AB Science Webconference

VOLUNTARY HOLD IN THE CLINICAL STUDIES OF MASITINIB

3 June 2021

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Participants

Introduction

- **Alain MOUSSY: CEO and Co-founder of AB Science**

The presentation will be delivered by AB Science Medical and Safety team

- **Dr Christian FASSOTTE: Chief Medical Officer**
  Medical Doctor with specialisation in Pharmaceutical Medicine, 33 years of experience in the pharmaceutical industry in medical/ regulatory affairs and R&D in groups such as Roche and Sanofi (member of the R&D board)

- **Dr Peter DE VEENE : Safety and Pharmacovigilance Director**
  Medical Doctor, 18 years of experience in the pharmaceutical industry, including Safety and Pharmacovigilance, Risk Management, EUQPPV, at ALEXION pharmaceuticals, Grunenthal GmbH, Daiichi Sankyo, after 10 years of safety experience at Roche

- **Pr Olivier HERMINE : Chairman of the AB Science Scientific Committee, Co-founder of AB Science**
  Medical Doctor, Professor of Hematology at the University of Paris, Head of the Adult Hematology Department - Necker Hospital, Coordinator and Founder of the National Reference Center for Mastocytosis and Mast Cells, Head of the Laboratory of Physiopathology and Treatment of Hematological Diseases, INSERM U1163 Imagine Institute, Coordinator of the Labex on Red Blood Cells (Grex), Member of the French Academies des Sciences

Overview

Situation

- AB Science is strongly focused on improving patients' lives and therefore we believe that AB Science has taken the right decision to voluntarily put a temporary hold on recruitment and randomization in the on-ongoing studies
- Safety data have been shared transparently and consistently with regulators and investigators
  - The Investigator's Brochure already includes comprehensive data on the potential risk of cardiovascular events
  - In addition, precautionary measures are implemented in all studies to mitigate the risk
  - Up to recently, no additional evidences had emerged to corroborate this potential risk
- After unblinding the phase 2B/3 studies with masitinib, we have run multiple safety analyses in a continuous effort to detect signals. In one of the exploratory analyses, pooling a subset of studies and a subset of patients, we have seen an imbalance of events of Ischemic Heart Disease (IHD) between masitinib and the control arm, which might be interpreted as a signal of increased risks of IHD
- As a consequence, the company consulted with external experts and decided to perform a meta-analysis on all available data from controlled and unblinded study data
  - This meta-analysis did not confirm the signal
  - These results were shared with national competent authorities across the world
  - French competent authority ANSM requested some additional analyses and data to finalize its own investigation
- Out of precaution, AB Science decided to hold inclusions in on-going studies pending completion of these investigations
- AB Science believes that it has made the right decision for the patient and is ready to resume enrolment, once the remaining investigation of this risk is completed

Definitions (WHO, EMA)

- **A signal (in this case 'ischemic heart disease') is essentially a hypothesis of a risk with a medicine with data and arguments that support it**, derived from data from one or more of many possible sources
  - Based on quantitative methods, e.g. statistical analysis
  - Based on qualitative methods, e.g. medical judgment

- The evidence in a signal is not conclusive. It is, in the technical sense, uncertain
- A signal is only an early indication (preliminary), as it may change substantially over time as more data accummulates

- **Potential risk (in this case 'potential risk of cardiovascular events')**
- An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed
- Examples include:
  - **non-clinical toxicological findings** that have not been observed or resolved in clinical studies;
  - adverse events observed in **clinical trials** for which the magnitude of the difference, compared with the comparator group, raises a suspicion of, but is not large enough to suggest, a causal relationship;
  - an event known to be associated with other active substances within the same **class** or which could be expected
  - to occur based on the properties of the medicinal product (e.g. mode of action)

Process Flow – Activities completed by AB Science so far

Analyses of pooled and unblinded studies to detect signal as part of pharmacovigilance activities

- One analysis in a subset of studies and a subset of patients shows imbalance of events of Ischemic Heart Disease (IHD) between masitinib and the control arm
- Might be interpreted as a signal of increased risks of IHD
- **A signal is not a risk but an hypothesis of risk until confirmed. It is something to explore further**

Meta-analyses based on Relative Risks (RR) methodology for all studies and all patients

- Meta-analyses based on RR of cardiovascular events based on multiple categorizations of events from all studies
- Rely on methodology described by the Cochrane Library (golden standard according to experts)
- **Based on these current results, no evidence of an increased risk of cardiovascular events (including ischemic heart disease) is observed**
- Therefore, based on current analyses, there is a low probability of a new signal

Communication to ANSM and other health authorities

- No definitive conclusion can be made
- Request for additional data and analyses

Voluntary hold of inclusions pending investigations

- Suspend inclusion of new patients
- Do not initiate treatment for patients already randomized
- Continue treatment for patients already under treatment, at the investigator's decision, provided positive individual benefit/risk is documented

Process Flow – Next steps to be performed

Provide to ANSM requested data and analyses

- Health Authorities usually do not rely solely on sponsors' analyses and request raw data to perform their own assessment
- Such data and analyses typically include quantitative (sensitivity analyses) and qualitative (listings, detailed narratives,, etc…) information

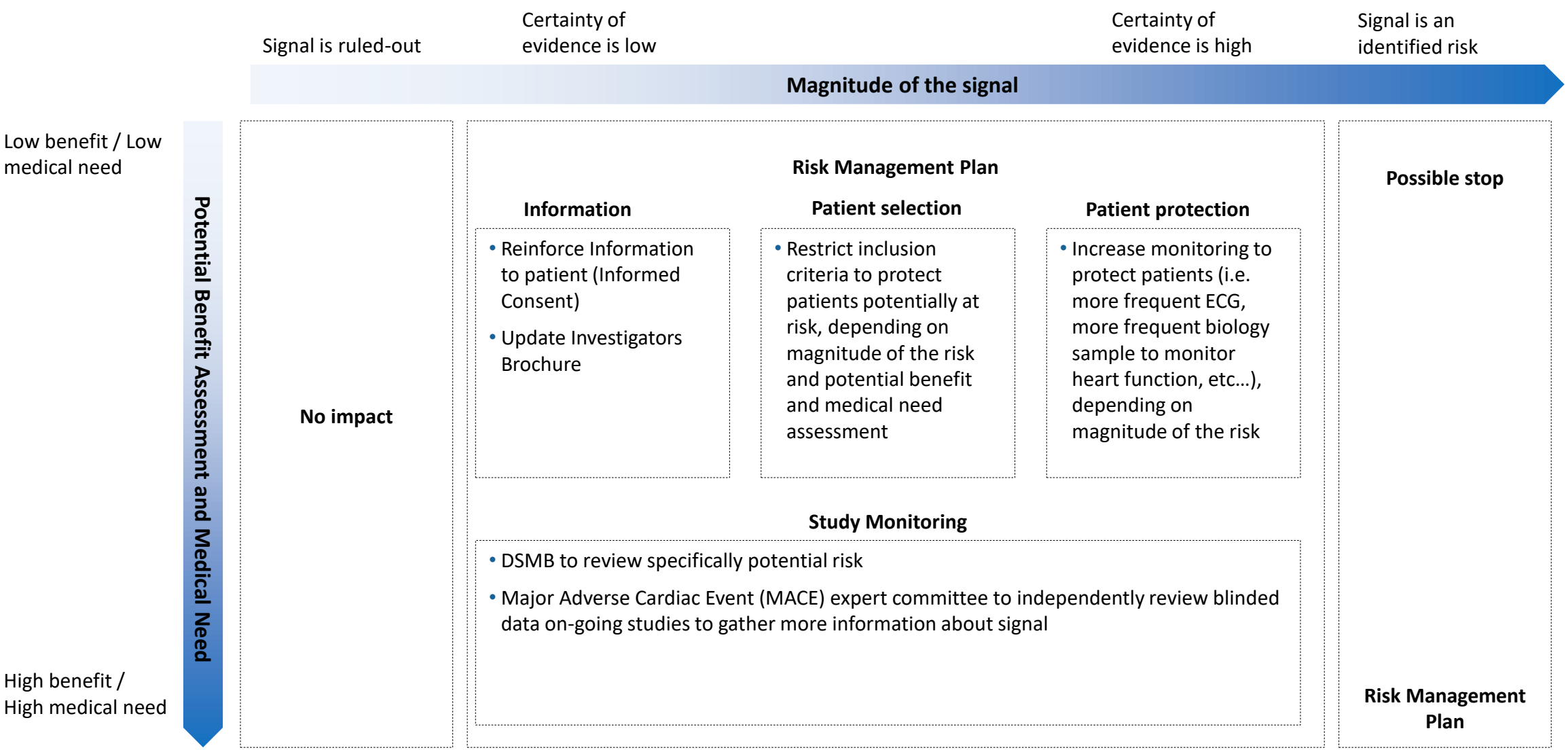
Assess magnitude and potential causality of the signal

- Signal is ruled-out
- Signal is low
- Signal becomes an identified risk

Assess Impact for each study

- An assessment is performed study by study, meaning that different risk mitigation measures can be adopted depending on the magnitude of the risk

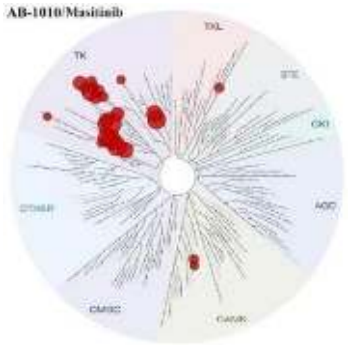
For any potential risk, a risk management plan is implemented



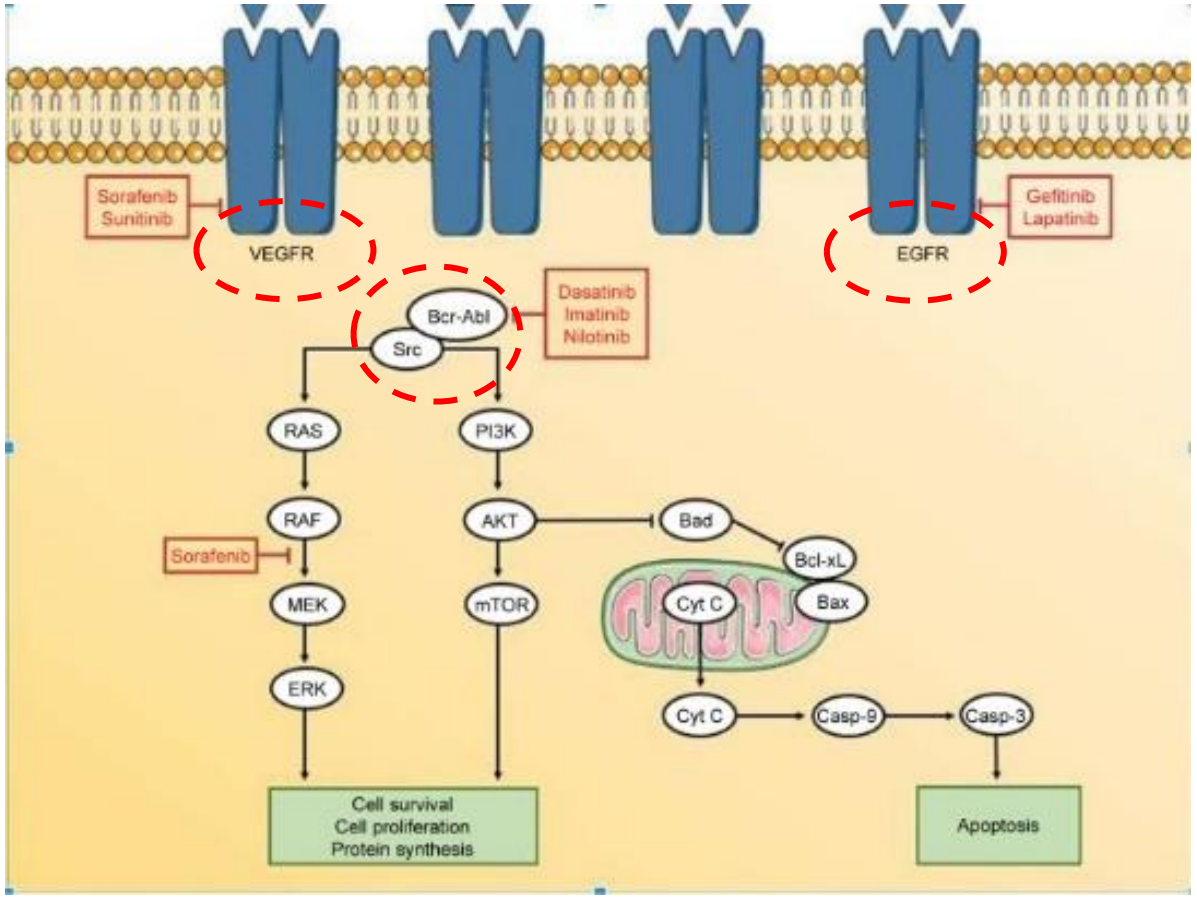
Masitinib vs Other TKIs on Cardiovascular Toxicity

Kinase inhibition profile of masitinib

Cellular Target	Molecular Target	IC_{50} [nM]	Kd [µM]
Mast cells	KIT wild-type (WT)	20	0.008
	FYN	240	0.14
	LYN	225	0.061
Microglia	MCSFR-1	90	0.0076



Tyrosine kinase inhibitors–associated cardiovascular toxicities *



AKT, protein kinase B; Bad, Bcl-2-associated death protein; Bax, Bcl-2-associated X protein; Bcl-xL, B-cell lymphoma extra large protein; Bcr-Abl, breakpoint cluster region-Abelson protein; Casp-3, caspase 3 protein; Casp-9, caspase 9 protein; Cyt C, cytochrome C protein; EGFR, epidermal growth factor receptor; ERK, extracellular signal regulated kinase; MeK, aka MAPK – mitogen activated protein kinase; mTOR, mammalian target of rapamycin protein; Pi3K, phosphoinositide 3 kinase; RAF, rapidly accelerated fibrosarcoma protein; Src, sarcoma proto-oncogene; Ras, Ras protein superfamily; VEGFR, vascular endothelial growth factor receptor.

* Source : Onco Targets Ther. 2018

Most Frequent Questions

Questions

What happens for the patients under treatment?

- Patients already under treatment at the time of the decision can stay in the study at the investigator's decision, provided positive individual benefit/risk is documented

- This request has been approved by the ANSM, pending the completion of on-going investigations.

Questions

Is this potential risk new?

Cardiotoxicity

- Cardiotoxicity is an identified risk with certain tyrosine kinase inhibitors (TKIs)
- This has been identified at the beginning of the clinical development program as a potential risk with masitinib based on TKI class-risk and data from one animal toxicology study
- This potential risk is already described in the Investigator's Brochure and the Informed Consent for the patient

Ischemic heart disease (IHD)

- IHD is the new signal we have detected and not an identified risk

Questions

Were deaths reported from ischemic heart disease (IHD) under masitinib?

- Deaths from IHD have been reported both under masitinib and placebo
- Some patients present with comorbidities that can lead to IHD in the course of the disease itself, and so when patients enter a clinical study, such IHD events can happen and also sometimes lead to major adverse cardiac events including death, whether the receiving masitinib or the placebo
- The role of the pharmacovigilance is to continuously evaluate these events when they occur, to analyze the medical history of the patients and many other parameters to know if the drug may be involved in the more frequent occurrence of these events

Questions

Can you quantify the number of cases and the seriousness of the cases?

- Number of cases and difference between masitinib and control vary across studies
- Some ischemic events are of grade 1 such as pain in chest and others are grade 5 (death), both in control and masitinib treatment arms
- This is the analysis of all studies and all parameters that give a signal

Questions

What additional analyses requested by ANSM need to be done?

- Health Authorities usually do not rely solely on sponsors' analyses and request data to perform their own assessment
- Such data and analyses typically include raw data and listings, detailed narratives, sensitivity analyses
- AB Science is actively cooperating in all transparency with all agencies and will timely provide the requested information so that on-going investigations can be completed

Questions

When will you know the conclusion of the investigation of this potential risk?

- AB Science will communicate when investigations are completed. In order to be conservative, we do not provide forecasts
- We work in close relationship with ANSM but also other agencies in the world
- Our current expectation is to be able to address rapidly the requests from ANSM
- Agencies, like us, are patient-driven and reactive on this topic, in particular in conditions with high unmet medical need

Questions

Given the nature of this potential risk, does it modify or prevent the benefit/risk in non-oncology indications to be positive?

- First, we don’t have the position of the agency
- Second, there is an expected benefit in each of the indications pursued due to the positive clinical phase 2B/3 results, and based on expected mechanism of action in COVID-19
- Therefore, if this potential risk is materialized, an assessment will be done indication by indication
- Moreover the risk mitigation plan can be adapted

Questions

Safety was a strength of masitinib. Does it mean the program is jeopardized?

- Expected benefits are unchanged and still present

- What is at stake today is to determine if there is an increased risk and how to protect the patients, including with risk management measures such as new exclusion criteria and cardiology preventive measures during the studies

Questions

What is the probability that the studies do not restart?

- There will be a specific decision for each study
- The decision to restart for each study will depend on the conclusion of the investigation of this risk
- The Benefit/Risk ratio will have to be analysed based on these conclusions, separately for each of the current and future development programs
- The Benefit/Risk takes into account the existence or not of a new risk, the risk management plan, the medical need, and the benefit based on existing results

Questions

Why you did not see this potential risk in previous studies?

- For each study, predefined analyses were performed and did not identify any signal
- When phase 2B/3 studies were unblinded and large amount of safety data were pooled, there was one analysis in a subset of studies and a subset of patients that might be interpreted as a signal of increased risks of IHD
- After we generated this exploratory analysis, we performed multiple other analyses, which did not at this time confirm the initial signal
- The situation is therefore contradictory at this stage and that is why, since there is some doubt, we suspended the inclusions

Questions

Does this potential risk come from the on-going studies?

- This potential risk comes from a retrospective analysis of subset of completed, controlled and unblinded studies, not from on-going studies in ALS, Mastocytosis, and COVID-19

Questions

Why do you take this precautionary measures only now?

- After an initial analysis which detected a signal on a study group, meta-analyzes performed on all the studies did not confirm this signal. These analyzes are therefore contradictory

- The ANSM has requested additional data and analyzes. Therefore, we concluded that a certain level of uncertainty remains and that is why we suspended inclusions

Questions

Why this potential risk has never been seen in the past. You never did such analysis?

- Cardiovascular events, including IHD, have occurred in masitinib clinical studies
- This potential risk has been analyzed in the past but was not previously detected
- This potential signal comes after the unblinding of the phase 2B/3 studies

Questions

Does this situation affect the data of past studies?

- We shared all the analyzes with all the agencies in the same way as we did with the ANSM
- We have not yet received positions from other agencies so far

Questions

Suspension of inclusion or discontinuation of patients will delay by how much the program?

- First, patients are not discontinued, subject to documentation by the investigator of the individual benefit/risk
- The program will be extended by the duration between the hold and the restart

Questions

What is the position of other agencies apart from ANSM?

- We shared all the analyzes with all the agencies and we will collaborate with these agencies in the same way as we do with the ANSM

AB Science Portfolio

Diversified Portfolio in High Unmet Needs for Most Indications

Compound	Therapeutic area	Indication	Preclinical	Phase 1	Phase 2	Phase 2B/3	Confirmatory Phase 3
Masitinib	Neurology Diseases	1. Amyotrophic Lateral Sclerosis*					
		2. Progressive forms of Multiple Sclerosis*					
		3. Alzheimer's Disease*					
	Inflammatory Diseases	4. Indolent Systemic Mastocytosis*					
		5. Severe Asthma Uncontrolled with OCS*					
		6. Severe Asthma Uncontrolled with ICS*					
	Oncology	7. Pancreatic Cancer*					
		8. Metastatic Prostate Cancer *					
	Viral Diseases	Moderate and severe COVID-19 *(anti-inflammatory)*					
AB8939	Oncology	Acute Myeloid Leukemia					

**** Positive Phase 2B/3 Results Reported***

Q&A