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Daiichi-Sankyo

Press Release

QuANTUM-Wild Phase 3 Trial of VANFLYTA® Initiated in Patients with Newly Diagnosed *FLT3*-ITD Negative AML

Tokyo and Basking Ridge, NJ – (December 10, 2024) – The first patient has been dosed in the QuANTUM-Wild phase 3 trial evaluating Daiichi Sankyo's (TSE: 4568) VANFLYTA® (quizartinib) in combination with standard intensive induction and consolidation chemotherapy followed by single-agent maintenance in adults with newly diagnosed *FLT3*-ITD negative acute myeloid leukemia (AML).

AML is an aggressive blood cancer with a five-year overall survival rate of approximately 32%.[1, 2] Targeted therapy with FLT3 inhibitors has improved survival for some patients with *FLT3* gene mutations, which most commonly occur as *FLT3*-ITD.[3] However, about 90% of patients with AML overexpress FLT3 regardless of mutational status.[1, 4, 5] No FLT3 inhibitors are currently approved for patients without *FLT3* mutations.

"Preliminary data have shown promising results for VANFLYTA in patients with *FLT3*-ITD negative acute myeloid leukemia, which includes patients without *FLT3* mutations and patients with *TKD* mutations," said Mark Rutstein, MD, Global Head, Oncology Clinical Development, Daiichi Sankyo. "We have initiated the QuANTUM-Wild trial to further confirm the potential role of VANFLYTA combined with standard chemotherapy and as subsequent maintenance monotherapy in this broader population of patients with AML who are in need of new treatment options to potentially reduce the risk of relapse and improve overall survival."

The QuANTUM-Wild trial was initiated based on results of the QUIWI phase 2 trial evaluating VANFLYTA in combination with standard intensive chemotherapy and as subsequent maintenance monotherapy in adult patients with newly diagnosed *FLT3*-ITD negative AML. The final results of QUIWI were presented at the 2024 American Society of Hematology Annual Meeting.[6]

About the QuANTUM-Wild Trial

QuANTUM-Wild is a randomized, double-blind, placebo-controlled global phase 3 trial evaluating the efficacy and safety of VANFLYTA in combination with standard intensive induction and consolidation

therapy, including allogenic hematopoietic stem cell transplant (HSCT), followed by maintenance monotherapy, in adult patients aged 18 to 70 with newly diagnosed *FLT3*-ITD negative AML. Patients will be randomized 2:2:1 into three treatment arms. In Arms A and B, patients will receive VANFLYTA or placebo, respectively, in combination with cytarabine and anthracycline induction and cytarabine consolidation chemotherapy, followed by up to three years of single-agent maintenance therapy. The primary endpoint for Arms A and B is overall survival. Secondary endpoints include event-free survival, duration of complete response, relapse-free survival, complete remission rate (CR), CR with minimal or measurable residual disease negativity, pharmacokinetic assessments and safety measures including treatment emergent adverse events.

For purposes of exploratory analyses in the maintenance setting, patients in a third study arm (Arm C), will receive VANFLYTA in combination with intensive induction and consolidation chemotherapy followed by placebo maintenance monotherapy.

QuANTUM-Wild is expected to enroll approximately 700 patients across Asia, Australia, Europe, North America and South America. For more information, please visit ClinicalTrials.gov.

About Acute Myeloid Leukemia

One of the most common forms of leukemia in adults, AML is an aggressive blood cancer with a five-year overall survival rate of approximately 32%.[1, 2, 3] Approximately 144,000 new cases of AML were diagnosed globally with more than 130,000 deaths reported in 2021.[7]

Targeted therapy with FLT3 inhibitors has improved survival for some patients with *FLT3* gene mutations, which most commonly occur as *FLT3*-ITD.[3] However, about 90% of all patients with AML overexpress FLT3 regardless of activating mutations.[1, 4, 5] No FLT3 inhibitors are currently approved for patients without *FLT3* mutations.

FLT3 is a receptor tyrosine kinase protein that plays an important role in blood cell development but, when constitutively activated, FLT3 can contribute to AML development and growth.[8]

About VANFLYTA

VANFLYTA is an oral, highly potent and selective type II FLT3 inhibitor approved in more than 30 countries in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as maintenance monotherapy following consolidation, for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD positive based on the results from the

QuANTUM-First trial. In the U.S., VANFLYTA is not indicated as maintenance monotherapy following allogeneic HSCT; improvement in overall survival with VANFLYTA in this setting has not been demonstrated.

VANFLYTA also is approved in Japan for the treatment of patients with relapsed/refractory AML that is *FLT3*-ITD mutation positive, as detected by an approved test, based on results from the QuANTUM-R trial.

About the VANFLYTA Clinical Development Program

The VANFLYTA clinical development program includes the QuANTUM-Wild phase 3 trial in adult patients with newly diagnosed *FLT3*-ITD negative AML, a phase 1/2 trial in pediatric and young adult patients with relapsed/refractory *FLT3*-ITD positive AML in Europe, Asia and North America and several phase 1/2 combination studies as part of a strategic collaboration with The University of Texas MD Anderson Cancer Center.

VANFLYTA U.S. 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 VANFLYTA 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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References
[1] Kennedy VE, et al. *Front Oncol*. 2020;10:612880.
[2] National Cancer Institute SEER Program. Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia.
[3] Loschi M, et al. *Int J Mol Sci*. 2021;22(11):5873.
[4] Li Y, et al. *Blood*. 2004;104(4):1137-44.
[5] Gilliland G and Griffin J. *Blood*. 1 September 2002;100:5
[6] Montesinos P, et al. Abstract #1512. ASH 2024 Annual Meeting.
[7] Zhou Y, et al. *Biomark Res*. 2024;12(1):101.
[8] Daver N, et al. *Leukemia*. 2019;33(2):299–312.