocardiogram endpoints should be measured and reported in the CRF:

- Left Ventricular Ejection Fraction at week 0, week 24 and end of study visit (primary)
- Fractional shortening (midwall mFS) at week 0, week 24 and end of study visit Systolic and diastolic left ventricular diameters
- Optionally, left ventricular contractility during Isovolumic Contraction at week 0, week 24 and end of study visit

Mean change from baseline of those three variables will be studied. Any abnormal findings should also be reported into the CRFs.

**Number of patients for ancillary study:**

Objective of the ancillary study is to demonstrate stability on the cardiac profile of the masitinib patients. LEVF will be studied as a binary criterion. The patient is classified as success if no measure of LEVF after baseline decreases more than 10% and if no major cardiac event occurred during the study.

The objective is to demonstrate that masitinib is not inferior to placebo on the LEVF. The required number of patients per treatment group is calculated using the following:

- \( H_0 \) (null hypothesis of inferiority): difference between Arm A and Arm B greater than 10%:
  \[ \Pi_{\text{masitinib}} - \Pi_{\text{placebo}} \geq 10\%; \]
- \( H_1 \) (alternative hypothesis of non-inferiority): difference between Arm A and Arm B less or equal to 10%:
  \[ \Pi_{\text{masitinib}} - \Pi_{\text{placebo}} < 10\%; \]
- Success rate: 96% of patients in each study arm;
- Maximal difference (\( \Delta \)): 10%;
- One-sided 95% Confidence Interval (CI): type I error fixed at 5%;
- Power fixed at 80%.

The total number of patients per group to be randomized in the PP is 48.

Number of patients per study arm = \( 2 \times (0.96 \times 0.004) \times (1.6449+0.8416)^2 / (0.10)^2 = 48 \)

As 5% of patients will be supposed to be excluded from the PP or prematurely withdrawn from the study, a total number of 100 patients (100 per arm) were to be included into the study.

**Statistical analyses:**

The one-sided 95% confidence interval of the difference between groups on success LEVF criteria will be considered in the PP population.

\[ \text{CI} = [\infty, (\Pi_b - \Pi_d) + z_{0.05} \times s_d] \text{ with } Z_{0.05} = 1.6445. \]
\( P_b \) is the success rate in Arm B and \( P_a \) the success rate in Arm A.

\( N_b \) is patient number in Arm B and \( N_a \) patient number in Arm A.

\[ s_d^2 = \frac{1}{n} \left( P_b(1-P_b)/N_b + P_a(1-P_a)/N_a \right) \]

is the estimated variance of the difference.

If \( CI \subset [-\infty, 10\%] \), inferiority hypothesis will be rejected in favour of the non-inferiority hypothesis with a one-tailed type I error fixed at 5%. For the main analysis, observed data values only will be considered. Description of LEVF will be provided at each time.

### 7.4 MRI ancillary study (optional):

Specific perfusion patterns measured by ASL-MRI has already suggest fundamental differences in the brain perfusion between patients suffering from cognitive troubles (Alzheimer disease, dementia,..) and cognitively healthy subjects.

Patients suffering from Mastocytosis could also suffer from cognitive disorders such as depression, memory losses, etc.

The patients enrolled in the present study protocol could, if they consent, be evaluated for brain perfusion. In such a case they will be evaluated using a MRI examination at Baseline and Week 24.

The Arterial Spin Labeling (ASL) method will be used when imaging the patient. ASL uses spatially selective inversion of inflowing arterial blood as a method to label blood flow (performed on the incoming carotid blood flow). The MRI signal from inverted blood is made negative relative to uninvverted blood. When the labeled blood reaches the brain, it attenuates the signal from the image of that tissue. Subtraction of a labeled image from a control image gives a measure of the amount of label which flowed into the tissue. This quantity is closely related to the tissue perfusion.

The Cerebral Blood Flow (CBF) mapping yields quantitative perfusion values using the ASL imaging and the « proton density » imaging acquired comcomitantly with the ASL image.

The MRI using ASL acquisition lasts 5 minutes and does not required injection of a contrast media.

Please find attached details of the imaging protocol.

**PATIENT POSITION IMAGING PARAMETERS:**
- Patient Entry Head First Imaging Mode 3D
- Patient Position Supine Pulse Sequence 3DASL
- Coil Configuration HNS Head Imaging Options EDR, Fast, Spiral, Plane AXIAL Acceleration Factor 1.00, Series Description 3D ASL (PLD=1525)
- SCAN TIMING SCAN RANGE: Receiver Bandwidth 62.50 FOV 24.0, Slice Thickness 4.0
- IMAGE ENHANCE ACQ TIMING: Filter Choice None Freq 512, Phase 8, Freq DIR A/P, NEX 3.00, Auto Shim Auto, Phase Correction No
- GATING/TRIGGER FMRI: Auto Trigger Type Off PSD Trigger Internal, Slice Order Interleaved, View Order Bottom/Up, # of Repetitions REST 0, # of Repetitions ACTIVE 0
- MULTI-PHASE SAT: # of Acquisition 0 Tag Type None, Separate Series 0, Mask Phase 0, Mask Pause 0
- DIFFUSION ASSET: Recon All Images On Slice Acceleration Factor 1.00, Phase Acceleration Factor 1.00

### 7.5 C-kit and Mast cell infiltration

**Skin / bone marrow biopsies**

**C-kit mutation:**

Both patients with either free of c-kit D816V mutation or patients bearing activation point will be eligible.

Skin biopsy is mandatory at screening visit for all patients with skin lesions. This biopsy will be used for c-kit sequencing and mast cell counting. A bone marrow aspirate or biopsy must be done for patients without cutaneous lesions.

**Centralized c-kit sequencing and mast cell counting:**
To harmonize results, a skin biopsy and a bone marrow aspirate and biopsy will be done at screening and at final visits and then sent to central laboratory (France) for sequencing and mast cell counting.

**Tryptase levels**

Serum tryptase levels will be performed according to the Visit Schedule. Blood will be collected in appropriate sampling kit then sent to central laboratory.
8 STUDY SCHEDULE AND PROCEDURES

An overview on study conduct is provided hereafter.

8.1 Screening visit

The screening phase comprises all activities of the investigator to select potential patients for a specific clinical study. The investigator may screen patients for screening criteria on a basis of (1) pre-existing data (e.g. medical charts of the sites for screening criteria, such as demographic data, indication etc) and/or (2) initial contact (routine visit, phone call) where only routine or non-study-specific questions are allowed. Patients fulfilling the screening criteria should be entered into the subject screening log.

All study-related procedures begin only after obtaining informed consent.

At this visit:
- Obtain the signed informed consent.
- Give patient card to the patient and ensure the patient understands and is able to follow the patient card procedures.
- Assess patient eligibility (Inclusion/Exclusion criteria).
- Document the demographics data including ethnicity, relevant past medical history, and current medical conditions not related to the diagnosis of mastocytosis. Ethnicity needs to be recorded to analyse potential differences in terms of adverse events frequency, especially with respect to drug related neutropenia.
- Document information related to diagnosis of mastocytosis.
- Record all previous / concomitant medications and/or non-drug therapies. Include the reason for administration.
- Record any disease related symptoms present at baseline: pruritus score, number of flushes per week, Hamilton rating scale for depression score, Fatigue Impact Scale, number of stools per day, number of micturition per day, QLQ-C30 score, Overall Patient Assessment, AFIRMM V2 score.
- Record adverse events present at screening.
- Record vital signs and weight.
- Perform physical examination.
- Perform laboratory tests: Haematology, Biochemistry.
- Perform urinalysis tests.
- Perform serum pregnancy test
- Perform a biopsy of a lesion in skin and/or bone marrow aspirate for potential c-Kit mutation detection (centralized analysis of c-Kit mutation) and a skin biopsy and/or bone marrow aspirate for mast cells infiltration.

8.2 Baseline visit

The baseline visit can occur from 1 day and up to 2 weeks after the screening visit when all results from the screening evaluation are available, and treatment is available at the study site. Each subject will undergo baseline procedures prior to treatment allocation.

At this visit:

Before drug administration
- Review inclusion/exclusion criteria.
Review concomitant medications and treatments.

- Record any disease related symptoms present at baseline: pruritus score, number of flushes per week, Hamilton rating scale for depression score, Fatigue Impact Scale, number of stools per day, number of micturition per day, QLQ-C30 score, Overall Patient Assessment, AFIRMM score.

- Record potential adverse events present at baseline.

- Perform vital signs, weight.

- Perform physical examination.

- Perform laboratory tests: Haematology, Biochemistry, NT proBNP (or BNP).

- Perform FSH, LH, Estradiol and Progesterone level assessments for pre-menopausal women not using hormonal contraceptive.

- Perform spermogram (optional procedure)

- Perform MRI (optional procedure)

- Perform tryptase level assessments.

- Assess the *Urticaria Pigmentosa* if applicable

- Perform urinalysis tests and urinary cytology including a specific search for transitional and/or malignant cells and NMP22 test

- Perform serum pregnancy test

- Perform an ECG, chest X-Ray Posterior-Anterior view (not required if chest X-ray performed within 3 months prior to baseline) and Doppler echocardiography

- Perform a pelvic ultrasound in women of childbearing potential

**Randomization** of the patient and first IMP dispensation: The first HDPE bottles of treatment will be dispensed. Procedures after allocation of treatment are as follows:

- Record patient number and treatment unit numbers on CRFs.

- Prescribe Cetirizine (during the first 60 days) and dispense study treatment to patient.

- The first dose of the treatment will be taken orally under supervision of site personnel. Record date and time of treatment dose taken at the study site on CRF.

- At hospital discharge, instruct the patient to take daily dose of treatment at approximately the same time each day. Inform that at subsequent visits up to week 24, the daily dose of treatment for the day of the visit will be taken under the supervision of site personnel.

- Instruct patients to store treatment at room temperature. Instruct that both used and unused HDPE bottles must be returned at the next and subsequent visits for treatment accountability.

- Instruct the patient that he/she will be called by the site staff every week during the first two months of treatment.

### 8.3 Week 4, Week 8, Week 12, Week 16 and Week 20 visits

At these visits:

- Record any disease related symptoms present at baseline: pruritus score, number of flushes per week, Hamilton rating scale for depression score, Fatigue impact scale, number of stools per day, number of micturitions per day, QLQ-C30 score, Overall Patient Assessment, AFIRMM score.
- Record adverse events.
- Record concomitant medication and treatment.
- Perform vital signs, weight.
- Perform physical examination.
- Perform laboratory tests according the flow chart (table 7): Haematology, Biochemistry.
- Perform urinalysis tests.
- Perform urinary cytology and NMP22 test at week 12.
- Perform ECG at week 12.
- Perform FSH, LH, Estradiol and Progesterone level assessments for pre-menopausal women not using hormonal contraceptive at week 12.
- Perform serum pregnancy test at week 12 and in case of suspected pregnancy
- Perform spermogram (optional procedure) at week 12
- Count tablets on returned HDPE bottles. Record the start and stop of treatment taken between visits. Any deviation from the treatment administration schedule and discrepancies identified must be recorded in source documents and on the appropriate CRF.
- Determine whether dose adjustment is necessary.
- Dispense next treatment unit of treatment.

### 8.4 Week 9 call

At week 9 the site will call the patient and ask questions to detect any signs which might be due to an underlying infection and ensure the absence of skin detachment and/or ulceration.

### 8.5 Week 24 visit

At this visit:
- Record any disease related symptoms present at baseline: pruritus score, number of flushes per week, Hamilton rating scale for depression score, Fatigue impact scale, number of stools per day, number of micturition per day, QLQ-C30 score, Overall Patient Assessment, AFIRMM score.
- Record adverse events.
- Record concomitant medication and treatment.
- Perform vital signs, weight.
- Perform physical examination.
- Perform laboratory tests: haematology, biochemistry.
- Perform FSH, LH, Estradiol and Progesterone level assessments for pre-menopausal women not using hormonal contraceptive.
- Perform spermogram (optional procedure)
- Perform MRI (optional procedure)
- Perform ECG and Doppler echocardiography
- Tryptase level assessments.
- Perform urinalysis tests and urinary cytology including a specific search for transitional and/or malignant cells and NMP22 test
- Assess the Urticaria Pigmentosa if applicable
- For organ mast cell infiltration evaluation, perform a biopsy of the skin and/or bone marrow biopsy.
- Count tablets on returned HDPE bottles. Record the start and stop of treatment taken between visits. Any deviation from the treatment administration schedule and discrepancies identified must be recorded in source documents and on the appropriate CRF.

For patients entering in the extension phase:
- Determine whether dose adjustment is necessary.
- Dispense next treatment unit of treatment for 12 weeks.

8.6 Extension visits

In case administration of study drug results in a significant improvement for a patient, and if required by the investigator, an extension of treatment will be proposed.

To enter the extension period of the protocol, the patient must fulfil the following criteria:
- to have completed the 24 weeks of treatment
- to present none of the exclusion criteria defined in the protocol
- for whom the treatment was beneficial, in the opinion of the investigator
- to be willing to enter the extension period
- men and women of child bearing potential must agree to use effective medically accepted contraception during the extension period and for 3 months following their participation in the study

The patient will continue with the same dosage of masitinib as received at Week 24. The treatment will be provided for a maximum treatment exposure of 2 years. After 2 years, patients will be allowed to continue the treatment on a case by case basis only if a documented favourable benefit/risk ratio is established by the investigator. In this case, an additional informed consent form will have to be signed by the patient to remind him about potential long term risks.

Assessments will be performed every 12 weeks (complete blood cell counts every 4 weeks/ECG every 12 weeks). The assessments performed are the same as for W4/W8/W12/W14/W20 visits. Additionally, ECG, urinary cytology, NMP22 test, spermogram (optional), FSH, LH, Estradiol and Progesterone level assessments will be performed every 12 weeks.

8.7 Final visit

Patients with adverse events or clinically significant abnormal laboratory test results at the final visit will be followed up by telephone calls, site visit, and/or additional evaluation until stabilization or resolution. Data obtained must be recorded on the appropriate form of the CRF.

Starting from one month after treatment discontinuation (for any reason)/end of the study, mastocytosis symptoms rebound evaluation assessment should be performed by telephone call or during site visit. Data obtained must be recorded on the appropriate form of the CRF. Treatments taken after the study discontinuation will be also recorded in the CRF.

If the final visit is performed at W24, the assessments already performed will not be repeated.

At this visit:
- Record any disease related symptoms present at baseline: pruritus score, number of flushes per week, Hamilton rating scale for depression score, Fatigue Impact Scale, number of stools per day, number of micturition per day, QLQ-C30 score, Overall Patient Assessment, AFIRMM score.
- Record adverse events.
- Record concomitant medication and treatment.
- Perform vital signs, weight.
- Perform physical examination.
- Perform laboratory tests: Haematology, Biochemistry.
- Perform serum pregnancy test.
- Perform tryptase level assessments.
- Perform FSH, LH, Estradiol and Progesterone level assessments for pre-menopausal women not using hormonal contraceptive
- Perform spermogram (optional procedure)
- Perform urinalysis tests, urinary cytology including a specific search for transitional and/or malignant cells, and NMP22 test
- Assess the Urticaria Pigmentosa if applicable
- Serum pregnancy test in females of child-bearing potential
- Perform an ECG and Doppler echocardiography
- Perform a pelvic ultrasound in women of childbearing potential
- Perform a chest X-ray
- Biopsy of a lesion in skin and/or bone marrow aspirate for mast cell infiltration.
- Count tablets on returned HDPE bottles. Record the start and stop of treatment taken between visits. Any deviation from the treatment administration schedule and discrepancies identified must be recorded in source documents and on the appropriate CRF.
9 STATISTICAL METHODS

9.1 Determination of sample size

Primary analysis:
A total of 142 patients (71 in masitinib group and 71 in placebo group) presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 will provide a 80% power with a two-sided 5% alpha in order to compare masitinib to placebo as primary analysis (GEE model for the cumulative response by patient*handicap : 4 handicaps / 5 visits), under the following hypotheses:

- Same response rate for all the 4 handicaps all along the study ie. 8.5% for placebo vs. 21% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 42.6% for the first study, 23.7% for the second and 30.6% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (24%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.

- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)

- 1:1 design ratio


Taking into account a percentage of non-evaluable patients around 5%, 150 patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 (75 in masitinib group and 75 in placebo group) will be randomized in the study.

Secondary analysis:
This sample size is sufficient to ensure a power ≥ 80% with an overall two-sided 5% alpha for the cumulative response on pruritus among patients with the handicap at Baseline.

- GEE model : 5 visits

- Same response rate all along the study ie. 6% for placebo vs. 24% for masitinib. Hypothesis for masitinib are based on the cumulative response observed on the phases II: respectively 25.0% for the first study, 38.5% for the second and 35.8% when pooling the 2 studies. Hypothesis has been adjusted taking into account the worst cumulative response observed between the 2 phases (25%) and the fact that phases 3 tend generally to generate slightly lower results than phases 2.

- Same correlation between any 2 measurements within a subject equals to 0.5 (exchangeable matrix)

- 1:1 design ratio

- With these hypotheses, 86 patients with handicap on pruritus at Baseline are needed. We expected that patients with handicap on pruritus at baseline will represent 65% of the patients included. Therefore, 132 patients are needed for this criterion.

9.2 Patients classification and analysis datasets

Protocols v5.0 and v6.0 changed handicaps definition from mild to moderate to severe. Additionally protocol v6.0 restricted the inclusion of patients with documented Smouldering or Indolent Systemic mastocytosis. With previous versions of the protocol, patients with cutaneous mastocytosis could be included. Protocol v6.0 restricted the inclusion to documented Smouldering or Indolent Systemic
mastocytosis as there was no or limited cutaneous mastocytosis in the 2 phase 2 studies and in an effort to improve the benefit/risk balance.

Thus, the objective of the study is to compare the safety and efficacy of masitinib to placebo in patients with documented Smouldering or Indolent Systemic mastocytosis with severe handicap. Therefore patients including before protocol v6.0 and presenting a cutaneous mastocytosis, a non-documented Smouldering or Indolent Systemic mastocytosis or a documented Smouldering or Indolent Systemic mastocytosis with non-severe handicap will be supportive. Efficacy and safety analysis of these patients will be exploratory and will consist in the presentation of individual listing.

- Intention-To-Treat (ITT) dataset

The ITT population will be defined as all patients randomized presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0. Patients will be classified according to the treatment arm to which they have been randomized, irrespective of the actual treatment received. The documented lack of taking at least one dose of the study drug after randomization and patients with no efficacy measure after randomization will be discussed.

- Modified Intent-To-Treat (mITT) dataset

The mITT dataset will include all ITT patients but patients withdrawing prematurely from the study for a well-documented non-treatment-related cause will be excluded. Among these causes, we could list withdrawal of consent for other reason than lack of efficacy or toxicity related to treatment, death for reason not related to treatment or no treatment intake.

- Per Protocol (PP) dataset

The PP data set consists of all patients of the mITT data set without any major protocol deviation. This is the set of patients who participated in the study as intended. Patients terminating the study prematurely will be included in the PP data set provided that there is no protocol deviation. Before locking the data base, the precise reasons for excluding patients from the PP data set will be fully defined and documented by the Data Review Committee.

Protocol deviations will be defined as:

- inclusion and non-inclusion criteria were not met
- intake of forbidden medication
- non-respect of visit dates
- missing value for main criterion without premature termination
- non-respect of protocol design
- any other deviations during the course of the study

Data Review Committee will classify as “minor” or “major” all the deviations of the study. This classification should be done prior to the unblinding the data.

- Safety population

The safety population consists of all patients presenting a documented Smouldering or Indolent Systemic mastocytosis with severe handicap as defined by protocol v6.0 who took at least one dose of study medication (masitinib or placebo).

9.3 Statistical analysis

9.3.1 General Considerations

The statistical analysis will be performed under the supervision of AB Science biostatistician. A statistical analysis plan will be written before database lock.

The type I (α) error will be 5% (two-sided) for efficacy (results will be presented with a two-sided 95% CI for the 2 analyses) and 5% (two-sided) for safety or quality of life.

Quantitative endpoints will be presented by treatment group and overall in terms of mean, standard-deviation, median, extreme values, quartiles and number of missing data.
Qualitative endpoints will be presented by treatment group and overall in terms of number and percentage for each modality. The number of missing data will be also given.

The primary data set to be analysed for efficacy in this difference study will be the mITT data set. Efficacy analyses will also be carried out on the Intent-To-Treat (ITT) and the per-protocol (PP) data set. Prematurely withdrawn patients will not be replaced.

For response criteria, if data are not available for assessment at week 24 because a patient left the study prematurely or had no measurement at the week 24 visit, missing data will be considered as failure (missing = failure as primary analysis). Sensitivity analysis with Last Observation Carried Forward (LOCF) and Observed Cases (data remain missing) will be provided as secondary analysis. For other criteria, all analysis will be provided (missing=failure, Observed Cases and LOCF).

Analysis of the patients including before protocol v6.0 and presenting a cutaneous mastocytosis, a non-documented Smouldering or Indolent Systemic mastocytosis or a documented Smouldering or Indolent Systemic mastocytosis will consist in the presentation of individual listings.

All data analyses and reporting procedures will use SAS v9.1 in a Windows XP operating system environment.

9.3.2 Analyses of Demographics and Data Characteristics

The initial description of the ITT, mITT and PP populations will be done per treatment group and for the total population for the following characteristics:

- Demographics (age, sex, country, ethnicity, reproductive status)
- Medical history
- Mastocytosis history, previous treatments and handicaps at baseline: pruritus score, number of flushes per week, Hamilton rating scale for depression score, FIS score, number of micturition per day, number of stools per day, OPA score, AFIRM M V2 score, mast cell infiltration, tryptase level
- Physical examination
- Vital signs
- ECG
- Quality of life assessment : QLQ-C30
- Haematology and blood biochemistry
- Concomitant treatments

Quantitative end-points normally distributed will be compared using the Student t-test with the Satterwhaite correction in case of unequal variance. The distribution of quantitative end-points will be analysed using the Shapiro-Wilk test.

Quantitative end-points non-normally distributed and ordinal end-points of 5 or more modalities will be compared using the Wilcoxon non-parametric exact test of ranks.

Ordinal end-points of less than 5 modalities will be compared using the Cochran-Mantel-Haenzel test.

Qualitative end-points will be compared using the Chi-square test or the Fisher Exact test if the hypotheses of the Chi-square test are not fulfilled.

If an important unbalance appears between the treatment groups at baseline, the choice of an adjustment variable, which was initially not planned, will be discussed according to its clinical relevance.

9.3.3 Extent of Exposure

Extent of exposure and compliance analyses will be performed on the ITT, mITT and PP populations.

Treatment duration is defined for each treatment group (placebo and masitinib) as the time from treatment onset to treatment end.

The following data will be described:
- Dosage of placebo and masitinib
- Dose intensity of placebo and masitinib (%). Dose intensity is defined as the ratio of dose of treatment received / theoretical dose * 100 at each visit and for each drug. Dose intensity will take into account the delay between two treatment discontinuations. Dose intensity will be compared between groups using the Student’s t-test or using Wilcoxon non-parametric exact test of ranks. The distribution of the dose intensity will be analysed using the Shapiro-Wilk test.
- Number and percentage of patients with a dosage modification and reason these modifications. This percentage will be compared between groups using the Chi-square test or the Fisher’s exact test if the hypotheses of the Chi-square test are not fulfilled.
- Number and percentage of patients with premature discontinuation of placebo and masitinib and reason for discontinuation. This percentage will be compared between groups using the Chi-square test or the Fisher Exact test if the hypotheses of the Chi-square test are not fulfilled.

9.3.4 Analysis of efficacy

All efficacy analyses will be performed on the mITT population and will be repeated on the ITT and PP populations.

For all efficacy analyses detailed below, handicaps are defined as:
- Main handicaps : pruritus score ≥ 9, number of flushes per week ≥ 8, HAMD-17 score ≥ 19, Fatigue Impact Scale ≥ 75
- Other handicaps : micturitions ≥ 8, stools ≥ 4

Response on a handicap is defined as: an improvement ≥ 75% for pruritus, flushes, Hamilton and fatigue.

9.3.4.1 Primary analysis

The primary analysis will be done on the mITT population. It is based on the cumulative response by patient*handicap:
- For all the patients, the response at each study visit (5 visits from week 8 to week 24) will be calculated on each handicap present at Baseline (among pruritus, flushes, Hamilton and FIS) as defined above
- So, from 5 to 20 responses will be calculated by patient : 5 if the patients presents only 1 handicap at Baseline corresponding to the 5 visits and 20 if the patients presents the 4 handicaps at Baseline corresponding to the 4 handicaps * the 5 visits

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

Difference between treatment groups (masitinib versus placebo) will be tested using a Generalized Estimating Equations (GEE) model using Logit as link function. This statistical model will include all the responses (yes/no) on handicaps observed from week 4 to week 24: so from 5 to 20 responses by patient (as described above). Beside the treatment, the following factors and covariables will be included in the model: handicap, visit and corresponding interactions. We will conclude in a difference between masitinib and placebo if the p-value associated to treatment is ≤ 5%.

Sensitivity analysis will be provided with Last Observation Carried Forward (LOCF) and Observed Cases (data remain missing) instead of missing=failure. Sensitivity analyses will also be provided on ITT and PP populations.
9.3.4.2 Secondary analysis

- Cumulative response on pruritus among patients with the handicap at Baseline

Cumulative response is calculated for pruritus as pruritus is considered as the most objective and representative measure in mastocytosis benefiting from a validated measure.

For the patients presenting the handicap at Baseline (i.e. score $\geq 9$), the response at each study visit (5 visits from week 8 to week 24) will be calculated as defined above. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Cumulative response is calculated for pruritus as it seems that pruritus is the most objective measure between pruritus, flushes, Hamilton and FIS.

Same analysis as for primary criteria will be done (i.e.GEE model using Logit as link function).

Sensitivity analysis: same 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.

9.3.4.3 Exploratory analyses

- OPA score

OPA score corresponds to the 53rd question of the AFIRMM questionnaire.

For the patients presenting the handicap at Baseline (i.e. OPA “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an OPA “normal” or “light” at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Same analysis as for primary criteria will be done (i.e.GEE model using Logit as link function).

Sensitivity analysis: same 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.

- Quality of Life (QoL) : QLQ-C30

Value at time point, absolute and relative change from Baseline for each scale (functional scales i.e. physical, role, cognitive, emotional and social; symptom scales i.e. fatigue, nausea/vomiting, pain and global scale ) and each individual items (8, 11, 13, 16, 17 and 28).

Difference between treatment groups will be tested with a repeated measurements analysis of covariance (GEE using Identity as link function) model.

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.

- AFIRMM questionnaire

For the global score, value at time point, absolute and relative change from Baseline will be given. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be replaced according to the Last Observation Carried Forward (LOCF) method.
Difference between treatment groups will be tested with a repeated measurements analysis of covariance (GEE using Identity as link function) model.

For each of the 52 items, cumulative response among patients with “severe” or “intolerable” handicap at Baseline will be given. For the patients presenting the handicap at Baseline (i.e. answer “severe” or “intolerable”), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an answer “normal” or “light” at the visit.

If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Same analysis as for primary criteria will be done (i.e.GEE model using Logit as link function).

*Sensitivity analysis: same 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.*

- Cumulative response on micturitions among patients with the handicap at Baseline

For the patients presenting the handicap at Baseline (i.e. ≥ 8), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Same analysis as for primary criteria will be done (i.e.GEE model using Logit as link function).

*Sensitivity analysis: same 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.*

- Cumulative response on stools among patients with the handicap at Baseline

For the patients presenting the handicap at Baseline (i.e. ≥ 6), the response at each study visit (5 visits from week 8 to week 24) will be calculated. Response being defined as an improvement ≥ 75% at the visit. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis). So, 5 responses will be calculated by patient.

Same analysis as for primary criteria will be done (i.e.GEE model using Logit as link function).

*Sensitivity analysis: same 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.*

- Urticaria Pigmentosa (UP) evaluation

Percentage of patients with UP improvement at time point. At each time point percentages between treatment groups will be compared using a Chi-square test.

- Mastocytosis symptoms rebound evaluation

Percentage of patients who experiencing a rebound effect on at least one symptom after discontinuation. Mean number of symptoms showing a rebound per discontinued patients. Percentage of patients who experiencing a rebound effect per symptom. Mean time of the occurrence of the rebound effect. Symptom severity will be described. Patient overall wellbeing from treatment period will be also described.
9.3.5 Safety

Analysis of safety will be performed on the safety data set, by treatment group.

9.3.5.1 Adverse Events

Summary of adverse events

Number and percentage of patients with at least one adverse event will be presented by treatment group. Same analysis will be provided for:

- Serious adverse events (All SAEs, non-fatal SAEs, deaths)
- Severe adverse events
- Adverse events leading to permanent discontinuation
- Severe adverse events leading to permanent discontinuation
- Adverse events leading to dose reduction

This summary of adverse events will be repeated for related adverse events.

Description of adverse events

Adverse events will be coded using MedDRA.

Number and percentage of patients with at least one adverse event will be presented by System Organ Class and Preferred term, per treatment group. An analysis per dose of occurrence and intensity will be done.

Analysis will be presented for all adverse events and for:

- Serious adverse events (All SAEs, non-fatal SAEs, deaths)
- Severe adverse events
- Adverse events leading to permanent discontinuation
- Severe adverse events leading to permanent discontinuation
- Adverse events leading to dose reduction
- Any adverse events of interest

This analysis of adverse events will be repeated for related adverse events. Percentages will be compared between groups using the Chi-square test or the Fisher’s exact test if the hypotheses of the Chi-square test are not fulfilled.

9.3.5.2 Concomitant treatments

Concomitant medications will be presented by treatment groups and according to ATC (Anatomical Therapeutic Chemical) classification system.

9.3.5.3 Clinical Laboratory Evaluations

For each parameter, the following analyses will be performed:

- Absolute change between baseline and last observation available
- Shift table (number, %) of worst grade during the study according to grade at Baseline

9.3.5.4 Physical Examinations/Vital Signs

For each parameter, the following analyses will be performed:

- Absolute change between baseline and last observation available
- Shift table (number, %) of worst grade during the study according to grade at Baseline

9.3.5.5 Other Safety Analyses

Abnormal findings regarding chest X-ray and ECG occurring during the trial will be reviewed and presented in the Clinical Study Report. Special attention will be paid to cardiac safety.
### 9.4 Interim analysis

No interim analysis is planned for this study. The IDMC will review primary criterion by treatment group twice during the study. The IDMC will recommend the discontinuation of the study due to lack of efficacy: lack of efficacy being defined as a conditional power < 10%. If needed, the sample size might be revisited further to IDMC analysis.

### 9.5 Subgroup analyses

Efficacy subgroup analysis will be performed on patients bearing c-kit mutation (especially D816V mutation) and patients for whom the detection of kit816 is negative or unknown in the organ biopsied. Potential chimeric patients (D816V in one tissue and WT/unknown in a second one) will be considered as patient bearing c-kit mutation.

Tests based on this covariate will be considered exploratory as it is a stratification by non-minimization covariate.

### 9.6 Control of overall family-wise type I error rate

To guard against spurious inflation of the Type I error rate, if primary analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

| Primary analysis | Cumulative response by patient*handicap on mITT population. If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

If this analysis is conclusive at a 5% level, secondary analysis will be conducted at a 5% level to control a family-wise error rate of 5%.

**Sensitivity analysis:**
- same 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
- same analysis on ITT and PP populations instead of mITT |

| Secondary analysis | Cumulative response on pruritus among patients with the handicap at Baseline (i.e. score $\geq 9$). If data are not available for assessment at a visit because a patient left the study prematurely or had no measurement at the visit, missing data will be considered as failure (missing = failure as primary analysis).

If this analysis is conclusive at a 5% level, analyses of efficacy will be continued with exploratory analyses.

**Sensitivity analysis:**
- same 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
- same analysis on ITT and PP populations instead of mITT |

| Exploratory analyses | Analyses on OPA, QLQ, AFIRMM, micturitions, stools, Urticaria Pigmentosa and mastocystosis symptoms rebound effect.

These analyses are exploratory. |
9.7 Independent Data monitoring committee

An Independent Data monitoring committee (IDMC) with expertise and experience in the diagnosis and management of mastocytosis, and without direct involvement in the conduct of the study will be set up specifically to monitor safety data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. All adverse events occurring during the trial will be forwarded to this Committee.

The Committee recommends a closer follow-up on the events occurring during the study with an evaluation of the data quarterly independently from the sponsor and reserves the possibility of alerting the Scientific Committee of AB Science in the event of observation of highly unexpected events compared to the initial assumptions in early term of lack of efficacy, limiting toxicity or early efficacy. In case of alert:

- AB SCIENCE should consider discussing an action with Competent Authority(ies) (EMA, FDA) in advance.
- If this alert concerns early efficacy, Head of Biometry should develop appropriate stopping rules and adjustment of type I error before examining the data.

The IDMC will review efficacy criteria by treatment group twice during the study. The IDMC will recommend the discontinuation of the study due to lack of efficacy; lack of efficacy being defined as a conditional power < 10%. If needed the sample size might be revisited further to IDMC analysis.

9.8 Data collection and Trial monitoring

Data collection

The Investigator/coordinator at each side must enter the information required by the protocol onto the CRF provided by AB Science. These will be forwarded to the sponsor, AB Science. All additions to the CRF during the study and SAE forms must be forwarded to the sponsor. Details on response need to be accurately documented in the patient's hospital records.

Trial monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, an AB Science representative will review the protocol and case report forms (CRFs) with the investigators and their staff.

A Clinical Research Associate (CRA) will be appointed by the sponsor to monitor this study and periodically contact the site, including conducting on site visits.

Monitoring visits to the investigational site will be made regularly to ensure that all aspects of the protocol, GCP, as well as national and local requirements are followed.

Source documents will be reviewed for verification of consistency with data on case report forms. The investigator guarantees direct access to source documents by the sponsor. Source data verification is performed in accordance with data protection regulations and guidelines and all information reviewed will be kept confidential.

The investigator is responsible for completing the CRFs within 5 days of the patient’s visit and the AB Science monitor is responsible for reviewing them and clarifying and resolving any data queries. The completed and corrected CRFs for completed visits will be collected by the AB Science monitor initially, and may then be either collected or sent for data processing, as arranged by the AB Science monitor. A copy of the CRFs is retained by the investigator, who must ensure that it is stored with other study documents, such as the protocol, the investigators brochure and any protocol amendments, in a secure place.
10 DATA MANAGEMENT

Data from the CRFs are entered into the study database using EDC (Electronic Data Capture). Subsequently, the information entered into the database is systematically checked:

- On line with automatic checks
- Off line by Data Management staff

using error messages from validation programs or database listings.

Error message will be entered on Data Clarification Forms and entered into the database by the investigator using EDC. Investigator will sign the final CRF with electronic signature. This process follows until the lock of the data-base. Quality control audits of all key safety and efficacy data in the database will be made by the data-manager before locking the data-base.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events will be coded using MedDRA.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Head of Clinical Operations and Head of Biometry.
11 ETHICS

11.1 General requirements

The study will be performed according to this study protocol, the Declaration of Helsinki, the guidelines of ICH GCP and the respective national legal requirements. Special emphasis will be placed on data protection. As this clinical study will be carried out both in the US and in Europe the study will be conducted according to the EU directive on data protection (95/46/EC) as well as the US code of Federal Regulations.

The sponsor is obliged to obtain evidence of the investigator's qualification to perform the clinical study. Therefore, the investigator has to provide a dated and signed copy of his professional curriculum vitae (no older than 2 years and preferably one page in English) prior to the start of the clinical study, including information about his experience in conducting clinical studies according to the guidelines for GCP.

11.2 Data safety monitoring board

A Data Safety Monitoring Board, an independent committee, will be set up specifically to monitor safety data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. All serious adverse events occurring during the trial will be forwarded upon receipt to the DSMB.

11.3 Independent ethics committee (IEC) or institutional review board (IRB)

Prior to the start of the study, the sponsor or investigator will submit the study protocol, patient information, informed consent(s) and other study-related documents as required by local regulations to the respective regulatory authorities and the responsible IEC/IRB for written approval.

The sponsor or investigator will inform the IEC/IRB and regulatory authorities according to local regulations about protocol amendments including any new information that require an ethical reconsideration of the study protocol.

In addition to the written approval of the IEC/IRB the sponsor or investigator should obtain a statement from the IEC/IRB that the institution is composed and organized according to and adheres to GCP and applicable regulations.

As required by local regulation, by the IEC/IRB, or regulatory authorities the sponsor or investigator will also submit the financial arrangements for the study or other financial interests of the investigator in the IMP or sponsor company to the IEC/IRB and regulatory authorities.

Furthermore, if required by local regulation the sponsor or investigator will submit a summary of the clinical study results to the IEC/IRB.

Unless otherwise instructed by the IEC/IRB or local regulation, the sponsor or the investigator must submit to the IRB/IEC:

- information on adverse events that are serious AND unexpected AND associated with the IMP from the investigator’s site, as soon as possible;
- expedited safety reports from the sponsor, as soon as possible;
- periodic reports on the progress of the study.

The study will be conducted under an Investigational New Drug application

11.4 Subject information and consent

The following applies for both eligibility informed consent and informed consent:

Patients will be informed both verbally and in writing about the objectives of the study, the methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. All items
must be explained by the investigator in a language and in terms that are easy to understand for the patient. Patients will also be informed that the participation is voluntary and that they have the right to withdraw from study participation at any time without giving the reasons and without any disadvantages for their subsequent care. They will confirm their consent in writing prior to study start and any study-related procedure.

The patients must be given enough time to decide on their participation in the study. The informed consent must be personally dated and signed by both the patient and investigator. Patients must be provided with a copy of the patient information and the signed informed consent.

The patient is not obliged to give reason(s) for withdrawing prematurely from the study. However, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the patient's rights. In case of any changes in the written patient information or informed consent the investigator ensures that all patients still participating in the study receive the updated patient information in a timely manner and are asked for written consent to the changes.
12 ADMINISTRATIVE PROCEDURES

12.1 Changes to Protocol (protocol amendment)

The study will strictly follow this protocol. Changes will be appended to the study protocol as amendments. Amendments have to be submitted to the involved IECs/IRBs and to the regulatory authorities by the sponsor or investigator or according to international and local requirements. If an IEC/IRB demands modifications to the study protocol, the patient information, and/or the informed consent form already approved by other IECs/IRBs, the sponsor will decide case by case whether these changes shall be adopted for the respective investigational site only or for all sites.

12.2 Recording of data/retention of documents

Data on patients collected on CRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, both AB Science and the investigator are bound to keep this information confidential.

All the information required by the protocol should be provided and any omissions require explanation. All CRFs must be completed and available for collection no more than 5 days after the patient’s visit, so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the investigator and transmit the data to AB Science.

All entries to the CRFs must be made clearly in black ballpoint pen, to ensure the legibility of self-copying or photocopied pages. Corrections are made by placing a single horizontal line through the incorrect entry, so that it can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the investigator’s research team authorized to make CRF entries. Correction fluid must not be used.

The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents, which are generally maintained in the patient's file. The source documents should contain all demographic and medical information, including laboratory data, electrocardiograms, etc, also a copy of the signed informed consent form, which should indicate the study number and title of the trial.

The investigator, as listed below, must retain essential documents, as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). AB Science will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- IRB/IEC approvals for the study protocol and all amendments
- all source documents and laboratory records
- CRF copies
- patients’ informed consent forms
- any other pertinent study document.

12.3 Auditing Procedures

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance Unit exists within AB Science. This unit conducts audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of Good Clinical Practice.

A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the investigator must inform AB Science...
immediately that this request has been made. The investigator must provide direct access to source documents.

12.4 Publication of results

Any formal presentation or publication of data collected from this trial will be considered as a joint publication by the investigator(s) and the appropriate personnel of AB Science. For this multicentre study, it is mandatory that the first publication is based on data from all centres, analyzed as stipulated in the protocol by AB Science statisticians, and not by the investigators themselves. Investigators agree not to present data gathered from one centre or a small group of centres before the full, initial publication, unless formally agreed to by all other investigators and AB Science.

AB Science must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). AB Science will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and to provide any relevant supplementary information. Authorship of communications arising from pooled data will include members of each of the contributing centers as well as AB Science personnel.

12.5 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by AB Science in strict confidence and to request similar confidentiality from his/her staff and the IRB/EC. Study documents provided by AB Science (protocols, investigators’ brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by AB Science to the investigator may not be disclosed to others without direct written authorization from AB Science, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

12.6 Financial Disclosure

According to 21 CFR Part 54, the sponsor will obtain a financial disclosure from the investigator(s) and sub-investigators to whom the investigator delegates significant study-related responsibilities (i.e. individuals listed in Form FDA 1572).

12.7 Discontinuation of study

The sponsor reserves the right to discontinue the study for safety, ethical or administrative reasons. All investigators will be notified in writing, outlining the reasons for the discontinuation of the study or their site. Instructions will be provided if assessments beyond the regular per protocol procedures should be necessary.

If a study is prematurely terminated, the sponsor will promptly inform IEC/IRB and competent authorities of the termination and its reason(s).
13 REFERENCES

2- Valent, Leukemia research 2003
3- Longley et al., PNAS 1999
4- Heinrich et al., Blood 1999
5- Ma et al., JID 2000
6- Zermati et al., Oncogene 2001
7- Pardanani et al., Lancet 2003
8- Drogendijk et al., Cancer 2006
9- Nosir YF and al. Accurate measurement of left ventricular ejection fraction by three-dimensional echocardiography. A comparison with radionuclide angiography. Circulation. 1996 Aug 1;94(3):460-6
14 APPENDICES

14.1 Signed agreement to the protocol

I have read this protocol and agree to conduct the trial in accordance with all stipulations and in accordance with the Good Clinical Practice and the Declaration of Helsinki.

Study code: AB06006

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Date and signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Alain MOUSSY</td>
<td>C.E.O.</td>
<td></td>
</tr>
<tr>
<td>Pr. Olivier HERMINE</td>
<td>Medical expert</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Project Manager</td>
<td></td>
</tr>
<tr>
<td>Nereida LLOrente</td>
<td>Drug Safety Officer</td>
<td></td>
</tr>
<tr>
<td>Pr. Olivier LORTHOLARY</td>
<td>Coordinating Investigator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Investigator</td>
<td></td>
</tr>
</tbody>
</table>
### 14.2 Pruritus score

The presence of pruritus is to be assessed by means of a questionnaire and scored as follows:

<table>
<thead>
<tr>
<th>ITEM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of pruritus:</strong></td>
<td>pruritus is present</td>
</tr>
<tr>
<td></td>
<td>Everyday</td>
</tr>
<tr>
<td></td>
<td>every second day</td>
</tr>
<tr>
<td></td>
<td>Sporadically</td>
</tr>
<tr>
<td><strong>Intensity of pruritus:</strong></td>
<td>disabling</td>
</tr>
<tr>
<td></td>
<td>significant</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
</tr>
<tr>
<td></td>
<td>mild</td>
</tr>
<tr>
<td><strong>Localization:</strong></td>
<td>head</td>
</tr>
<tr>
<td></td>
<td>back</td>
</tr>
<tr>
<td></td>
<td>anterior surface of the trunk</td>
</tr>
<tr>
<td></td>
<td>one hand</td>
</tr>
<tr>
<td></td>
<td>both hands</td>
</tr>
<tr>
<td></td>
<td>one leg</td>
</tr>
<tr>
<td></td>
<td>both legs</td>
</tr>
<tr>
<td><strong>Influence on well-being:</strong></td>
<td>enormous</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
</tr>
<tr>
<td></td>
<td>little</td>
</tr>
</tbody>
</table>
# 14.3 QLQ-C30 score

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: 

Your birthdate (Day, Month, Year): 

Today’s date (Day, Month, Year): 

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.</td>
<td>Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4.</td>
<td>Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5.</td>
<td>Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**During the past week:**

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7.</td>
<td>Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8.</td>
<td>Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9.</td>
<td>Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10.</td>
<td>Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11.</td>
<td>Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12.</td>
<td>Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13.</td>
<td>Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14.</td>
<td>Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15.</td>
<td>Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16.</td>
<td>Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Please go on to the next page
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

| 1 Very poor | 2 | 3 | 4 | 5 | 6 | 7 Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 Very poor | 2 | 3 | 4 | 5 | 6 | 7 Excellent |
### 14.4 Hamilton rating scale for Depression (HAMD-17)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressed mood</strong></td>
<td></td>
</tr>
<tr>
<td>Sad, hopeless, helpless, worthless</td>
<td></td>
</tr>
<tr>
<td>0 = Absent</td>
<td></td>
</tr>
<tr>
<td>1 = Gloomy attitude, pessimism, hopelessness</td>
<td></td>
</tr>
<tr>
<td>2 = Occasional weeping</td>
<td></td>
</tr>
<tr>
<td>3 = Frequent weeping</td>
<td></td>
</tr>
<tr>
<td>4 = Patient reports highlight these feelings states in his/her spontaneous verbal and non-verbal communication.</td>
<td></td>
</tr>
<tr>
<td><strong>Feelings of guilt</strong></td>
<td></td>
</tr>
<tr>
<td>0 = Absent</td>
<td></td>
</tr>
<tr>
<td>1 = Self-reproach, feels he/she has let people down</td>
<td></td>
</tr>
<tr>
<td>2 = Ideas of guilt or rumination over past errors or sinful deeds</td>
<td></td>
</tr>
<tr>
<td>3 = Present illness is punishment</td>
<td></td>
</tr>
<tr>
<td>4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations. Delusions of guilt.</td>
<td></td>
</tr>
<tr>
<td><strong>Suicide</strong></td>
<td></td>
</tr>
<tr>
<td>0 = Absent</td>
<td></td>
</tr>
<tr>
<td>1 = Feels life is not worth living</td>
<td></td>
</tr>
<tr>
<td>2 = Wishes he/she were dead, or any thoughts of possible death to self</td>
<td></td>
</tr>
<tr>
<td>3 = Suicide, ideas or half-hearted attempt</td>
<td></td>
</tr>
<tr>
<td>4 = Attempts at suicide (any serious attempt rates 4)</td>
<td></td>
</tr>
<tr>
<td><strong>Insomnia, early</strong></td>
<td></td>
</tr>
<tr>
<td>0 = No difficulty falling asleep</td>
<td></td>
</tr>
<tr>
<td>1 = Complaints of occasional difficulty in falling asleep i.e. more than half-hour</td>
<td></td>
</tr>
<tr>
<td>2 = Complaints of nightly difficulty falling asleep</td>
<td></td>
</tr>
<tr>
<td><strong>Insomnia, middle</strong></td>
<td></td>
</tr>
<tr>
<td>0 = No difficulty</td>
<td></td>
</tr>
<tr>
<td>1 = Patient complains of being restless and disturbed during the night</td>
<td></td>
</tr>
<tr>
<td>2 = Walking during the night – any getting out of bed rates 2 (except voiding bladder)</td>
<td></td>
</tr>
<tr>
<td><strong>Insomnia, late</strong></td>
<td></td>
</tr>
<tr>
<td>0 = No difficulty</td>
<td></td>
</tr>
<tr>
<td>1 = Waking in the early hours of the morning but goes back to sleep</td>
<td></td>
</tr>
<tr>
<td>2 = Unable to fall asleep again if he/she gets out of bed</td>
<td></td>
</tr>
<tr>
<td><strong>Work and activities</strong></td>
<td></td>
</tr>
<tr>
<td>0 = No difficulty</td>
<td></td>
</tr>
<tr>
<td>1 = Thoughts and feelings of incapacity related to activities: work or hobbies</td>
<td></td>
</tr>
<tr>
<td>2 = Loss of interest in activity – hobbies or work – either directly reported by patient or indirectly seen in listlessness, in decisions and vacillation (feels he/she has to push self to work or activities)</td>
<td></td>
</tr>
<tr>
<td>3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities</td>
<td></td>
</tr>
<tr>
<td>4 = Stopped working because of present illness. In hospital rate 4 if patient engages in no activities except supervised ward chores</td>
<td></td>
</tr>
<tr>
<td><strong>Retardation</strong></td>
<td></td>
</tr>
<tr>
<td>Slowness of thought and speech; impaired ability to concentrate; decreased motor activity</td>
<td></td>
</tr>
<tr>
<td>0 = Normal speech and thought</td>
<td></td>
</tr>
<tr>
<td>1 = Slight retardation at interview</td>
<td></td>
</tr>
<tr>
<td>2 = Obvious retardation at interview</td>
<td></td>
</tr>
<tr>
<td>3 = Interview difficult</td>
<td></td>
</tr>
<tr>
<td>4 = Interview impossible</td>
<td></td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td></td>
</tr>
<tr>
<td>0 = None</td>
<td></td>
</tr>
<tr>
<td>1 = Fidgetiness</td>
<td></td>
</tr>
<tr>
<td>2 = Playing with hands, hair, obvious restlessness</td>
<td></td>
</tr>
<tr>
<td>3 = Moving about; can’t sit still</td>
<td></td>
</tr>
<tr>
<td>4 = Hand wringing, nail biting, hair pulling, biting of lips, patient is on the run</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety, psychic</strong></td>
<td></td>
</tr>
</tbody>
</table>
Demonstrated by:

- subjective tension and irritability, loss of concentration
- worrying about minor matters
- apprehension
- fears expressed without questioning
- feelings of panic
- feeling jumpy

   0 = Absent
   1 = Mild
   2 = Moderate
   3 = Severe
   4 = Incapacitating

**Anxiety, somatic**

Physiological concomitants of anxiety such as:

- gastrointestinal: dry mouth, wind, indigestion, diarrhea, cramps, belching
- cardiovascular: palpations, headaches
- respiratory: hyperventilation, sighing
- urinary frequency
- sweating
- giddiness, blurred vision
- tinnitus

   0 = Absent
   1 = Mild
   2 = Moderate
   3 = Severe
   4 = Incapacitating

**Somatic symptoms: general**

   0 = None
   1 = Heaviness in limbs, back or head; backaches, headaches, muscle aches, loss of energy, fatigability
   2 = Any clear-cut symptom rates 2

**General Symptoms**

Symptoms such as: loss of libido, menstrual disturbances

   0 = Absent
   1 = Mild
   2 = Severe

**Hypochondriasis**

   0 = Not present
   1 = Self-absorption (bodily)
   2 = Preoccupation with health
   3 = Strong conviction of some bodily illness
   4 = Hypochondrial delusions

**Loss of Weight**

Rate either ‘A’ or ‘B’:

A When rating by history:

   0 = No weight loss
   1 = Probable weight loss associated with present illness
   2 = Definite (according to patient) weight loss

B Actual weight changes (weekly):

   0 = Less than 1 lb (0.5 kg) weight loss in one week
   1 = 1-2 lb (0.5 kg-1.0 kg) weight loss in week
   2 = Greater than 2 lb (1 kg) weight loss in week
   3 = Not assessed
Insight

0 = Acknowledges being depressed and ill
1 = Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.
2 = Denies being ill at all

TOTAL SCORE:
14.5 Fatigue Impact Scale

**Fatigue Impact Scale**

Visit Date: ________________

Below is a list of statements that describe how fatigue may cause problems in people’s lives. Please read each statement carefully. Circle the number that indicates how much of a problem fatigue has been for you these past four (4) weeks, including today. Please circle one number for each statement and do not skip any statements.

<table>
<thead>
<tr>
<th>Circle one number on each line</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my fatigue... I feel less alert.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Because of my fatigue... I feel that I am more isolated from social contact.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Because of my fatigue... I have to reduce my workload or responsibilities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Because of my fatigue... I am more moody.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Because of my fatigue... I have difficulty paying attention for a long period of time.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Because of my fatigue... I feel like I cannot think clearly.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Because of my fatigue... I work less effectively. (This applies to work inside or outside the home).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Because of my fatigue... I have to rely more on others to help me or do things for me.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Because of my fatigue... I have difficulty planning activities ahead of time because my fatigue may interfere with them.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Because of my fatigue... I am more clumsy and uncoordinated.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Because of my fatigue... I find that I am more forgetful.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Because of my fatigue... I am more irritable and more easily angered.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Because of my fatigue... I have to be careful about pacing my physical activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Because of my fatigue... I am less motivated to do anything that requires physical effort.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Because of my fatigue... I am less motivated to engage in social activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Because of my fatigue... My ability to travel outside my home is limited.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Because of my fatigue... I have trouble maintaining physical effort for long periods.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Because of my fatigue... I find it difficult to make decisions.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

French version of the Fatigue Impact Scale - Copyright 1991 J.D. Fisk, P.G. Ritvo & C.J. Archibald

Mapi Research Institute, ID 2115

AB06006-CRF-130509-Version 1 1/2  QUESTIONNAIRE NUMBER: US 1000
14.6 **AFIRMM score V2**

The AFIRMM Score V2 is a composite score built on the following items:

- 52 symptoms classified in 15 categories (skin, allergy, anaphylactic shock, flushes, gastrointestinal track, rheumatology, constitutional, cardiology, neurology/psychiatry, respiratory, urology, infection/ignition, libido, endocrinology, and social life). Each symptom was graduated from...
0 to 4 to define the level of handicap of symptom. The higher is the grade, the more severe is the handicap.

- Impact of the handicap in each category
- Grade of the handicap
- Weight of each handicap grade

The AFIRMM Score V2 for each patient is calculated by capturing handicaps importance by the grade and by weighting this grade.

\[
\text{AFIRMM score V2} = \sum_{i=1}^{52} (\text{Grade}_{\text{handicap } n} \times \text{Weight}_{\text{handicap } n}) = \sum_{i=1}^{52} (\text{Point}_{\text{handicap } n})
\]

- Grade \((0,1,2,3,4) = (0,1,2,3,4)\)
- Weight \((0,1,2,3,4) = (1,2,3,4,5)\)
- Point \((0,1,2,3,4) = (0,2,6,12,20)\)

The resulting AFIRMM Score V2 can range from 0 to 1040. The higher is the score, the more severe is the handicap of patient.

The patient should fill-in the two columns GRADE and MEASURE (Tick the corresponding cell, or indicate the number corresponding to the question), and the complementary questionnaires.

The column MEASURE and the complementary questionnaires should be filled in only at baseline and at week 24.
**Thank you for answering all questions below:** Please circle one number for each question and do not skip any one.

**Visit date:** [ ] [ ] [ ] [ ] [ ] [ ] [ ]

<table>
<thead>
<tr>
<th>Category</th>
<th>Nº</th>
<th>Handicap</th>
<th>Severity of the Handicap (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not affected</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>Pruritus (itching)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythematous crisis (inflammation:</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>getting red)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychological impact</td>
<td>0</td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
<td>Food allergy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug allergy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olfactive intolerance (tobacco, perfume…)</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td></td>
<td>Anaphylactic shock, syncope, dizziness</td>
<td>0</td>
</tr>
<tr>
<td>Flushes</td>
<td></td>
<td>Flushes (redness, feeling of heat on</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the face)</td>
<td></td>
</tr>
<tr>
<td>Gastro intestinal track</td>
<td></td>
<td>Aerophagia, excitation</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anus/vomiting</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epigastric pain</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stools</td>
<td>0</td>
</tr>
<tr>
<td>Gastro intestinal track (continued)</td>
<td></td>
<td>Pseudo occlusive syndrome &quot;Cohir Like&quot;</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haemorrhoids</td>
<td>0</td>
</tr>
<tr>
<td>Rhematology</td>
<td></td>
<td>Bone pain</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle and joint pain, cramps</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mobility</td>
<td>0</td>
</tr>
<tr>
<td>Constitutional</td>
<td></td>
<td>Asthenia, tiredness, lightheadedness</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anorexia and loss of weight</td>
<td>0</td>
</tr>
<tr>
<td>Constitutional (continued)</td>
<td></td>
<td>Performance status</td>
<td>0</td>
</tr>
<tr>
<td>Category</td>
<td>No</td>
<td>Handicap</td>
<td>Severity of the Handicap (grade)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>----------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not affected</td>
</tr>
<tr>
<td>Cardiology</td>
<td>21</td>
<td>Hypertension</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Chest pain</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Tachycardia, palpitation</td>
<td>0</td>
</tr>
<tr>
<td>Neurology/pyschiatry</td>
<td>24</td>
<td>Cephalgia (headache)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Vertigo</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Memory loss (ability to remember names, words)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Social interaction (resistance to stress)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>Inability</td>
<td>0</td>
</tr>
<tr>
<td>Neurology/pyschiatry</td>
<td>29</td>
<td>Concentration difficulty</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Paranoia, hallucination</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>Depression</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>32</td>
<td>Cough</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>Dyspnea, asthma (breathing difficulties, shortness of breath)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>Respiratory difficulty</td>
<td>0</td>
</tr>
<tr>
<td>Urology</td>
<td>35</td>
<td>Pollakiuria</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Pain</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>Dysuria (difficulties to urinate)</td>
<td>0</td>
</tr>
<tr>
<td>Urology (continued)</td>
<td>38</td>
<td>Incontinence</td>
<td>0</td>
</tr>
<tr>
<td>Category</td>
<td>№</td>
<td>Handicap</td>
<td>Severity of the Handicap (grade)</td>
</tr>
<tr>
<td>-------------------</td>
<td>----</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>ORL infection (neck and head pain, laryngitis, rhinitis, conjunctivitis, otitis, sinusitis)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>Pulmonary infection (bronchitis)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>Facialitis</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>Tinnitus (acouphene, tinni)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>Ocular discomfort (dry eyes, red eyes, stinging eyes)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>Stomatitis (gum inflammation or hemorrhage, tooth loss)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Warts</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Libido</td>
<td>46</td>
<td>Sexual relation (frequency of intercourse)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Libido (continued)</td>
<td>47</td>
<td>Erectile function, possibility to have sexual relationship</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>48</td>
<td>Sweat</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Social Life</td>
<td>49</td>
<td>Impact on couple</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Impact on professional life</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>Impact on friends and family</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>Impact on daily living activity (to make shopping, to go out, holidays,...)</td>
<td>0 1 2 3 4</td>
</tr>
</tbody>
</table>

**Overall Patient Assessment (OPA)**

<table>
<thead>
<tr>
<th>Handicap</th>
<th>Severity of the Handicap (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Handicap (pain, general status, impact on life)</td>
<td>Not affected</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
14.7 Sampling procedure

Analysis of tryptase:

Blood will be collected in appropriate sampling kit (sampling device, transfer tubes, labels, frozen samples transport kits).

Samples will be shipped to a central laboratory.

Skin and Bone marrow biopsy procedures:

**Skin:**
- 2 to 3 punches ≥4 mm²
- Preserve one with RNA later for C kit sequencing and the other ones undergo formol fixation for mast cell counting.
- Send:
  - to central laboratory for c-Kit sequencing and mast cell counting

**Bone marrow:**

- Aspirate
  - Perform a 3mL aspirate
  - Preserve with EDTA
  - Send:
    - to central laboratory for C-kit sequencing and mast cell counting
  - BM aspirate performed at screening and at W24 should be done on the same location (sternum or on iliac crest bone).
- Biopsy
  - Perform a biopsy in iliac crest bone
  - Undergo formol fixation and prepare slides
  - Send to central laboratory for mast cell counting

14.8 C-Kit mutation analysis, normalised procedure

RNA preparation and c-Kit sequencing

Total RNA was extracted from biopsies using the Rneasy mini kit (Qiagen). Complementary DNA was synthesised by using random hexamers and oligo dT as oligonucleotide primer from 200 ng total RNA using the stratascript first-strand synthesis system (Stratagene) in a total volume of 50 µl as recommended by the manufacturer. Then, 2.5 µl of cDNA was introduced in each polymerase chain reaction (PCR).

c-Kit gene were amplified by PCR using HotStartTaq™ DNA polymerase (Qiagen S.A. France). A total of 40 cycles were performed using the either 9700 or 2700 Gene Amp PCR Systems (Applied biosystems) at 94°C for 30 sec, 57°C for 30 sec and 72°C for 45 sec.

c-Kit coding sequences were amplified from complementary DNA with the PCR by using primer pairs indicated in Table 19. For the specific detection of the mutation at the 816 position, we used the primer pairs (2295s & 2661r) indicated in Table 19.

Direct amplimer sequencing was carried out after the purification of the PCR products with the geneclean III kit (Qbiogene). They were directly sequenced with Big dye terminator V 1.1 (Applied biosystems) on an ABI Prism 3130 sequencer (Applied biosystems) and analyzed with the Seqscape software (Applied biosystems) using 2295s & 2647r sequencing primers described in Table...
19. **Table 19 - Primer positions indicated from the published c-Kit sequence (NCBI accession number X06182)**

<table>
<thead>
<tr>
<th>Name of the ex17 primers</th>
<th>Nucleotide Sequence</th>
<th>localisation (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2295s &amp; 2295sF</td>
<td>GGATGACGAGTTGGCCCTAGA</td>
<td>2295 to 2315</td>
</tr>
<tr>
<td>2661r &amp; 2661rF</td>
<td>GTAGAAACTTAGATCGACCGCA</td>
<td>2639 to 2661</td>
</tr>
<tr>
<td>2647r (sequencing)</td>
<td>CGACC CGGCA TTCCAGGATAG</td>
<td>2628 à 2647</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nested ex17 primers and sequencing</th>
<th>Nucleotide Sequence</th>
<th>localisation (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2341s</td>
<td>TACCAGGTGGC AAGGGCATG</td>
<td>2341 to 2362</td>
</tr>
<tr>
<td>2600r</td>
<td>CTTC ATAGAAGAACAGCTCC</td>
<td>2600 à 2621</td>
</tr>
</tbody>
</table>

**D816V mutation detection**

D₈¹⁶V mutation was also confirmed by restriction digest analysis with BsmA1 and Ple1 restriction enzymes, which detect wild type and mutated form respectively. Purified fluorescent primers (2295sF & 2661rF see Table 19) were used for PCR reactions. Size of restriction digest fragments (201 for BsmA1 fragment and 179 and 187 for Ple1 fragment) were directly determined on a 16 capillary sequencer (ABI Prism 3130 sequencer) with the GeneMapper software (Applied biosystems) by comparison with size of the Genescan rox 500 markers (Applied biosystems).

In the case of detection of either a WT sequence or all suspicious mutated-D816 codons, an independent PCR was performed on cDNA. Same conditions as above were used for the PCR reaction, except that 30 cycles were used. Then, PCR products were digested by BsmA1 enzyme in order to increase a putative mutated signal. The BsmA1 digested products are then amplified in a 25 cycles nested-PCR reaction using 2341s and 2600r primer pairs (see Table 19). Same conditions of temperature and time as above were applied for this reaction. Purified nested PCR products were then sequenced with 2341s and 2600r primer pairs as described above and analyzed with the Seqscape software.
14.9 **Adverse event**

14.9.1 **Definitions**

14.9.1.1 **Adverse events**

An Adverse Event is any untoward medical occurrence in a patient or subject which does not necessarily have a causal relationship with any medical treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP, whether or not considered causally related to the IMP. This includes all intercurrent diseases (newly diagnosed concomitant diseases or symptoms), accidents, clinically relevant deteriorations of pre-existing diseases or clinically relevant deteriorations in clinically evaluated variables (e.g. laboratory, ECG, or physical examination). An event does not have to be documented as an AE in the CRF if the following holds true:

- untoward medical findings that occur prior to the administration of any IMP are not considered to be AEs if they occur in the scope of investigations that are performed to check inclusion or exclusion criteria;
- deviations in clinically evaluated variables are not considered to be AEs if similar deviations were already present prior to or at the baseline visit. These values should be reported as baseline conditions, if clinically relevant, and exclusion criteria must be obeyed;
- surgeries and other invasive procedures that are planned prior to the start of the study do not have to be documented as AEs. Planned procedures will be recorded in the CRF by the investigator at the baseline visit.

14.9.1.2 **Serious adverse events**

Serious adverse events (SAEs) are a subgroup of all AEs which fulfil internationally agreed upon definitions. They require special attention by the investigator and sponsor.

A SAE is defined as any untoward medical occurrence that at any dose

- results in death: It should be respected that death itself is not an AE but rather the outcome of an event which should be described using medical terminology. Death as the description for an AE is only acceptable in the case of a sudden death when no diagnosis can be found;
- is life-threatening: This refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it had been more severe;
- requires inpatient hospitalization or prolongation of existing hospitalization: This is defined as inpatient care that covers more than one calendar day, even if the duration of hospitalization is shorter than 24 h;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is another medically important condition: This refers to an AE that may not be immediately life-threatening or results in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Based on medical and scientific judgment this should usually be considered serious.

If there is any doubt about whether or not an AE is serious, the investigator should contact the sponsor.
14.9.2 Reporting

14.9.2.1 Reporting of adverse events

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate.

As far as possible, each adverse event will also be described by:

- its duration (start and end dates)
- the severity
- its relationship to the study drug (suspected/not suspected/not assessable)
- the action(s) taken

Any Adverse Event occurring by the time of study completion (within two weeks of last drug intake) must be recorded on the Adverse Event CRF page.

14.9.2.2 Serious Adverse Events

Any SAE, whether or not considered as related to study drug, will be reported on a SAE form and faxed to AB Science within 24 hours of occurrence or Investigator’s knowledge of this event, even if it does not appear to be treatment-related.

The Investigator is also responsible for complying with the applicable requirements related to adverse experiences reporting.

Any SAE, including a serious clinical laboratory abnormality occurring in a patient after providing informed consent, whilst receiving study treatment and until 28 days (4 weeks) after stopping it must be reported. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated. All serious adverse events must also be reported for the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Follow-up information about a previously reported serious adverse event must also be reported to AB Science within 24-hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug, the AB Science Medical Expert and/or the AB Science Drug Safety Associate may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug that this serious adverse event has been reported.

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study drug and fax the completed form within 24-hours to the AB Science Safety Department. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site. The monitor will review and collect a copy of the Serious Adverse Event Form.

Follow-up information is also to be sent, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one resent (with the new information highlighted and a new date provided). The follow-up should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained.

The telephone and telefax numbers of the local contact person in the AB Science Safety Department will be provided to each site and a copy will be kept in the Investigator File provided by AB Science.

Specific questions referring directly to the patient and the serious adverse event and questions concerning the fax transmission of a Serious Adverse Event Form must be directed to the AB Science Safety Department contact person.
According to local requirements, the sponsor will take care of reporting the AE to the regulatory authorities, ethic committees and other investigators.

### 14.9.3 Causality assessment

The investigator has to assess the causal relation of the AE to the IMP. The investigator should base the assessment of a causal relationship on the following scale:

#### Not suspected

There is an evident other explanation for the AE, e.g.
- the AE is obviously explained by the patient's disease(s) or
- the AE is in accordance with the effect or adverse effect of a concomitant medication or
- the AE has occurred already prior to administration of the IMP in comparable intensity and/or frequency or
- the AE started before the first intake of IMP.

#### Suspected

There is a reasonable temporal relation between the AE and the intake of the IMP, there is plausible reasons point to a causal relation with the IMP.

#### Not assessable

Due to conflicting medical information and/or patient status, no causal relationship can be stated.

### 14.9.4 Intensity of adverse events

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

### 14.9.5 Actions taken in response to an adverse event

The actions taken in response to an adverse event are described on a numerical scale, from 1 to 5 that cover the various possibilities. One of these is to be selected.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No action taken</td>
</tr>
<tr>
<td>2</td>
<td>Study drug dosage reduced</td>
</tr>
<tr>
<td>3</td>
<td>Study drug temporarily interrupted</td>
</tr>
<tr>
<td>4</td>
<td>Study drug permanently discontinued due to this adverse event</td>
</tr>
<tr>
<td>5</td>
<td>Study drug temporarily interrupted and dosage reduced</td>
</tr>
</tbody>
</table>

### 14.9.6 Follow-up of ongoing adverse events at study termination

Patients who discontinue the study (either on schedule or prematurely) with reported AEs that have not yet completely resolved must return for one or more follow-up visit(s).
Adverse events will be followed-up until resolution or until stabilisation stated by the investigator.

Particular attention should be given to:
- SAEs;
- ongoing non-serious AEs likely or definitely related to the IMP according to the investigator's causality assessment;
- ongoing AEs leading to the patient's premature discontinuation;
- any laboratory value or vital signs being beyond the sponsor-defined alert limit;
- any adverse event judged as important by AB Science safety department.

The investigator should perform one or more follow-up visits during the first 28 days after the patient's treatment phase to examine whether the AE resolved. The AE is monitored until either normalization, return to the baseline value or identification of a permanent change. In case of minor AEs a phone call to the patient may be acceptable. If necessary, additional safety investigations and queries will be done during and after this time period.

Follow-up information on the outcome must be recorded on the respective AE page in the CRF or in the data clarification form. All efforts to achieve follow-up information must be documented in the source data. Source data information has to be available upon request.

Follow-up investigations may also be necessary according to the investigator's medical judgment even if the patient has no AE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be recorded in the source documentation.

14.9.7 Handling of neutropenia < 0.5x10^9/L

Any neutropenia with an absolute neutrophils count less than 0.5x10^9/L reporting in a patient receiving masitinib during the study, or in a patient having received masitinib within 7 days before the diagnosis of neutropenia should be reported as an SAE. The completed SAE form should be sent by fax (fax number written on the SAE form). If the investigator considers that neutropenia is not a serious adverse event, no seriousness criteria should be ticked.

14.9.8 Handling of pregnancy or fathering cases

Any pregnancy or fathering of a child within 90 days (12 weeks, 3 months) after the last masitinib intake has to be reported and recorded as an SAE.

If pregnancy is suspected during the study, the IMP must be immediately withheld until the result of a laboratory pregnancy test is available. Should pregnancy be confirmed, the patient must be withdrawn from study participation and the sponsor must be notified within 24 hours of the day, the investigational site becomes aware of the pregnancy. In case of blinded trial, the sponsor will break the blind for the respective patient. The investigator must inform the patient about her medication immediately after receiving this information from the sponsor. In case the patient had received placebo no further actions are required. In case the patient had received masitinib, the patient must be asked to participate in the AB Science Pregnancy Surveillance program. If the patient agrees to participate, an Initial Pregnancy Questionnaire must be completed and sent to AB Science within two weeks. Within two weeks of the estimated date of delivery, the sponsor will request information on the course and the outcome of the pregnancy from the patient's health care professional during pregnancy. The AB Science pregnancy surveillance program is also applicable in case of pregnancy occurring within 90 days (12 weeks, 3 months) after the last masitinib intake and in case of pregnancy of partner (in case of male patients).
14.9.9 Notification of the Independent Ethics Committee/Institutional Review Board and the Health Authorities

The relevant health authorities and IECs/IRBs will be notified by the sponsor of all safety aspects according to national regulations.
14.10 Coordinating investigator CV
14.11 Statement on Insurance Policy
14.12 IRB Approval
14.13 Laboratory and Vital Sign Alert Values (Sponsor defined)

HEMATOLOGY

Hemoglobin: male < 10 g/dL   female < 9.5 g/dL  
Erythrocytes: male < 3,5 x 10⁶/µL or > 7 x 10⁶/µL   female < 3,0 x 10⁶/µL or > 6.5 x 10⁶/µL
White Blood Count (WBC): < 2,800/mm³ or > 16,000/mm³
Eosinophils: > 600/ mm³
Platelet Count: < 75,000/mm³ or > 600,000/mm³

CHEMISTRY

SGOT (ASAT): > 3x ULNR  
SGPT (ALAT): > 3x ULNR  
Gamma-GT: > 5x ULNR  
Alkaline Phosphatase (AP): > 3x ULNR  
CK: > 3x ULNR  
Creatinine: > 1.5x ULNR  
Total Bilirubin: > 2x ULNR  
Potassium: > 6.0 mmol/L  or< 3.0 mmol/L  
Sodium: > 150 mmol/L  or< 130 mmol/L  
Glucose: > 2 x ULNR

VITAL SIGNS

BP systolic: > 170 mmHg or < 85 mmHg  
BP diastolic: > 105 mmHg  
Difference systolic BP at Tx (increase or decrease) compared to pre-treatment > 40 mmHg  
Resting Heart Rate: > 120 bpm or < 50 bpm – lower limit not applicable for all healthy volunteer studies  
Difference HR at Tx (increase or decrease) compared to pre-treatment > 30 bpm

ULNR = Upper Limit of Normal range
14.14 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964

and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases
and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the
individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics
committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless
it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject’s dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

- Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**
34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.
14.15 List of CYP450 substrates

Drugs known to be metabolized by CYP450 isoenzymes 3A4, 2D6 and 2C9

- **CYP2D6**
  - **Substrates**
    - Amitriptyline (hydroxylation), Amphetamine, Betaxolol, Bisoprolol, Brofaromine, Butyrolool, Bupropion, Captopril, Carvedilol, Cevimeline, Chlorpheniramine, Chlorpromazine, Cinnarizine, Clopimipramine (hydroxylation), Clozapine (minor pathway), Codeine (hydroxylation, o-desmethylation), Cyclobenzaprine (hydrolylation), Cyclophosphamide, Debrisoquin, Delavirdine, Desipramine, Dextfenfluramine, Dextromethorphan (o-desmethylation), Dihydrocodeine, Diphenhydramine, Dolaseton, Donepezil, Doptex, Encainide, Fenthuramine, Flename, Fluoxetine, Flecainide, Fluticasone, Imipramine (hydroxylation), Labelatol, Loratadine, Magrotrine, M-Chlorophenylpiperazine (m-CPP), Meperidine, Methadone, Methylphenidate, Metoprolol, Metoprolol, Mexetidine, Mianserin, Mirtazapine (hydroxylation), Molindone, Morphine, Nortriptyline (hydroxylation), Olanzapine (minor, hydroxymethylation), Ondansetron, Oxycodone, Papaverine, Paroxetine (minor pathway), Penbutolol, Pentazocine, Perhexiline, Perphenazine, Phenformin, Pindolol, Promethazine, Propafenone, Proranolol, Quetiapine, Remoxipride, Risperidone, Ritonavir (minor), Ropivacaine, Selegiline, Sertraline, Sertraline (minor pathway), Sparteine, Tamoxifen, Thioridazine, Tiagabine, Timolol, Tolterodine, Trimadol, Travoprost, Venlafaxine (o-desmethylation), Yohimbine.

- **Inhibitors**
  - Amiodarone, Cefalexin, Chloroquine, Chlorpromazine, Cimetidine, Citralopram, Clopimipramine, Codeine, Deaivurdine, Desipramine, Dextfenpropoxyphepine, Ditiuzem, Doxorubicin, Entacapone (high dose), Fluoxetine, Fluphenazine, Fluvoxamine, Haloperidol, Labelatol, Lobile, Lomitine, Methadone, Mibefradil, Mocllobemide, Northoxetine, Paroxetine, Perphenazine, Propafenone, Quinacrine, Quinidine, Ranitidine, Risperidone (weak), Ritonavir, Sertraline, Sertraline (weak), Thiothidine, Vaprolc acid, Venlafaxine (weak), Viniblastine, Vinristine, Vinorelline, Yohimbine.

- **CYP3A4**
  - **Substrates**

- **Inducers**
  - Carbamazepine, Dexamethasone, Ethosudum, Eglucorticoid, Grgiseofulvin, Nafcinil, Nelfinavir, Neprinav, Oxcarbazepine, Phenobarbital, Phenylbutazone, Phenyoit, Primidone, Progesterone, Rifabutin, Rifampin, Rofecoxib (mild), St John’s Wort, Sulfadimidine, Sulfinpyrazone, Trogliotazone

- **Inhibitors**
  - Amiodarone, Anastrozole, Azithromycin, Cannabinoids, Cimetidine, Clarithromycin, Clotrimazole, Cyclopipalmine, Danazol, Delavirdine, Dexamethasone, Diethyldithiocarbamate, Ditiuzem, Dirithromycin, Disulfiram, Entacapone (high dose), Erythromycin, Ethynol estradiol, Fluconaolone (weak), Fluoxetine, Fluvoxamine, Gestodene, Grapefruit juice, Indinavir, Isoniazid, Itraconazole, Ketoconazole, Metronidazole, Mibefradil, Miconazole (moderate), Nefazodone, Nelfinavir, Neprinav, Norflaxacin, Norfluroxetine, Omeprazole (weak), Oxiconolone, Paroxetine (weak), Propoxyphepine, Quinidine, Quinidine, Quimoprinin and dalfoprinin, Ranitidine, Ritonavir, Saqunavir, Sertraline, Sertraline, Troleandomycin, Troleandomycin, Vinprop, Verapamil, Zafirlukast, Zileten.

- **CYP2C9**
  - **Substrates**
    - Anti inflammatory Drugs, Flurbiprofen, Diclofenac, Naproxen, Piroxicam, Superox, Ibuprofen, Mefenamine, Celecub, Oral propyacoline, Tolbutamide, Glyburide, Gipipzide, Glimiperide, Oral anticoagulant, (S)-Warfarin, (S)-Acenocumaro, Propophrocin, Duiretics and uricosuric, Onomone, Ticrynafen, Sulfinpyrazone sulhide, Angiotensin II blockers, Losartan, Irbesartan, Candesartan, Antithasthmetics, Zafirlukast, Zileten, Anticonvulsants, Phenyoit, Phenobarbital, Trimethadone, Anticancer agents, Cyclophosphamide, Tamoxifen, Mestranol, Fluvastin, Delta-9 tetrahydrocannabinol, Benzopyrene, Pyrene, Fluoxetine, Sildenafil, Rosiglitazone
### Inducers
- Rifampicin, Secobarbital, Hyperforin

### Inhibitors
- Amiodarone, Fenofibrate, Fluconazole, Fluvastatin, Fluvoxamine, Isoniazid, Lovastatin, Probenecid, Sertraline, Sulfamethoxazole, Teniposide, Voriconazole, Zafirlukast


14.16 Documentation of severe skin toxicity

Severe skin / mucous toxicity:

- Please ask for a dermatologic advice
- Please ask for a skin biopsy
- Please take pictures
- Please complete this document and sent it back to pharmacovigilance@ab-science.com

Study number: Patient number:

15 Description of the severe skin / mucous toxicity

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Present</th>
<th>If yes and if applicable, localization of the lesions and percentage of the body surface area involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial swelling</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Tongue swelling</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Hives</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Skin pain</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Red or purple skin rash</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Blisters on the skin</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Skin shedding</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Blister on mucous membranes</td>
<td>□ Yes   □ No</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Please specify:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ mouth □ nose □ eye □ genital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ other localization, please specify:</td>
<td></td>
</tr>
</tbody>
</table>

Please take pictures of the skin and mucous lesions and join them to the questionnaire.
16 Description of the associated signs or symptoms:

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Sore throat</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Cough</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Burning eyes</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Reactivation of herpes</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Other, please specify</td>
<td></td>
</tr>
</tbody>
</table>

17 Biological abnormalities:

<table>
<thead>
<tr>
<th></th>
<th>Value at the time of the event</th>
<th>Baseline value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
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<td></td>
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</tr>
<tr>
<td>ALT (IU/L)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White blood cells</td>
<td></td>
<td></td>
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<tr>
<td>count (giga/L)</td>
<td></td>
<td></td>
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<tr>
<td>Eosinophils count</td>
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<td></td>
<td></td>
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<tr>
<td>(giga/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytosis</td>
<td>□ Yes □ No</td>
<td>□ Yes □ No</td>
<td></td>
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<tr>
<td>&gt; 5%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Human herpes virus 6</td>
<td>□ Yes □ No</td>
<td>□ Yes □ No</td>
<td></td>
</tr>
<tr>
<td>reactivation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, please specify</td>
<td></td>
<td></td>
<td></td>
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</table>
18 Concomitant medications:

<table>
<thead>
<tr>
<th>Tradename</th>
<th>INN</th>
<th>Start date</th>
<th>End date</th>
<th>Dose administered</th>
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<tr>
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Name:

Date:

Signature:
The original protocol of the AB06006 study (Version 1.0 dated 25 February 2008) was initially submitted to the ANSM on 15 May 2008.

The following modifications were applied to the protocol during the study:

**ROW:** - **Protocol Version 2.0** from 15.07.2008 incorporated the following changes: section related to neutropenia risk (surveillance and management) was updated with the requirement for patients to perform locally routine blood cell counts every week during the first two month of treatment, at week 10 and then at least every 4 weeks.

**FRA:** - **Protocol Version 2.0/FR.01** from 10.12.2008 incorporated the following changes: section related to neutropenia risk (surveillance and management) was updated with the requirement for patients to perform locally routine blood cell counts every week during the first two month of treatment, at week 10 and then at least every 4 weeks.

As part of the international study, French patients enrolled in the study, entered a specific cardiac surveillance in order to study potential effect of masitinib on myocardial contractibility. As per study protocol, patients will have to perform at baseline and at the final visit a doppler echocardiography. The following echocardiogram endpoints should be measured:

- Left Ventricular Ejection Fraction at week 24 (primary)
- Fractional shortening (midwall mFS) at week 24
- Systolic and diastolic left ventricular diameters at 24
- Optionally, left ventricular contractility during Isovolumic Contraction at week 24

Enhanced cardiac surveillance included: addition of an ECG at week 12 and every 12 weeks during the extension treatment phase; updated of exclusion criteria related to cardiac pathology, updated cardiac safety monitoring plan.

- **Protocol Version 3.0** dated 04 Aug 2009 incorporated the following changes:

FSH, LH, Estradiol and Progesterone level assessment for all pre-menopausal women not using hormonal contraceptive at baseline and every 12 weeks during the course of the study, and optional spermogram at baseline, week 24 visit and/or final visit were added to the protocol. Measurement of BNP was substituted with NT-ProBNP for monitoring cardiac function. A randomization vendor Cardinal System was introduced in the study. Better definition of risk management plans and clarifications throughout the protocol.

- **Protocol Version 4.0** dated 04 July 2011 incorporated the following changes:

Further to thorough analysis of the cardiac safety profile of masitinib in various indications, AB Science decided to fine-tune the exclusion criterion of patient with previous/current cardiac disorders, cardiac surveillance and the rules for study treatment interruption. Limitation of the maximal dose of masitinib to 600 mg/day. Implemented mITT population as primary population in addition of ITT and PP. Clarification of hypotheses for sample size calculation in a two sided design, a difference (two sided) instead of a superiority (one sided). Added an exploratory logistic regression analysis. Standardisation of the way of analysis of safety data.

- **Protocol Version 5.0** dated 10 May 2012 incorporated the following changes:

Enhancement of the handicaps thresholds at baseline according to discussion with experts and the European Medicines Agency: Hamilton rating scale for depression (HAMD-17) ≥ 10 to ≥ 14 and Fatigue Impact Scale total score ≥40 to ≥75. Enhanced patient information throughout a more detailed patient card and prophylactic measures (ie regular calls to the patients / Prescription of antibiotic). Enrollment was restricted to moderate and severe patients.
Addition of a specific pharmacogenomics assay in case the patient experiences either a severe neutropenia or a severe skin toxicity. Prophylactic prescription of antibiotics to be taken by patient in case of fever. Enhanced risk management plan regarding potential occurrence of skin reaction and updated information related to concomitant treatments with drugs known at risk of SJS. Added information about planned futility analysis.

Statistical section of the study protocol was updated to reflect changes related to improvement of the response definition according the experts and EMA discussions and fine-tuning of the primary and secondary endpoints; statistical hypotheses was changed according to phases 2 clinical data without having an impact on the study sample size.

**- Protocol Version 6.0 dated 16th May 2013 incorporated the following changes:**

To increase the benefit/risk ratio following discussion with authorities for indications in non-oncology, protocol was amended to include only mastocytosis patients with smouldering systemic and indolent systemic mastocytosis. EMA was consulted on this question through scientific advice in October 2011 (EMA/CHMP/H/SA/573/2/FU/2/2011/PA/SME/II) and EMA validated the increase of severity of handicaps. The inclusion criteria for Handicaps were strengthened

- Pruritus score from ≥ 6 to ≥ 9
- Flashes frequency per week from ≥ 7 to ≥ 8
- Hamilton score from ≥ 14 to ≥ 19

Number of patients was changed to 150 with documented Smouldering or Indolent Systemic mastocytosis with severe handicap (75 patients per group).

Limit of haemoglobin level was added to inclusion criteria in order to avoid enrolling anemic patients. 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. Threshold of albumin has been increased to avoid hypoalbuminemia that could potentially interfere with PK of masitinib. 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 were clarified and risk management plans were updated.

**- Protocol Version 6.0/GE01 dated 16th May 2013 additionally incorporated the following changes:**

Added urinary cytology and NMP22 test at baseline and then every 12 weeks.

**Protocol Version 7.0/FRA03 dated February 13th, 2015 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 will be allowed to continue the treatment on a case by case basis only if a documented favourable 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 event were supplemented with NMP test at 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 risk of uterine carcinoma was added. Prescription of broad spectrum antibiotherapy will be considered and executed by clinical study physician in case subjects will present themselves with signs or symptoms suggesting the occurrence of severe neutropenia and/or severe skin toxicity.

Information about AB Science pregnancy surveillance program (for confirmed pregnancy).

Frequency for (optional depending on patients’ consent) semen analysis for male patients was increased to 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. Serum pregnancy test was added to screening procedures. Introduced rebound evaluation assessment of symptoms after treatment discontinuation. Updated severe skin toxicity questionnaire.