ORYZON presents preliminary data from ongoing Phase Ib FRIDA trial with iadademstat plus gilteritinib in relapsed/refractory FLT3-mut AML patients at EHA-2024

- **Data from the first two cohorts demonstrated that combination of iadademstat plus gilteritinib was safe and showed strong antileukemic activity**
- **A third cohort is ongoing following FDA's OPTIMUS guidance**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, June 14th, 2024 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with strong unmet medical need, today presents preliminary data from its ongoing Phase Ib FRIDA study investigating iadademstat in combination with gilteritinib in relapsed/refractory acute myeloid leukemia (AML) patients harboring a FMS-like tyrosine kinase mutation (FLT3 mut+) at the European Hematology Association (EHA) 2024 congress, being held in Madrid (Spain) on June 13–16. Dr. Amir Fathi, from the Massachusetts General Hospital and Principal Investigator of the study, will present a poster communication entitled "*Preliminary results of the FRIDA study: iadademstat and gilteritinib in FLT3-mutated R/R AML*".

Dr. Carlos Buesa, Oryzon's CEO, stated, "We are very excited with these preliminary results, which showed in a mostly refractory patient population a higher-than-expected antileukemic activity in the first two cohorts. We, and others, have previously described the strong synergism of the combination of iadademstat with gilteritinib, and these clinical data confirm this synergism. The observed LSD1 full occupancy data in the first two cohorts outlines that we need to reduce the dose to optimize the marrow recovery and achieve a higher degree of complete responses. With the capability to quantify the levels of LSD1 occupancy, we are in an optimal situation to follow the FDA's OPTIMUS guidance. The safety profile is so far adequate as expected and recruitment continues."

Summary of the main results reported at EHA-2024

- The combination of iadademstat and gilteritinib appears safe and well-tolerated, with no dose limiting toxicities (DLTs) reported in the 28-day DLT evaluation period in the first two cohorts: initial cohort (n=6, iadademstat 100 µg) and DL-1 cohort (n=7, iadademstat 75 µg). There were no unexpected Treatment Emergent Adverse Events (TEAEs).

- Encouraging antileukemic activity observed, with 9 out of 13 patients (69%) achieving bone marrow (BM) blast clearance in the first cycle. Five out of 13 patients (38%) achieved complete remission

(CR), complete remission with partial hematological recovery (CRh) or complete remission with incomplete blood count recovery (CRi). Of note, 11 out of 13 patients were refractory to prior standard regimens including venetoclax, 7+3 and midostaurin. Two patients have undergone hematopoietic stem cell transplantation.

- Platelet count recovery has been slow in most patients, limiting so far a rapid transition from morphologic leukemia-free state (MLFS) to CR/CRh. Since LSD1 plays a key role in hematopoiesis and both iadademstat doses evaluated in the first two cohorts (starting dose and DL-1) showed full LSD1 target engagement (≈90%), lower doses are being investigated with the aim of maintaining efficacy and to improve platelet recovery, in accordance with the FDA's Optimus Project requiring to identify the minimum safe and biologically active dose.

- FRIDA is currently accruing patients to the third cohort, DL-2 (iadademstat 75 µg, 3 weeks treatment per cycle). Two patients have been enrolled, with no reported DLTs to date.

- Pharmacokinetic (PK) data support there is no drug-drug interaction between iadademstat and gilteritinib.

FRIDA (NCT05546580) is an escalation/expansion, open-label, single arm, multicenter Phase Ib trial to establish the safety, tolerability, and the recommended Phase II dose (RP2D) of the combination of iadademstat with gilteritinib. The study has been designed according to the FDA's Project Optimus and consists of 2 parts: a dose finding part to evaluate the safety, tolerability, pharmacokinetic, pharmacodynamic and emerging activity of the combination, and to determine the pharmacologically-active dose (i.e., the minimum safe and biologically active dose) of iadademstat in combination with gilteritinib, and an expansion part at the specific dose(s) selected to evaluate the activity of iadademstat in combination with gilteritinib in patients with FLT3-mutated R/R AML. The trial is conducted in the US and plans to accrue up to approximately 45 patients.

Oryzon is further expanding the clinical development of iadademstat in AML through an Investigator-initiated study (IIS) led by Oregon Health & Science University (OHSU). This trial is a Phase Ib dose-finding study to evaluate iadademstat in combination with the SoC, venetoclax and azacitidine, in first line AML patients and is expected to begin enrolling patients in the coming weeks. In addition, in neuroendocrine tumors, in the context of the CRADA agreement between Oryzon and the NIH, the NCI is sponsoring a randomized Phase I/II trial in 1L extensive disease small cell lung cancer combining iadademstat with immune checkpoint inhibitors. The IND for this trial was recently approved by the FDA.

A copy of the EHA-2024 poster is available here.

About Oryzon

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company and the European leader in epigenetics, with a strong focus on personalized medicine in CNS disorders and oncology. Oryzon's team is composed of highly qualified professionals from the pharma industry located in Barcelona, Boston, and San Diego. Oryzon has an advanced clinical portfolio with two LSD1 inhibitors, vafidemstat in CNS and iadademstat in oncology, in several Phase II clinical trials. The company has other pipeline assets directed against other epigenetic targets like HDAC-6, where ORY-4001 has been nominated as clinical candidate for the treatment of certain neurological disorders such as CMT and ALS. In addition, Oryzon has

a strong platform for biomarker identification and target validation for a variety of malignant and neurological diseases. For more information, visit www.oryzon.com

About Iadademstat

Iadademstat (ORY-1001) is a small oral molecule, which acts as a highly selective inhibitor of the epigenetic enzyme LSD1 and has a powerful differentiating effect in hematologic cancers (see Maes et al., Cancer Cell 2018 Mar 12; 33 (3): 495-511.e12.doi: 10.1016 / j.ccell.2018.02.002.). A FiM Phase I/IIa clinical trial with iadademstat in R/R AML patients demonstrated the safety and good tolerability of the drug and preliminary signs of antileukemic activity, including a CRi (see Salamero et al, J Clin Oncol, 2020, 38(36): 4260-4273. doi: 10.1200/JCO.19.03250). Iadademstat has shown encouraging safety and efficacy data in combination with azacitidine in a Phase IIa trial in elder 1L AML patients (ALICE trial) (see Salamero et al., ASH 2022 oral presentation). Iadademstat is currently being evaluated in combination with gilteritinib in the ongoing Phase Ib FRIDA trial in patients with relapsed/refractory AML with FLT3 mutations. Beyond hematological cancers, the inhibition of LSD1 has been proposed as a valid therapeutic approach in some solid tumors such as small cell lung cancer (SCLC), neuroendocrine tumors (NET), medulloblastoma and others. In a Phase IIa trial in combination with platinum/etoposide in second line ED-SCLC patients (CLEPSIDRA trial), preliminary activity and safety results have been reported (see Navarro et al., ESMO 2018 poster). Iadademstat is being evaluated in a collaborative Phase II basket study with the Fox Chase Cancer Center (FCCC) in combination with paclitaxel in R/R neuroendocrine carcinomas, and the company is preparing a new trial in combination with immune checkpoint inhibitors (ICI) in SCLC. Oryzon has entered into a Cooperative Research and Development Agreement (CRADA) with the U.S. National Cancer Institute (NCI) to collaborate on potential further clinical development of iadademstat in different types of solid and hematological cancers; a first trial in combination with ICI in SCLC has recently received FDA IND approval. In total iadademstat has been dosed so far to more than 130 cancer patients in four clinical trials. Iadademstat has orphan drug designation for SCLC in the US and for AML in the US and EU.

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