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Press Release

VANFLYTA® First FLT3 Inhibitor Approved in the U.S. Specifically for Patients with Newly Diagnosed *FLT3*-ITD Positive AML

- First and only FLT3 inhibitor approved across three phases of AML treatment based on QuANTUM-First results demonstrating VANFLYTA added to chemotherapy improved overall survival
- Third innovative medicine from the oncology pipeline of Daiichi Sankyo approved in the U.S.

Tokyo and Basking Ridge, NJ – (July 20, 2023) – Daiichi Sankyo (TSE: 4568) today announced that VANFLYTA® (quizartinib) has been approved by the U.S. Food and Drug Administration (FDA) in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is *FLT3*-ITD positive as detected by an FDA-approved test. VANFLYTA is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with VANFLYTA in this setting has not been demonstrated.

AML is one of the most common forms of leukemia in adults and an estimated 20,380 new cases will be diagnosed in the U.S. in 2023.[1] Up to 37% of newly diagnosed patients with AML have a *FLT3* gene mutation and approximately 80% of these are *FLT3*-ITD mutations, which drive cancer growth and contribute to increased risk of relapse and shorter overall survival.[2,3] The five-year survival rate for patients with *FLT3*-ITD AML has been reported at approximately 20%.[4]

VANFLYTA is the first and only FLT3 inhibitor to be approved by the FDA specifically for *FLT3*-ITD positive AML and across the three phases of treatment – induction, consolidation and maintenance in patients without transplant – for newly diagnosed AML. VANFLYTA will be available by prescription in the U.S. in the coming weeks.

The approval by the FDA was based on results of the QuANTUM-First trial published in *The Lancet*.[5] In QuANTUM-First, VANFLYTA combined with standard cytarabine and anthracycline induction and standard cytarabine consolidation, and continued as maintenance monotherapy following consolidation, resulted in a 22% reduction in the risk of death compared to standard chemotherapy alone (HR = 0.78 [95% CI: 0.62-0.98; 2-sided p=.0324]) in patients with newly diagnosed *FLT3*-ITD positive AML. While complete remission (CR) rates were similar between both arms of the trial, the median duration of CR was more than

three times longer at 38.6 months (95% CI: 21.9, NE) for patients receiving VANFLYTA compared to 12.4 months for those receiving placebo plus standard chemotherapy alone (95% CI: 8.8-22.7).

"The approval of VANFLYTA represents a significant advancement for the treatment of patients with newly diagnosed *FLT3*-ITD positive AML, which is one of the most aggressive and difficult-to-treat subtypes," said Harry P. Erba, MD, PhD, Professor of Medicine, Department of Medicine, Division of Hematologic Malignancies and Cellular Therapy, Duke Cancer Institute. "In the QuANTUM-First trial, VANFLYTA added to standard chemotherapy and continued as maintenance resulted in longer remission and prolonged overall survival and it will be a much-needed new treatment option that has potential to change the way *FLT3*-ITD positive AML is treated."

The safety of VANFLYTA was evaluated in 265 patients with newly diagnosed *FLT3*-ITD positive AML who received VANFLYTA once daily (35.4 mg with chemotherapy, 26.5 to 53 mg as maintenance) in the QuANTUM-First trial. VANFLYTA is approved with a Boxed WARNING for QT prolongation, torsades de pointes and cardiac arrest. Treatment emergent QT interval prolongation events of any grade were reported in 14% of patients who received VANFLYTA, including 3.0% who experienced a grade 3 or 4 event. Of the 265 patients treated with VANFLYTA and standard chemotherapy, QTcF >500 ms occurred in 2.3% of patients based on central ECG review and 10% of patients had an increase from baseline QTcF greater than 60 ms.

The most common adverse reactions (frequency ≥10% all grades with a difference between arms of ≥2%), including laboratory abnormalities, in patients receiving VANFLYTA included lymphopenia (60%), hypokalemia (59%), hypoalbuminemia (53%), hypophosphatemia (52%), alkaline phosphatase increased (51%), hypomagnesemia (44%), febrile neutropenia (44%), diarrhea (42%), mucositis (38%), nausea (34%), hypocalcemia (33%), abdominal pain (30%), sepsis (30%), neutropenia (29%), headache (28%), creatine phosphokinase increased (26%), vomiting (25%), upper respiratory tract infection (21%), hypertransaminasemia (19%), thrombocytopenia (18%), decreased appetite (17%), fungal infections (16%), epistaxis (15%), hyperkalemia (15%), herpes virus infection (14%), insomnia (14%), electrocardiogram QT prolonged (14%), hypermagnesemia (14%), hypernatremia (13%), dyspepsia (11%), anemia (11%) and eye irritation (11%).

Because of the serious risk of QT prolongation, torsades de pointes, and cardiac arrest, VANFLYTA will be available only through a restricted program called the VANFLYTA Risk Evaluation and Mitigation Strategy (REMS). VANFLYTA may only be prescribed and dispensed by certified healthcare providers and

pharmacies. More information will be available at www.VANFLYTAREMS.com or by calling 1-855-212-6670.

"Today's FDA approval of VANFLYTA is an important milestone, as patients with the *FLT3*-ITD subtype of AML can now be treated with the first ever FLT3 inhibitor approved across the three phases of treatment these patients typically receive," said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. "VANFLYTA represents the third oncology medicine from Daiichi Sankyo to be approved in the U.S. and reflects our commitment to continuously deliver innovative medicines that improve the current standard of care."

To identify patients with *FLT3*-ITD mutations who may be eligible for treatment with VANFLYTA, genetic and molecular testing of newly diagnosed patients is needed. The FDA concurrently approved a companion diagnostic test to detect *FLT3*-ITD mutations in patients with newly diagnosed AML.

Daiichi Sankyo is committed to ensuring that patients in the U.S. who are prescribed VANFLYTA can access the medication and receive appropriate financial support. Provider and patient support and information regarding distribution, access, and reimbursement will be provided, upon availability of VANFLYTA, through Daiichi Sankyo Access Central by visiting www.DSIAccessCentral.com or calling 1-866-4-DSI-NOW (1-866-437-4669).

Please see www.VANFLYTA.COM for full Prescribing Information including Boxed WARNING and Medication Guide.

About QuANTUM-First

QuANTUM-First is a randomized, double-blind, placebo-controlled global phase 3 study evaluating VANFLYTA in combination with standard induction and consolidation therapy, including HSCT, and as maintenance monotherapy, in adult patients aged 18-75 with newly diagnosed *FLT3*-ITD positive AML. Patients were randomized 1:1 to receive VANFLYTA or placebo combined with cytarabine and anthracycline induction and cytarabine consolidation chemotherapy followed by up to three years of single-agent maintenance. There was no re-randomization at the start of post consolidation therapy.

The primary endpoint of QuANTUM-First was overall survival. Secondary endpoints included event-free survival, post-induction rates of CR and composite complete remission (CRc), and the percentage of patients who achieve CR or CRc with *FLT3*-ITD measurable residual disease negativity. Safety and pharmacokinetics, along with other exploratory efficacy and biomarker endpoints including duration of CR,

were also evaluated. QuANTUM-First enrolled 539 patients at 193 study sites across Asia, Europe, North America, Oceania and South America. For more information, visit ClinicalTrials.gov.

About *FLT3*-ITD Positive Acute Myeloid Leukemia

More than 474,500 new cases of leukemia were reported globally in 2020 with more than 311,500 deaths.[6] AML accounts for 23.1% of total leukemia cases worldwide and is most common in adults.[7,1] In the U.S., an estimated 20,380 new cases of AML will be diagnosed in 2023 with the five-year survival rate reported at 31.7%.[1,8]

A number of gene mutations have been identified in AML, and *FLT3* (FMS-like tyrosine kinase 3) mutations are the most common.[3] Up to 37% of newly diagnosed cases of AML have a *FLT3* gene mutation and approximately 80% of these have *FLT3*-ITD mutations, which drive cancer growth and contribute to particularly unfavorable prognosis including increased risk of relapse and shorter overall survival.[2,3] The five-year survival rate for patients with *FLT3*-ITD AML has been reported at approximately 20%.[4]

The conventional treatment for fit patients with newly diagnosed AML is intensive induction and consolidation chemotherapy, with or without targeted therapy, and HSCT for eligible patients.[9] Options for post-consolidation / maintenance therapy are recommended for some patients who achieve remission [10]

About VANFLYTA

VANFLYTA® (quizartinib) is an oral, highly potent, type II FLT3 inhibitor that selectively targets *FLT3*-ITD mutations and has been specifically developed for patients with *FLT3*-ITD positive AML.[3]

VANFLYTA is approved in the U.S. in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD positive as detected by an FDA-approved test. VANFLYTA is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with VANFLYTA in this setting has not been demonstrated. The FDA had granted Priority Review and Fast Track Designation to VANFLYTA for this indication.

VANFLYTA also is approved in Japan for the treatment of AML that is *FLT3*-ITD mutation positive, including for use in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy and as maintenance monotherapy for adult patients with newly diagnosed *FLT3*-ITD positive AML, and as a monotherapy for relapsed/refractory AML that is *FLT3*-ITD

positive as detected by an approved test. VANFLYTA is an investigational medicine in all countries outside of Japan and the U.S.

About the VANFLYTA Clinical Development Program

The VANFLYTA clinical development program includes a phase 1/2 trial in pediatric and young adult patients with relapsed/refractory *FLT3*-ITD positive AML in Europe and North America, and several phase 1/2 combination studies as part of a strategic research collaboration with The University of Texas MD Anderson Cancer Center.

A regulatory application for VANFLYTA in newly diagnosed *FLT3*-ITD positive AML is currently under review in the EU based on the results of the QuANTUM-First trial.

Important Safety Information

WARNING: QT PROLONGATION, TORSADES DE POINTES, and CARDIAC ARREST

- **VANFLYTA® (quizartinib) prolongs the QT interval in a dose- and concentration-related manner. Prior to VANFLYTA administration and periodically, monitor for hypokalemia or hypomagnesemia, and correct deficiencies. Perform electrocardiograms (ECGs) to monitor the QTc at baseline, weekly during induction and consolidation therapy, weekly for at least the first month of maintenance, and periodically thereafter.**
- **Torsades de pointes and cardiac arrest have occurred in patients receiving VANFLYTA. Do not administer VANFLYTA to patients with severe hypokalemia, severe hypomagnesemia, or long QT syndrome.**
- **Do not initiate treatment with VANFLYTA or escalate the VANFLYTA dose if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms.**
- **Monitor ECGs more frequently if concomitant use of drugs known to prolong the QT interval is required.**
- **Reduce the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure.**
- **Because of the risk of QT prolongation, VANFLYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the VANFLYTA REMS.**

Indication

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)–positive as detected by an FDA-approved test.

Limitations of Use:

VANFLYTA is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with VANFLYTA in this setting has not been demonstrated.

Contraindications
VANFLYTA is contraindicated in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes.

Warnings and Precautions
QT Prolongation, Torsades de Pointes, and Cardiac Arrest (See BOXED WARNING)
VANFLYTA prolongs the QT interval in a dose- and concentration-dependent manner. The mechanism of QTc interval prolongation is via inhibition of the slow delayed rectifier potassium current, I_{Ks}, as compared to all other medications that prolong the QTc interval, which is via the rapid delayed rectifier potassium current, I_{Kr}.

Therefore, the level of QTc prolongation with VANFLYTA that predicts the risk of cardiac arrhythmias is unclear. Inhibition of I_{Ks} and I_{Kr} may leave patients with limited reserve, leading to a higher risk of QT prolongation and serious cardiac arrhythmias, including fatal outcomes. Torsades de pointes, ventricular fibrillation, cardiac arrest, and sudden death have occurred in patients treated with VANFLYTA.

Of the 1,081 patients with AML treated with VANFLYTA in clinical trials, torsades de pointes occurred in approximately 0.2% of patients, cardiac arrest occurred in 0.6% of patients, including 0.4% with a fatal outcome, and 0.1% of patients experienced ventricular fibrillation. These severe cardiac arrhythmias occurred predominantly during the induction phase.

Of the 265 patients with newly diagnosed FLT3-ITD–positive AML treated with VANFLYTA in combination with chemotherapy in the clinical trial, 2.3% were found to have a QTcF greater than 500 ms and 10% of patients had an increase from baseline QTcF greater than 60 ms. The clinical trial excluded patients with a QTcF ≥450 ms or other factors that increased the risk of QT prolongation or arrhythmic events (eg, NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome).

Therefore, avoid use in patients who are at significant risk of developing torsades de pointes, including uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, tachyarrhythmias, uncontrolled hypertension, high-degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism.

Do not initiate treatment with VANFLYTA if the QTcF interval is greater than 450 ms. Do not use VANFLYTA in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes. Perform an ECG and correct electrolyte abnormalities prior to initiation of treatment with VANFLYTA.

During induction and consolidation, perform an ECG prior to initiation and then once weekly during VANFLYTA treatment or more frequently as clinically indicated. During maintenance, perform ECGs prior to initiation, once weekly for at least the first month following dose initiation and escalation, and as clinically indicated thereafter.

Do not escalate the dose if QTcF is greater than 450 ms. Perform ECG monitoring of the QT interval more frequently in patients who are at significant risk of developing QT interval prolongation and torsades de pointes, or following dose escalation.

Monitor and correct hypokalemia and hypomagnesemia prior to and during treatment with VANFLYTA. Maintain electrolytes in the normal range. Monitor electrolytes and ECGs more frequently in patients who experience diarrhea or vomiting. Monitor patients more frequently with ECGs if coadministration of VANFLYTA with drugs known to prolong the QT interval is required.

Reduce the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure. Reduce VANFLYTA if QTc increases to greater than 480 ms and less than 500 ms. Interrupt and reduce VANFLYTA if QTc increases to greater than 500 ms. Permanently discontinue VANFLYTA in patients who develop recurrent QTc greater than 500 ms or QTc interval prolongation with signs or symptoms of life-threatening arrhythmia. VANFLYTA is available only through a restricted program under a REMS.

VANFLYTA REMS
VANFLYTA is available only through a restricted distribution program under a REMS called the VANFLYTA REMS because of the serious risk of QT prolongation, torsades de pointes, and cardiac arrest.

Notable requirements of the VANFLYTA REMS include the following:

- Prescribers must be certified in the VANFLYA REMS by enrolling and completing training.
- Prescribers must counsel patients receiving VANFLYTA about the risk of QT prolongation, torsades de pointes, and cardiac arrest, and provide patients with a Patient Wallet Card.
- Pharmacies that dispense VANFLYTA must be certified with the VANFLYTA REMS and must verify prescribers are certified through the VANFLYTA REMS

Further information about the VANFLYTA REMS is available at www.VANFLYTAREMS.com or by telephone at 1-855-212-6670.

Embryo-Fetal Toxicity
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VANFLYTA and for 7 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with VANFLYTA and for 4 months after the last dose.

Adverse Reactions
The safety of VANFLYTA (35.4 mg orally once daily with chemotherapy, 26.5 mg to 53 mg orally once daily as maintenance) in adult patients with newly diagnosed FLT3-ITD positive AML is based on QuANTUM-First.

Serious adverse reactions in ≥5% of patients who received VANFLYTA plus chemotherapy were: febrile neutropenia (11%). Fatal adverse reactions occurred in 10% of patients who received VANFLYTA plus chemotherapy, including sepsis (5%), fungal infections (0.8%), brain edema (0.8%), and one case each of febrile neutropenia, pneumonia, cerebral infarction, acute respiratory distress syndrome, pulmonary embolism, ventricular dysfunction, and cardiac arrest.

Permanent discontinuation due to an adverse reaction in patients in the VANFLYTA plus chemotherapy arm occurred in 20% of patients. The most frequent (≥2%) adverse reaction which resulted in permanent discontinuation in the VANFLYTA arm was sepsis (5%).

Dosage interruptions of VANFLYTA due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption in ≥2% of patients in the VANFLYTA arm included neutropenia (11%), thrombocytopenia (5%), and myelosuppression (3%).

Dose reductions of VANFLYTA due to an adverse reaction occurred in 19% of patients. Adverse reactions which required dosage reductions in ≥2% of patients in the VANFLYTA arm were neutropenia (9%), thrombocytopenia (5%), and electrocardiogram QT prolonged (4%).

The most common adverse reactions (≥10% with a difference between arms of ≥2% compared to placebo), including laboratory abnormalities, were decreased lymphocytes, decreased potassium, decreased albumin, decreased phosphorus, increased alkaline phosphatase, decreased magnesium, febrile neutropenia, diarrhea, mucositis, nausea, decreased calcium, abdominal pain, sepsis, neutropenia, headache, increased creatine phosphokinase, vomiting, upper respiratory tract infections, hypertransaminasemia, thrombocytopenia, decreased appetite, fungal infections, epistaxis, increased potassium, herpesvirus infections, insomnia, QT prolongation, increased magnesium, increased sodium, dyspepsia, anemia, and eye irritation.

Drug Interactions
Strong CYP3A Inhibitors
VANFLYTA is a CYP3A substrate. Concomitant use of VANFLYTA with a strong CYP3A inhibitor increases quizartinib systemic exposure, which may increase the risk of VANFLYTA adverse reactions. Reduce the dosage of VANFLYTA.

Strong or Moderate CYP3A Inducers
Concomitant use of VANFLYTA with strong or moderate CYP3A inducers decreases quizartinib systemic exposure, which may reduce VANFLYTA efficacy. Avoid concomitant use of VANFLYTA with strong or moderate CYP3A inducers

QT Interval–Prolonging Drugs
VANFLYTA prolongs the QT/QTc interval. Coadministration of VANFLYTA with other drugs that prolong the QT interval may further increase the incidence of QT prolongation. Monitor patients more frequently with ECG if coadministration of VANFLYTA with drugs known to prolong the QT interval is required.

Use in Specific Populations
Pregnancy
VANFLYTA can cause embryo-fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus.

Lactation
Advise women not to breastfeed during treatment with VANFLYTA and for one month after the last dose.

Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status in females of reproductive potential within 7 days before starting treatment with VANFLYTA

Contraception
Females
Advise female patients of reproductive potential to use effective contraception during treatment with VANFLYTA and for 7 months after the last dose.
Males
Advise male patients with female partners of reproductive potential to use effective contraception during treatment with VANFLYTA and for 4 months after the last dose.

Infertility
Females
Based on findings from animal studies, VANFLYTA may impair female fertility. These effects on fertility were reversible.
Males
Based on findings from animal studies, VANFLYTA may impair male fertility. These effects on fertility were reversible.

Pediatric Use
Safety and effectiveness of VANFLYTA have not been established in pediatric patients.

Geriatric Use
No overall differences in safety or efficacy were observed between patients 65 years of age and older and younger adult patients.

Renal Impairment
No dosage adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to 89 mL/min). VANFLYTA has not been studied in patients with severe renal impairment (CLcr <30 mL/min).

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment or moderate hepatic impairment. VANFLYTA has not been studied in patients with severe hepatic impairment.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc, at 1-877-437-7763 or the FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see Full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

About Daiichi Sankyo

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical need. For more information, please visit www.daiichisankyo.com.

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PP-US-VN-0083
07/23

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