

## Web-Conference Clinical Development Update

December 2024



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AB Science has three platforms, platform 1 with masitinib, in phase 3, primarily centered around neuro-degenerative diseases, platform 2 with AB8939 in AML and platform 3 with new discovery projects



Platform	Drug	Therapeutic area Indication		Development Stage		
	Masitinib (Oral)	Neuro-degenerative Diseases (NDD)	Amyotrophic Lateral Sclerosis	Phase 3		
			Progressive Forms of Multiple Sclerosis	Phase 3		
Tyrosine Kinase			Alzheimer's Disease	Phase 3		
Inhibitor		Mast Cell Diseases	Indolent Systemic Mastocytosis	Phase 3		
			Mast Cell Activation Syndrome	Phase 2		
		Blood diseases	Sickle Cell Disease <sup>(1)</sup>	Phase 2		
Oncology Platform	AB8939 (IV)	Hematology	Acute Myeloid Leukemia (AML)	Phase 1		
	ABXXXX (oral)	Oncology	Sarcoma, Solid Tumors	Preclinical		
Drug Discovery Platform		Target 1: undisclosed for neurodegenerative diseases Target 2: undisclosed for neurodegenerative diseases		Drug Discovery		

(1) Collaborative programme with Assistance Publique - Hôpitaux de Paris (AP-HP) as sponsor, publicly funded as part of the "hospital-university health research" projects under the Future Investment Programme.

## **AB8939 PLATFORM**



### **Target Product Profile**

Pharmacology Data

Phase 1 Preliminary Safety and Efficacy

Preliminary Activity in MECOM

Planned Phases 2

Intellectual Property

AB8939 is a next generation synthetic microtubule destabilizer and targeted stem cell ALDH1/2 inhibitor with key differentiating factors for treatment of refractory/relapsing acute myeloid leukemia (AML)



#### **Scientific Rationale**

- Microtubules are critical for cell division
- Cancer cells and Microtubule
- Microtubule targeting chemotherapies are gold standard in many cancers, but, subjected to multidrug resistance (efflux by PgP) and are degraded by myeloperoxidase (produced by cancer cells) in AML

Cancer <u>stem</u> cells and ALDH

- ALDH plays critical role in cancer stem cells
- AML cells with high ALDH activity are more resistant to chemotherapeutic agents
- ALDH is over-expressed in MECOM

#### **AB8939 Target Product Profile**

#### 1. BLOCKING PROLIFERATING LEUKEMIA CELLS THROUGH MICROTUBULES

- AB8939 destabilizes microtubules
- AB8939 is not subjected to multidrug resistance (no PgP binding)
- AB8939 is not degraded by myeloperoxidase

#### 2. TARGETING OF LEUKEMIA CANCER STEM CELLS THOUGH ALDH

- AB8939 inhibits ALDH1
- AB8939 favors the bone marrow repopulation of normal progenitors

#### 3. TREATMENT OF REFRACTORY/RELAPSING AML

- AB8939 has activity seen across refractory AML cell lines
- AB8939 has an additive effect with cytarabine, azacitidine and venetoclax
- AB8939 has shown a signal of efficacy in AML with MECOM gene rearrangement, a subset of patients that show extreme resistance to chemotherapies

#### 4. LOW HEMATOLOGICAL TOXICITY

AB8939 shows absence of hematological toxicity based on clinical data

Acute Myeloid Leukemia:

 relapsed or refractory patients

**Targeted Indications** 

- and
- AML patients with MECOM gene rearrangement

### AB8939 has a potential to improve treatment of relapsed / refractory AML



		Relapsed / refracto	ry AML (R/R AML) *
	Line 1	Line 2	Line 3
Patients <u>eligible</u> to high dose chemotherapy	Anthracyclines + cytarabine + targeted therapies (IDH/FLT3)	High dose chemotherapy or Low dose chemotherapy	No approved drug Low dose chemotherapy or Best supportive care
Patients <u>ineligible</u> to high dose chemotherapy	Hypomethylating agents (azacitidine / venetoclax) + targeted therapies (IDH/FLT3)	No approved drug Low dose chemotherapy or Best supportive care	No approved drug Best supportive care
AB8939 current p	ositioning in AML	* One Menin inhibitors recently registered for R/R AML patients with KMT2Ar rearrangement or NPM1 mutation	

Anthracyclines = Daunorubicin or Idarubicin Cytarabine = Ara C Azacitidine = Vidaza Venetoclax = Venclyxto The objective is to position AB8939 combination treatment to be the standard of care in refractory/relapsing AML, which represents a market size potential above EUR 2 billions per annum, including EUR 100 millions for AML with MECOM gene rearrangement



Region	Incidence Case (1)	% Relapse or Refractory (2,3)	% Insured Patients (4)	Drug Price (€)	<b>Market Size</b> (per in in Mio EUR)
USA / CANADA	23,700		90%	100,000 <sup>(5)</sup>	1 000 000
EUROPE	27,600	50%	90%	60,000	770 000
APAC	27,800		30%	60,000	250 000
INDIA	11,000		30%	60,000	100,000
LATAM	7,200		30%	60,000	65 000
MENA	3,900		30%	60,000	35 000
TOTAL	90,200				2 200 000

EUROPE = EU27 + Norway + United Kingdom + Switzerland ; APAC = Australia, People's Republic of China , Japan, New Zealand, Singapore, Taiwan ; LATAM = Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico ; MENA = Algeria, Bahrain, Egypt, Israel, Kuwait, Morocco, Oman, Qatar, Saudi Arabia, Tunisia, United Arab Emirates.

(1) Zhou, Y et al. Global, regional, and national burden of acute myeloid leukemia, 1990–2021: a systematic analysis for the global burden of disease study 2021. Biomark Res 12, 101 (2024).

(2) Ravandi F. Relapsed acute myeloid leukemia: Why is there no standard of care Best Pract Res Clin Haematol. 2013;26(3):253-9

(3) Walter RB et al. Resistance prediction in AML: analysis of 4601 patients from MRC/NCRI, HOVON/SAKK, SWOG and MD Anderson Cancer Center. Leukemia (2015) 29:312–20.

(4) Estimated

(5) Choi M. et al. Costs per patient achieving remission with venetoclax-based combinations in newly diagnosed patients with acute myeloid leukemia ineligible for intensive induction chemotherapy. Journal of Managed Care & Specialty Pharmacy Volume 28, Number 9. https://doi.org/10.18553/jmcp.2022.22021



### Target Product Profile

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## AB8939 is active against chemotherapy naive or chemotherapy refractory/relapsing patient's AML cancers cells *ex vivo*



- 69% of blasts isolated from a cohort of 99 AML patients at diagnosis are sensitive to AB8939 (IC50<1  $\mu$ M),
- Among the blasts isolated from this cohort that are resistant to Ara-C, 66% remain sensitive to AB8939



### AB8939 eradicates blasts in Blood and Bone Marrow in 5-AraC-resistant (Cytarabine) PDX





### C. Blasts quantification in blood and bone marrow (hCD45+, flow cytometry)



#### **B.** Bioluminescence monitoring

D14



Red luminescence detects cancer cells

## AB8939 increase survival and has an additive effect in combination with reference treatment Azacitidine



#### A. Study Design



#### B. Unlike Vidaza, AB8939 does not induce any hematotoxicity



 AB8939/ vidaza combination allows the clearing of leukemia blasts in blood, spleen and bone marrow (C) without adding toxicities.





### AB8939 increase survival and has a potential additive effect in combination with reference treatment Venetoclax

# ABSCIENCE



B. AB8939 monotherapy or combined with Venetoclax is well-tolerated: absence of any toxicity (left: weight curves) or hematotoxicity (right: hematopoietic progenitors mCD45)



#### C.

AB8939/ Venetoclax combination allows the clearing of leukemia blasts in blood, spleen and bone marrow without adding toxicities.



BLOOD



## ALDHs expression is a hallmark of cancer stem cells (CSCs) and AB8939 is an inhibitor of ALDH1/2



 Reverse proteomic analysis revealed ALDHs as main AB8939 interactors Preliminary *in vitro* studies have shown that AB8939 inhibits both recombinant ALDH1A1 and ALDH2 with a sub-micromolar potency



Accession number	Gene	AB8939 beads peptides count	Control beads peptides count	Ratio 8939/contr ol	
Experiment 1 (Pool of	33 cell lines	lysates)			
P05091	ALDH2	34,5	1	34,5	
P47895	ALDH1A3	4,5	1	4,5	
P30837	ALDH1B1	7	1	7	
P00352	ALDH1A1	2	1	2	
Experiment 2 (CLS354-4 cell lysate)					
P30837	ALDH1B1	60	1	60	
P05091	ALDH2	178	4	45	
P47895	ALDH1A3	102	33	3	
P30838	ALDH3A1	7	3	2	



### AB8939 eradicates Leukemia Cancer Stem Cells in a human PDX AML model



- Preliminary AB8939 treatment eradicates most of leukemia cells in the bone marrow (step 1).
- AB8939 reduces the re-occurrence of leukemia following re-transplanted of leukemia cells indicating that AB8939 treatment eradicates both leukemic blast and leukemia cancer stem cells(Step 2).
- AB8939 is likely to kill highly dividing blasts through microtubule disruption while it kills resting cancer Stem cells through inhibition of ALDHs.





Target Product Profile

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## The objective of the phase 1 is to determine the maximum tolerated dose (MTD) for three different cycles of AB8939





Case Report 1 in non MECOM patient: Response in refractory AML patient with intermediate-risk prognosis receiving low dose of AB8939 and stable disease after at least 108 days





### Case Report 2 in non MECOM patient: Response after first cycle of 14 days



#### Step 2, 14 days, single agent AB8939 Dose



#### **Baseline characteristics (ES-07-006)**

- Patient (38 years old) with high-risk AML
- Adverse cytogenetic risk
- Mutation :+8,+21[10]
- In relapse from previous treatments (LMA flow and Flag –Ida)

### Response achieved after 1 cycles of 28 days with 14 consecutive daily injections at 21.3 $\ensuremath{\text{mg/m^2}}$

- Dramatic decrease of % blast in bone marrow after 1 cycle from **55% at baseline to 8%**
- Decrease of % blasts in blood in after 1 cycle from 3,3% to 0.6%
- Only neutrophils met hematological criteria (>1G/L) after 28 days,



Target Product Profile

Pharmacology Data

Phase 1 Preliminary Safety and Efficacy

**Preliminary Activity in MECOM** 

Planned Phases 2

Intellectual Property

## MECOM is associated with a dismal outcome, with short survival and only 14% response rate<sup>(1)</sup> in relapsed or refractory setting



t(15;17) (n=607) t(8;21) (n=421) inv(16)/t(16;16) (n=284) t(9;11) (n=61) t(6;9) (n=42) MRC/NCRI AML Trials: Overall Survival inv(3)/t(3;3) (n=69) t(9;22) (n=44\*) Ages 16-59 Other t(11q23) (n=60\*) t(3:5) (n=25\*) 100 -5/del(5q) (n=258\* -7/del(7q) (n=336\*) AML with other MDS-related (n=343\*\*) 75 % alive 50 25 MECOM

Years from entry

Impact of cytogenetic entities recognized in 2008 WHO classification24 on survival.

Survival of AML with 3q abnormality treated with AZA according to prior treatments. Survival was expressed in months and calculated using Kaplan Meier estimate.



AML: acute myeloid leukemia; IC: intensive chemotherapy.

\*Excluding patients with t(15;17), t(8;21), inv(16), t(9;11), t(6;9),inv(3)/t(3;3). \*\*Excluding patients with any other abnormalities listed previously.

Grimwade et al. Blood. 2010 Jul 22;116(3):354-65. doi: 10.1182/blood-2009-11-254441.

Wanquet et al. Am. J. Hematol. 90:859–863, 2015.

(1) G. Richard-Carpentier et al. Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2). Haematologica | 108 September 2023. https://doi.org/10.3324/haematol.2022.282030

### AB8939 is a stem cell ALDH targeted therapy with potential use in AML with MECOM

# AB SCIENCE

### **Scientific Rationale**

- ALDH gene expression is a marker of survival prognosis in AML. The higher the expression, the worse the prognosis
- MECOM is associated with the worst prognosis in AML
- Mecom is a rearrangement or a mutation of the chromosome 3 locus Q26 that codes for the transcription factor gene EVI1 (Ecotropic virus integration site-1)
- The expression of ALDH1A1 is regulated by EVI1 and has an outstanding role in the formation and transformation of hematopoietic cells and in particular leukemia stem cells
- The hypothesis is that:
  - in MECOM, the rearrangement of chromosome 3 Q26 lead to EVI1 over-expressing ALDH1A and induce high resistance of leukemia stem cells
  - AB8939 should have an impact on leukaemia stem cells by inhibiting ALDH1
  - This is what we observe in the experiment described in slide 15

## Case Report 1 in MECOM patient: Response in a refractory AML patient with MECOM rearrangement receiving low dose of AB8939





### Case Report 2 in MECOM patient: Response after first cycle of 14 days



#### Step 2, 14 days, single agent AB8939 Dose



#### **Baseline characteristics (GR-04-001)**

- Patient (63 years old) with AML with myelodysplasia-related changes
- add(2)(q13), del(3)(q21q26), add(5)(q11.2), add(12)(p13), der(13)t(2;13), (q24;q22), dlc(17;20)(p12;11.2)[13]/45,idem, -7, [13]/45, idem, der(8)t(1;8)(p32;24)[2], TP53 (VAF 75.5%)
- Adverse Cytogenetic risk category (MECOM)
- Refractory to azacitidine treatment

#### Response after 1 cycles of 14 consecutive daily injections at 16 mg/m<sup>2</sup>

- Reduction of blast bone marrow blast from 13% to 3%
- Decrease of % blasts in blood in after 1 cycle from 3,3% to 0.6%
- Increase of neutrophils: From 2,900/μL to 10,600/μL after first cycle
- Stability of platelets: From 26,000/µL to 23,000/µL after first cycle

## AB8939 has shown activity on MECOM rearrangement, based on non-clinical data and early clinical data with 50% response rate observed



#### 50% response rate in *in-vitro* tests

Non clinical in vitro evidence In-vitro, AB8939 was effective (IC50 of 50nM and 13nM) against 2 out of 4 patient blasts with MECOM rearrangement

Drug sensitivity (IC50 $\mu$ M) in MECOM Karyotype						
Patient ID	AML type	AraC	AB8939	Azacitidine		
1135	MO	>20	>2	49,90		
1156	MO	>20	>5	>50		
C1005	M1 refractory	4,1	0,05	NT		
C1012	M4 refractory	7,9	0,013	9,7		

#### Clinical evidence in MECOM

#### • 50% response rate in early phase 1

2 out of 4 patients with MECOM after 1 cycle of 3 days or 14 days AB8939 treatment below the MTD

Patient ID	AB8939	Best Response
ES-12-001	0,9 mg/m <sup>2</sup> , 3 days	Early discontinuation
ES-07-001	1.8 mg/m <sup>2</sup> , 3 days,	Response (BM blast from 55% to 5%)
ES-07-002	16 mg/m <sup>2</sup> , 14 days	Stable disease
GR-04-001	16 mg/m <sup>2</sup> ,14 days	Response (BM blast from 13% to 3%)



Target Product Profile

Pharmacology Data

Phase 1 Preliminary Safety and Efficacy

Preliminary Activity in MECOM

**Planned Phases 2** 

Intellectual Property

## The first intended step is to capture the market potential of AB8939 in patients with MECOM AML through accelerated approval based on response rate

# AB SCIENCE

#### MECOM accounts for around 5% of AML and is a sizable market >100 million euros

Region	Incidence Case (1)	Market Size (per in in Mio EUR)
R/R AML	90,200	2 200 000
AML with MECOM gene		5%
rearrangement		≈ 100

#### Seek accelerated approval based on phase 2

A possible design could be the following:

- Phase 2 single arm study
- Less than 60 patients
- AB8939 single agent or in combination (venetoclax / azacitidine)
- Objective: beat response rate of 14% based on literature <sup>(1)</sup>
- Preliminary evidence indicate 50% response rate with AB8939 single agent

<sup>(1)</sup> G. Richard-Carpentier et al. Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2). Haematologica | 108 September 2023. https://doi.org/10.3324/haematol.2022.282030

## the first MENIN inhibitor, targeting AML with specific rearrangement, has been registered based on a phase 1/2 study with less than 100 patients in relapse/refractory patients



Drug	Trial (ClinicalTrials.gov ID)	Phase	Regimen	Patient Population	Eligibility
Revumenib (SNDX-5613)	AUGMENT- 101 ( <u>NCT04065399</u> )	1/11	Revumenib monotherapy	95 Adults and 57 in phase 2	R/R KMT2Ar AL, NPM1c AML
	AUGMENT-102 ( <u>NCT05326516</u> )	Ι	-AML: Revumenib/FLA ± Revumenib/FLA -ALL/MPAL: Revumenib/Pred/VCR/ASP/DNR	30 Adults and children	R/R KMT2Ar AL, NPM1c or NUP98r AML
	(NCT05761171)	П	Revumenib/FLA, MTX	Children (recruiting)	R/R KMT2Ar ALL
	SAVE ( <u>NCT05360160</u> )	ı/II	Revumenib/ASTX727/VEN	8 Adults and children (recruiting)	R/R AML or MPAL
	BeatAML substudy ( <u>NCT03013998</u> )	Ι	Revumenib/VEN/AZA	13 Adults	Newly diagnosed KMT2Ar or NPM1c AML
Ziftomenib (KO-539)	KOMET-001 ( <u>NCT 04067336</u> )	1/11	Ziftomenib monotherapy	30 Adults	Phase 1a: R/R AML Phase 1b/2: KMT2Ar or NPM1c AML
	KOMET-007 ( <u>NCT05735184</u> )	I	-Newly diagnosed AML: Ziftomenib/7 + 3 -R/R AML: ziftomenib/VEN/AZA	20 Adults	Newly diagnosed and R/R KMT2Ar or NPM1c AML



Revumenib, from the American biotech Syndax, has been registered in AML with KMT2Ar rearrangement or NPM1 mutation with

- a phase 1/2 study of 95 adult patients including an efficacy population of 57 evaluable patients.
- complete or near-complete response rate of 23%

Ziftomenib developed by Kuva is the second Menin inhibitor in development and, like AB8939, has done phase 1 with limited number of patients

## The second objective is to capture the full market potential of AB8939 in broader forms of AML and position AB8939 in relapse/refractory



The third objective could be to also position AB8939 in first line

A possible design could be the following:

- Phase 2 controlled study
- Objective #2 : In relapsed or refractory AML as single agent or in combination, with 17,5% complete response rate as a historical control to beat based on literature <sup>(1)</sup>
- Objective #3 : Followed with First line AML in combination (venetoclax and azacitidine), with 37% complete response rate as a historical control to beat based on literature<sup>(2)</sup>

<sup>(1)</sup> Salvage Therapy Outcomes in a Historical Cohort of Patients With Relapsed or Refractory Acute Myeloid Leukaemia Ravandi, Farhad et al. Clinical Lymphoma, Myeloma and Leukaemia, Volume 20, Issue 11, e871 - e882

<sup>(2)</sup> DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E, Havelange V, Leber B, Esteve J, Wang J, Pejsa V, Hájek R, Porkka K, Illés Á, Lavie D, Lemoli RM, Yamamoto K, Yoon SS, Jang JH, Yeh SP, Turgut M, Hong WJ, Zhou Y, Potluri J, Pratz KW. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629. doi: 10.1056/NEJMoa2012971. PMID: 32786187.



Target Product Profile

Pharmacology Data

Phase 1 Preliminary Safety and Efficacy

Preliminary Activity in MECOM

Planned Phases 2

**Intellectual Property** 

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 through a 'second medical use' patent. AB Science is the sole proprietary holder of AB8939 and its family of compounds



Protection	Exclusivity period	Enforcement
Orphan drug status Composition of Matter patent	7-year protection as of FDA approval 10-year protection as of EMA approval Until February 2036	<ul> <li>Granted in the USA</li> <li>To be filed with EMA</li> <li>Granted (United States / Europe / China / Hong Kong / Japan / South Korea / India / Mexico / Israel / Brazil / South Africa / Russia / Australia)</li> </ul>
Second Medical Use patent	Until February 2044 (if granted)	<ul> <li>PCT patent application filed for AML subpopulation with chromosome abnormality</li> </ul>

## **MASITINIB PLATFORM**

### The strategy is to continue masitinib development through partnerships



- Discussion for masitinib partnership is on-going
- AB Science will provide an update of masitinib in neuro-degenerative diseases during next communication

## FINANCE

AB Science raised 5 millions euros in Q4 2024, which provides financial runway for more than 12 months



Financing Strategy

Masitinib

- Neuro-degenerative diseases : Financing through partnership
- Sickle Cell Disease : Financing of phase 2 through RHU collaborative program with APHP (9.2M€)

AB8939

- Phase 1 : Financing through equity
- Phase 2 : Financing through equity or partnership