AB Science Web Conference

Development Update

04 March 2024

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CONDITIONAL APPROVAL OF MASITINIB IN ALS WITH EMA AND HEALTH CANADA

Decision from EMA on conditional marketing authorization for masitinib in ALS is expected in Q2 2024 and decision from Health Canada on NOC/c reconsideration is expected in Q3 2024

EMA

- Application filed in August 2022
- Whereas an Oral Explanation was planned in January, CHMP proposed that AB Science submit a written response to the List of Outstanding Issues at D195 of the procedure, instead of addressing these issues through the Oral Explanation, which is unusual
- Decision expected in end of Q2 2024

Health Canada

- Health Canada has issued a Notice of Deficiency-Withdrawal (NOD/w)
- AB Science intends to submit a Request for Reconsideration
- Reconsideration process involves new assessors and offers the possibility to have an opinion from a panel of experts
- Decision expected in end of Q3/Q4 2024

Health Canada - Key Major Clinical Objection

Key Major Clinical Objection Outstanding

Multiple amendments have been made that create uncertainty of the reliability of the study data

Concern Resolved

- Changing study status from phase 2 to phase 3
- Multiple amendments may be an inevitable
- Amendments were not data-driven
- Study had broad inclusion criteria and there may be a need to limit heterogeneity
- Post-onset decline of 1.1 point per month may be relevant

Concern unresolved and intended counterarguments

Amendments were late and not sufficiently justified

The distinction between Normal and Fast progressors was made in an entirely blinded and sufficiently prospective manner

- Timing : 2.5 years prior to study completion
- Data accrual
  - 12% of the enrolled patients who could have reached the study's primary analysis timepoint, meaning 88% of the data remained to be acquired
  - When removing the 12% enrolled patients, the study remains positive
  - Only 8 Fast progressor patients, across 3 treatment arms could have reached the study's primary analysis timepoint
  - Study was positive at interim analysis

The amendment was justified

- Because of transition from phase 2 to phase 3, it was necessary to minimize expected high missing data due to discontinuations from Fast progressors with a long time-point of 48-weeks and with a tablet
- AB Science provided new data on discontinuation in Fast progressors at week 48, validating the necessity to exclude Fast progressors

Patient Status	Placebo	M4.5
Normal	26.5%	30.5%
Fast	**52.6%**	**56.5%**

- Decided by the PI, validated by the steering committee, all investigators and authorized by all Health Authorities

Health Canada - Key Major Clinical Objection

Key Major Clinical Objection Outstanding

Missing data have been treated in the planned primary and sensitivity analyses with LOCF, potentially creating a bias in favor of treatment

Concern Resolved

- The non-linearity of the distribution of the ALSFRS-R data set used for the test of the primary analysis (ANCOVA test) was resolved by the positive pre-specified rerandomization test

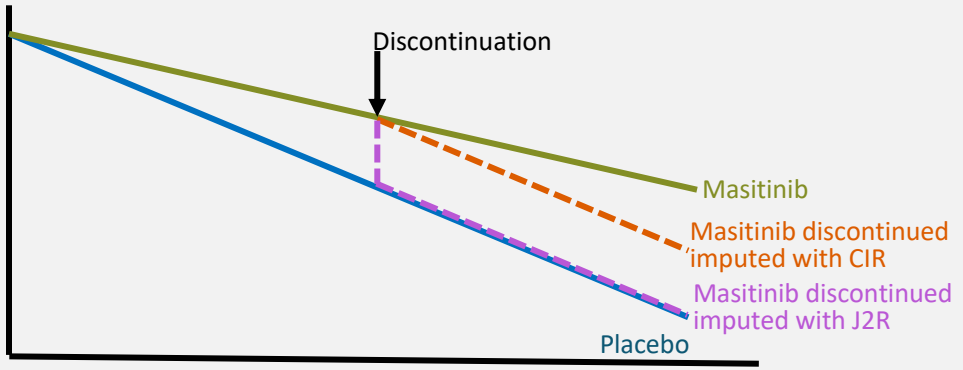
Intended counterarguments

- **Missing data is inherent to ALS trials with a 48-week endpoint**
  - 30% discontinuation at 48 weeks study is consistent with other ALS trials
- **Sensitivity analysis of the primary analysis based on non LOCF recognized methods are successful and convergent**
  - Sensitivity analysis based on Cluster Imputation is successful (p=0.0176)
  - Sensitivity analysis based on Multiple Imputation model is successful (p=0.020)
  - Sensitivity analysis based on Jump to Reference (JTR), jumping to placebo in case of masitinib discontinuation not at random due to lack of efficacy, or any AE related or not, is successful (p=0.039)
  - Sensitivity analysis based on Copy Increment in Reference (CIR) is successful (p=0.0477) CIR assumes progressive return to placebo
  - JTR and CIR have been recommended by EMA
- **CAFS endpoint, incorrectly assumed by the Agency to be based on LOCF methodology, whereas it is not, approached the conventionally statistically significant outcome of 5% (p=0.0776), even though the study was not powered for this secondary endpoint.**

Comparison of discontinuation rates

Discontinuation rate	Week 24 time-point	Week 48 time-point
Masitinib	12%	33%
AMX0035 NCT03127514	33%	
Edaravone NCT01492686 (OLE)		23%
Levosimendan NCT03505021		34%
Tirasemtiv NCT02496767		37%
Ozanezumab NCT01753076		30%

CIR versus J2R



Health Canada - Key Major Clinical Objection

Key Major Clinical Objection Outstanding

- New proposed claim in patients prior to any loss of function is considered post hoc
- OS could have been biased by confounding factors

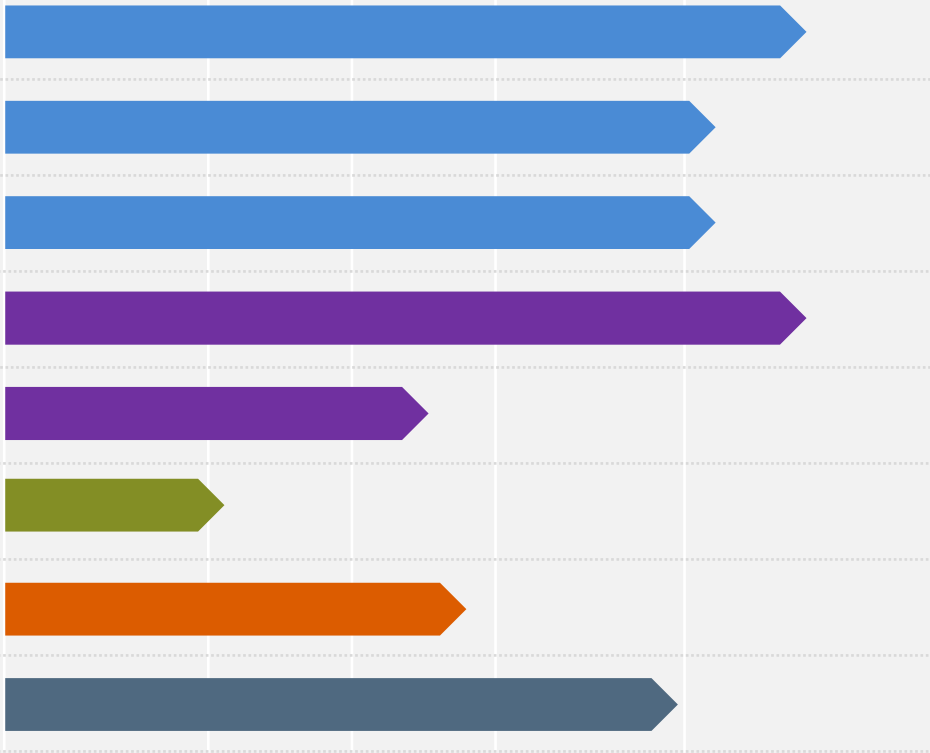
Intended counterarguments

- **EMA guidance (EMA/CHMP/539146/2013) on the investigation of subgroups in confirmatory clinical trials is applicable**
  - The Agency considered that this EMA guidance was only applicable for pre-specified subgroups
  - In fact, this EMA guidance states that “it might be of interest to identify a subgroup that has not been pre-specified as part of the confirmatory testing strategy, where efficacy and risk-benefit would be convincing”
- **In this claim, the treatment effect is exceptionally strong**
  - Significant CAFS (p= 0.0290)
  - Significant long-term median OS benefit of +10 months (p=0.0395), and +22 months (p=0.0192) when placebo-treated patients who switched to masitinib during the extension period are censored at the time of the switch
- **OS is the gold standard endpoint in ALS and is unbiased regardless of post study treatments because no drug has demonstrated OS benefit (except riluzole which was available to all patients) and because all patients had the same possibility to benefit from tracheostomy or permanent or non-permanent ventilation**

MASITINIB PLATFORM CLINICAL DEVELOPMENT PROGRAM

Masitinib offers a late stage and diversified platform primarily centered around neuro-degenerative diseases (NDD) and mast cell diseases

Therapeutic area	Indication	Preclinical	Phase I	Phase II	Phase IIB/III	Confirmatory Phase III
Neuro-degenerative Diseases	Amyotrophic Lateral Sclerosis					
	Progressive Forms of Multiple Sclerosis					
	Mild & Moderate Alzheimer's Disease					
Mast Cell Diseases	Indolent Systemic Mastocytosis					
	Mast Cell Activation Syndrome					
Blood Disorders	Sickle Cell Disease					
Viral Diseases	COVID-19					
Oncology	Metastatic refractory prostate cancer eligible to docetaxel					



In ALS, no drug has generated a consensus based on definitive evidence of efficacy

Landscape Highlights

- **AMX0035**
  - Approved at FDA based on 24 weeks study but not approved at EMA
  - Confirmatory phase III based on 48 weeks study on-going
- **Edaravone analogue**
  - Study of new oral formulation failed its primary endpoint in 48 weeks phase III study
- **RIPK1**
  - Study of RIPK1 inhibitor failed its primary endpoint
- **Tofersen**
  - Conditionally approved at FDA and EMA
  - Targets familial forms of ALS (<5% of ALS)

Masitinib Phase 3

- AB19001 study is ongoing
- Study enrollment is slower than previous study AB10015 due to its design features
  - 3 months run-in period without the drug
  - Moderate ALS only (Baseline functional score ≥ 2 on each ALSFRS-R items)
  - No concomitant ALS treatment newly registered (Edaravone, Relyvrio) other than riluzole
  - Blinded extension after week 48

Progressive MS – Positioning & Status

There is no approved drugs for non-active SPMS and only one for PPMS, and masitinib stands-out as the only non BTKi into phase 3

Landscape Highlights

- **Only Ocrevus (Roche) is approved in primary progressive MS**
- **BTKi had issues recently**
  - Tolebrutinib & Fenebrutinib on FDA hold due to liver injury
  - Evobrutinib phase III missed its primary endpoint in RRMS
- ***"This situation potentially paves the way for masitinib to emerge as a standout oral option in the landscape" (GLOBE NEWSWIRE)***

Masitinib Phase 3

- Phase 2B/3 was positive and published[1]
- Confirmatory phase 3 study is authorized by FDA and key European countries
- Initiation expected in 2024

1. Vermersch P, et al. Neurol Neuroimmunol Neuroinflamm. 2022;9(3):e1148.

PPMS: Primary progressive MS ; nSPMS:Non-active primary progressive MS ; RRMS: Relapsing Remitting MS

Masitinib is positioned in mild and moderate forms of Alzheimer's Disease

Landscape Highlights

- **Two drugs have been approved in early AD with a different positioning[1] from masitinib**
  - Lecanemab (Eisai/Biogen): MMSE [22 – 30]
  - Donanemag (Eli Lilly): MMSE [20 – 28]
  - By contrast, similar drug (gantenerumab with similar positioning (MMSE ≥ 22), failed
- **Three therapeutic strategies are pursued**
  - β-Amyloid plaque : Approved in early AD
  - Tau protein : No positive phase 3 at this time
  - Immune response and neuro-inflammation : Leading drugs starting phase 3
    - Blarcamesine (Anavex) in early and mild AD: MMSE [20 – 28]
    - Masitinib in mild/moderate AD: MMSE [14 – 25]

Masitinib Phase 3

- Phase 2B/3 was positive and published[2]
- Confirmatory phase 3 study is authorized by FDA and key European countries
- Initiation expected in 2024

1. Drugs are positioned according to severity measured with MMSE: Prodromal AD = MMSE [>26]; Mild AD = MMSE [21–26]; Moderate AD = MMSE [10–20]. NICE Technology appraisal guidance, www.nice.org.uk/guidance/ta217
2. Dubois B, et al. Alzheimers Res Ther. 2023;15(1):39.

Masitinib has a different positioning than the c-Kit816 inhibitors in indolent systemic mastocytosis

Landscape Highlights

- **Two mechanisms of action**
  - Kit816 inhibitors : avapritinib (Approved), elenestinib, bezuclastinib
  - Kit Wild Type, Lyn Fyn inhibitor: masitinib
- **The benefit of C-kit816 inhibitors and masitinib is optimum on different symptoms**
  - C-kit816 inhibitors are more effective against skin spots and GI symptoms
  - Masitinib is more effective against neurological symptoms (depression), pruritus, flush
- **The efficacy of C-kit816 inhibitors and masitinib seems similar**
  - Avapritinib : A 50% reduction of symptoms is observed for 25% of patents versus 10% with placebo[1] (15% difference)
  - Masitinib : A 75% reduction of symptoms is observed for 19% of patents versus 7% with placebo[2] (12% difference)
- **The long-term safety is well known for masitinib and at this stage is unknown for C-kit816 inhibitors**
  - Masitinib long-term safety is well known with more than 7,000 patients randomized including 1,000 exposed for more than 1 year and some patients are exposed up to 10 years
  - C-kit816 inhibitors long-term safety is unknown at this stage. Selection of clone needs to be monitored

Masitinib Phase 3

- AB15003 study is on-going
- Additionally, a phase 2 study is ongoing in MCAS (AB20006)

1. Gotlib J, et al. Avapritinib versus Placebo in Indolent Systemic Mastocytosis. NEJM Evid. 2023;2(6):EVIDoa2200339.
2. AB06006 study data

There is an increasing interest in SCD with several new drugs being in clinical development; however, unlike masitinib, none target mast cells

Landscape Highlights

- **Treatment for SCD can be curative based on gene therapy (targets the HbS mutation), but such an option remains limited due to scarcity of donors, safety challenges, and high costs**
  - Lyfgenia cost of $3.1M USD per patient, box warnings: Hematologic malignancies
  - Casgevi cost of $2.2M USD per patient, sustained increase in hemoglobin concentration
  - Target 5% of patients with severe SCD
- **Recently, new drugs have been registered by the FDA, but significant unmet need remains to reduce vaso-occlusive crisis**
  - Deferiprone: Reduction in liver iron, Box Warnings: Agranulocytosis, neutropenia
  - L-glutamine: No impact on anemia, Estimated use = 3.3%, not approved by EMA
  - Crizanlizumab: Estimated use = 2.1%, revoked by EMA
  - Voxelotor: Increases hemoglobin, Estimated use = 2.9%

Masitinib Phase 2

- Phase 2 financed by RHU program for a budget of 10M€
  - Part 1: Research of biomarkers to detect a mast cell signature
  - Part 2 : Phase 2 study to assess the efficacy of masitinib in the treatment of acute and chronic complications
- AB Science will be free to continue the development of masitinib in SCD based on phase 2 data with biomarkers

There is no drug registered in combination with docetaxel in the label metastatic prostate cancer eligible to docetaxel

Landscape Highlights

- Many drugs are registered in metastatic prostate cancer sensitive or refractory to hormonotherapy before docetaxel
- There is an unmet medical need in metastatic prostate cancer after failure to hormonotherapy and eligible to docetaxel

Masitinib Phase 3

- First phase 3 was positive
- Confirmatory phase 3
  - Scientific Advice from EMA and FDA done, validating radiographic PFS as primary endpoint and no need to prove a benefit on OS
  - Phase 3 IND submission planned in 2024

Read-out of the two Phase 2 studies expected in 2024

Two Phase 2 studies

- First Phase 2 (AB20001) evaluating masitinib anti-inflammatory activity in adult hospitalized patients in need of oxygen with moderate and severe COVID-19
- Second Phase 2 (AB21002) evaluating masitinib anti-viral activity in ambulatory or hospitalized patients with symptomatic mild and moderate COVID-19, with comorbidities

- Read-out of both studies expected in 2024

MASITINIB PARTNERSHIP

Masitinib licensing with a pharmaceutical company is expected in 2024

- Discussions are ongoing
- The process is expected to be completed by 2024
- Discussions are with companies which do not condition the signature of a binding offer to a positive opinion from EMA and Health Canada in ALS
- Scope of the license is mainly neurodegenerative indications, including ALS

AB Science is currently aiming to develop a liquid formulation for masitinib in ALS

A liquid formulation is beneficial for ALS patients

- ALS patient have difficulties in swallowing and liquid formulation will prolong administration of masitinib

A liquid formulation is beneficial for masitinib development plan

- Differential pricing will be facilitated between ALS (liquid formulation) and other indications (tablets)

Bioequivalence

- It will request bioequivalence study. The timing of the project including development of the formulation and bioequivalence is expected to be 2 years

MICROTUBULIN PLATFORM DEVELOPMENT PROGRAM

Microtubule destabilizer agents (MDAs) platform is focused in haemato-oncology with two drugs

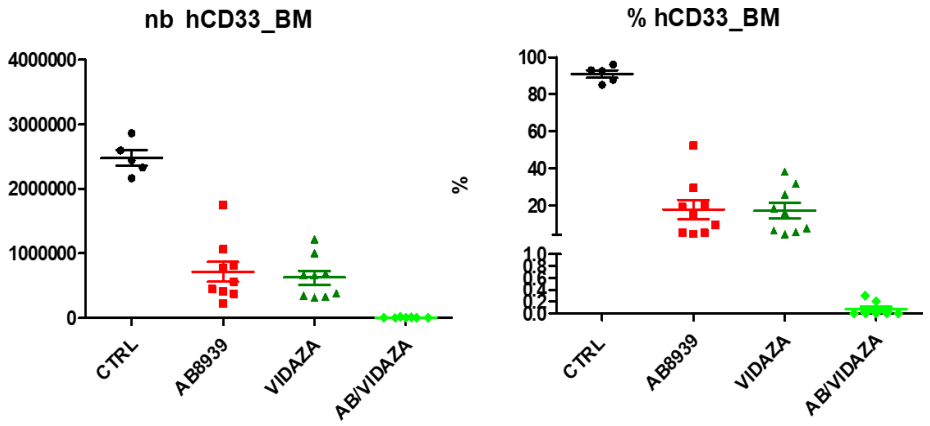
Program	Therapeutic area	Indication	Preclinical	Phase I	Phase II	Phase IIB/III	Confirmatory Phase III
AB8939 (IV)	Hematology	Acute Myeloid Leukemia (AML)					
ABXXXX (oral)	Oncology	Sarcoma, Solid Tumors					

AB8939 has the potential to improve AML treatment based on three differentiating features of its mechanism of action

Key differentiating features

- AB8939 is not metabolized by an enzyme called myeloperoxidase, produced by the disease itself, unlike other MDAs
- AB8939 avoids multidrug resistance because it does not bind and is not transported by PgP/BRCP, so it is not washed out from the cells, unlike other MDAs
- AB8939 has strong synergistic effect with reference treatment azacitidine, called Vidaza (similar to venetoclast)

Synergy with Vidaza



AB8939 has strong activity in Ara-C resistant PDX model and AB8939/azacitidine combination allows the clearing of leukemia blasts in bone marrow without adding toxicities

MTD has been reached in Step 1 of Phase 1 and key agencies have authorized to proceed with Step 2

Step 1

MTD* 3 DAYS
AB8939 alone

- Dose 1: 0.9 mg/m²
- Dose 2: 1.8 mg/m²
- Dose 3: 3.6 mg/m²
- Dose 4: 6.0 mg/m²
- Dose 5: 9.0 mg/m²
- Dose 6: 12.0 mg/m²
- Dose 7: 16.0mg/m²

- Extra doses added

Step 2

MTD 14 DAYS
AB8939 alone

- Dose 1: MTD3d- 1
- Dose 2: MTD3d

Step 3

MTD 14 DAYS
AB8939 + Azacitidine

- Dose 1: MTD14d- 1
- Dose 2: MTD14d

Step 4

MTD 28 DAYS
AB8939 alone

- Dose 1: MTD14d- 1
- Dose 2: MTD14d

- Phase 1 (steps 1 to 4) is expected to be completed in 2024
- Phase 2 will be initiated in 2025 with a the intention to design the study to support accelerated approval

Highlights of Step 1

- Neutrophil count are stabilized or even increased, which is unusual for a cytotoxic agent and could make AB8939 eligible as a chronic treatment in high-risk myelodysplastic syndrome (MDS)
- We observed a response in a MECOM rearrangement, which is a very aggressive subset of patients

INTELLECTUAL PROPERTY

Masitinib is protected until 2036 and up to 2042 through use of patents strategy

IP protection

Indication	Duration until	Orphan drug status*
Amyotrophic Lateral Sclerosis *	2037	Yes
Multiple sclerosis	2041	No
Alzheimer's disease	2041	No
Indolent systemic Mastocytosis *	2036	Yes
Sickle Cell Disease	2040	Possible
Metastatic Refractory Prostate Cancer	2042	No

* Orphan drug status granted by both EMA and FDA, providing 10 years exclusivity post-registration in Europe and 7 years in the US

AB8939 intellectual property rights in AML are secured until 2036 through a ‘composition of matter’ patent and potentially until 2044 in AML with chromosome abnormality (MECOM) through a ‘second medical use’ patent

Protection	Item	Duration of protection	Status
Patent on composition of matter	Patent on composition of matter has been filed and delivered	Until 2036	Delivered
Patent on Phase 1 ‘second medical use’	Provisional patent application filed for AML subpopulation with chromosome abnormality	Until 2044	Filed
Orphan drug status	AB8939 has been granted orphan drug designation by the FDA	Exclusivity of 7 years	Delivered