swissmedic

Date: 24 June 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

VANFLYTA

International non-proprietary name: quizartinib as quizartinib dihydrochloride
Pharmaceutical form: film-coated tablet
Dosage strength(s): 26.5 mg, 17.7 mg
Route(s) of administration: oral
Marketing authorisation holder: Daiichi Sankyo (Schweiz) AG
Marketing authorisation no.: 69710
Decision and decision date: approved on 31 March 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FLT3-ITD	FMS-like tyrosine kinase 3 internal tandem duplication (mutation)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MDS	Myelodysplastic syndrome
Min	Minimum
MPN	Myeloproliferative neoplasm
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event

SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for quizartinib as quizartinib dihydrochloride in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 27 September 2018.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.

2.2.2 Approved indication

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.
VANFLYTA is not indicated for maintenance therapy after allogeneic haematopoietic stem cell transplantation (see "Properties/effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:

Before taking VANFLYTA, AML patients must have confirmation of FLT3-ITD positive AML using a CE-marked in vitro diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, confirmation of FLT3-ITD positive AML should be assessed by an alternative validated test. ECGs should be performed and electrolyte abnormalities should be corrected prior to initiation of treatment.
VANFLYTA should be administered in combination with standard chemotherapy at a dose of 35.4 mg (2 × 17.7 mg) once daily for two weeks in each cycle of induction. For patients who achieve complete remission (CR) or complete remission with incomplete haematologic recovery (CRi), VANFLYTA should be administered at a dose of 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy followed by VANFLYTA single-agent maintenance therapy initiated at 26.5 mg once daily. After two weeks, the maintenance dose should be increased to 53 mg (2 × 26.5 mg) once daily if the QT interval corrected by Fridericia's formula (QTcF) is ≤ 450 ms (see Table 2 and section 4.4). Single-agent maintenance therapy may be continued for up to 36 cycles.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	14 December 2023
Formal control completed	11 January 2024
List of Questions (LoQ)	6 May 2024
Response to LoQ	1 August 2024
Preliminary decision	1 November 2024
Response to preliminary decision	22 December 2024
Labelling corrections and/or other aspects	6 March 2025
Response to labelling corrections and/or other aspects	14 March 2025
Final decision	31 March 2025
Decision	approval

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the publicly available assessment report for VANFLYTA, published on 14 September 2023, Procedure No. EMEA/H/C/005910/0000, issued by EMA.

3 Medical context

Acute myelogenous leukaemia (AML) is a neoplastic disorder of haematopoiesis characterised by clonal expansion of myeloid progenitor cells (blasts) in the bone marrow, peripheral blood and/or other tissues.

Chemotherapy has long been the mainstay of treatment for patients with newly diagnosed AML. In patients eligible for induction chemotherapy, cytarabine in combination with an anthracycline remains the standard therapy in newly diagnosed AML, regardless of cytogenetic or molecular abnormalities.

The clinical management of AML with FLT3 mutations has been transformed by the development of multikinase inhibitors that target FLT3 mutations. The current approach is to combine them with conventional chemotherapy to increase the cytotoxic effect against leukaemia cells and reverse the poor prognosis for AML patients with FLT3 mutations (Döhner, 2017; Pollyea, 2021).

The application was submitted under Article 13 TPA with EMA as the foreign reference authority. The evaluation is partly based on the assessment of EMA as the foreign reference authority as well as previous regulatory decisions by the FDA.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority EMA The SwissPAR relating to quality aspects refers to the publicly available assessment report for VANFLYTA, published on 14 September 2023, Procedure No. EMEA/H/C/005910/0000, issued by EMA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report for VANFLYTA, published on 14 September 2023, Procedure No. EMEA/H/C/005910/0000, issued by EMA.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA and the FDA. The available assessment report and respective product information from EMA and the FDA were used as a basis for the clinical pharmacology evaluation.

6.2 Dose finding and dose recommendation

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA and the FDA. The available assessment report and respective product information from EMA and the FDA were used as a basis for the clinical pharmacology evaluation.

6.3 Efficacy

The applicant submitted the results of phase 3 study Quantum-First. Quantum-First is a double-blind placebo-controlled study evaluating quirzartinib in combination with induction and consolidation chemotherapy and as continuation therapy in patients with newly diagnosed FLT3-ITD (+) AML in comparison to a placebo arm.

Included patients were ≥18 years and ≤75 years, ECOG 0-2 with newly diagnosed primary AML or AML secondary to MDS or a MPN based on the WHO 2008 classification and presence of prospectively assessed FLT3-ITD activation mutation.

Induction therapy includes up to two cycles of cytarabine+anthracycline+quirzatinib (verum arm) or cytarabine+anthracycline+placebo (control arm). Patients with CR/CRi were allowed to start the consolidation phase, and entry to the continuation phase was possible upon blood count recovery. For details regarding study design and dosing please refer to the attached Information for healthcare professionals.

In total, 539 subjects were randomised; 268 to the quizartinib arm and 271 subjects to the placebo arm. All patients entered the induction phase and 65% entered the consolidation phase. In the consolidation phase, 30% of patients received chemotherapy followed by quirzartinib for 14 days, 2.3% of patients received allogenic HSCT only, and 32.8% received chemotherapy followed by quizartinib for 14 days followed by allogenic HSCT. No criteria for the decision to commence consolidation therapy were described in the study protocol. Overall, 39% of patients entered the continuation phase (44% quirzartinib arm, 43.3% placebo arm).

Pivotal study AC220-A-U302 met its primary endpoint of OS with a HR of 0.78 (95% CI: 0.62- 0.98) and a two-sided p value of 0.03. The median OS was 31.9 months for the quizartinib arm and 15.1 months for the placebo arm.

There was no statistically significant difference between the quizartinib and placebo arms (HR [95% CI] = 0.916 [0.754, 1.114]) for the key secondary endpoint of event-free survival (EFS) according to the FDA definition. Rates of CR, CR with FLT3-ITD MRD negativity, and CRc with FLT3-ITD MRD negativity were similar between the treatment arms.

Additional subgroup analyses for OS were provided. In patients with allogenic HSCT prior to continuation therapy (57% of patients), the HR for OS was 1.62 (95% CI: 0.62, 4.22) for the

quirzatinib arm compared with the placebo arm. In patients without allogenic HSCT prior to continuation, the HR of OS was 0.401 (95% CI: 0.192, 0.838) for the quirzatinib arm compared with the placebo arm. For further subgroup analyses depending on leukocyte count at the time of AML diagnosis, please refer to the attached Information for healthcare professionals.

6.4 Safety

Treatment with quizartinib is associated with substantial toxicity. The most frequently (>30%) reported TEAEs in the quizartinib arm in the Quantum-First study were febrile neutropenia, pyrexia, diarrhoea, hypokalaemia, and nausea. Grade 3/4 TEAEs were reported in approximately 80% of subjects in both treatment arms. The most frequently reported grade 3/4 TEAEs (≥10%) in the quizartinib arm were febrile neutropenia, neutropenia, hypokalaemia, and infections.

A higher incidence of TEAEs associated with death was reported with quizartinib compared to placebo (n=30 [11.3%] vs. n=23 [8.6%]), mainly caused by infections (mostly sepsis/septic shock). Most deaths occurred in the early induction and consolidation treatment phases. Older age and poor ECOG PS were identified as factors potentially associated with the observed early deaths in both the quizartinib and placebo arms. The higher early mortality in patients treated with quirzartinib in Quantum-First is described in the Information for healthcare professionals.

Furthermore, treatment with VANFLYTA is associated with cardiac adverse events that are critical in this vulnerable population, including QT prolongation, torsades des pointes, and cardiac arrest. A boxed warning has been included in the Information of healthcare professionals. For details, please refer to the attached Information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

The Quantum-First study met its primary endpoint of OS, demonstrating an OS difference of quizartinib add-on compared to placebo. However, additional subgroup analyses for OS depending on allogenic HSCT showed no OS benefit for patients with allogenic HSCT prior to consolidation therapy.

The safety of quirzatinib is manageable in the hands of experienced oncologists, and relevant safety risks, including the higher early mortality rate and cardiac-related risks, are adequately described in the Information for healthcare professionals.

In conclusion, the benefit-risk assessment is positive for quirzartinib in combination with induction and consolidation chemotherapy and as continuation therapy in patients with newly diagnosed FLT3-ITD (+) AML. However, a restriction of the indication, excluding maintenance therapy with quizartinib for patients with allogenic HSCT prior to continuation, was requested as a pre-approval requirement.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for VANFLYTA was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

IMPORTANT WARNING on the use of VANFLYTA: QT PROLONGATION, TORSADES DE POINTES, and CARDIAC ARREST

See full information for professionals for complete boxed warning.

- VANFLYTA prolongs the QT interval (see section “Pharmacodynamics”).

Prior to VANFLYTA administration and periodically, perform electrocardiograms (ECGs), monitor for hypokalemia or hypomagnesemia, and correct deficiencies (see sectins “Posology”, “Warnings and Precautions”).

- 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 (see sections “Contraindications”, “Warnings and Precautions”).
- 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 (see sections “Posology”, “Warnings and Precautions”).
- Monitor ECGs more frequently if concomitant use of drugs known to prolong the QT interval is required (see sections “Posology”, “Warnings and Precautions”).
- Reduce the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure (see sections “Posology”, “Warnings and Precautions”).

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

VANFLYTA

Composition

Active substances

Quizartinibum (ut Quizartinibi dihydrochloridum)

Excipients

VANFLYTA 17.7 mg film-coated tablets

Tablet core: Hydroxypropylbetadex, Cellulose, microcrystalline (E460), Magnesium stearate,
Film-coating: Hypromellose (E464), Talc (E553b), Triacetin (E1518), Titanium dioxide (E171).

VANFLYTA 26.5 mg film-coated tablets

Tablet core: Hydroxypropylbetadex, Cellulose, microcrystalline (E460), Magnesium stearate,
Film-coating: Hypromellose (E464), Talc (E553b), Triacetin (E1518), Titanium dioxide (E171), Yellow iron oxide (E172).

Pharmaceutical form and active substance quantity per unit

Film-coated tablet (tablet).

VANFLYTA 17.7 mg film-coated tablets

Each film-coated tablet contains 17.7 mg quizartinib corresp. 20 mg quizartinib dihydrochloride. White, round-shaped film-coated tablets, 8.9 mm in diameter and debossed with ‘DSC 511’ on one side.

VANFLYTA 26.5 mg film-coated tablets

Each film-coated tablet contains 26.5 mg quizartinib corresp. 30 mg quizartinib dihydrochloride. Yellow, round-shaped film-coated tablets, 10.2 mm in diameter and debossed with ‘DSC 512’ on one side.

Indications/Uses

VANFLYTA is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive.

VANFLYTA is not indicated for maintenance therapy after allogeneic haematopoietic stem cell transplantation (see “Properties/effects”).

Dosage/Administration

Treatment with VANFLYTA should be initiated by a physician experienced in the use of anti-cancer therapies.
Before taking VANFLYTA, patients must have confirmation of FLT3-ITD positive AML using a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, confirmation of FLT3-ITD positive AML should be assessed by an alternate validated test.
ECGs should be performed, and electrolyte abnormalities should be corrected prior to initiation of treatment (see “Warnings and precautions”).

Posology

A treatment course consists of up to 2 cycles of VANFLYTA in combination with induction cytarabine and anthracycline, up to 4 cycles of VANFLYTA in combination with high-dose cytarabine consolidation, and up to 36 cycles of VANFLYTA as maintenance therapy or until disease progression or unacceptable toxicity. VANFLYTA should be administered in combination with standard chemotherapy at a dose of 35.4 mg (2 × 17.7 mg) once daily for two weeks in each cycle of induction. For patients who achieve complete remission (CR) or complete remission with incomplete

haematologic recovery (CRi), VANFLYTA should be administered at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy.
VANFLYTA maintenance therapy should be initiated following consolidation chemotherapy upon blood count recovery of absolute neutrophil count >500/mm^3 and platelet count >50,000/mm^3.
VANFLYTA single-agent maintenance therapy is administered according to dosing information in Tables 1 to 3 and “Warnings and precautions”. Single-agent maintenance therapy may be continued for up to 36 cycles.
For additional dosing information see Tables 1 to 3.

Table 1: Dose regimen

VANFLYTA initiation	**Induction** [a]	**Consolidation** [b]	**Maintenance**
	Starting on day 8 (For 7 + 3 regimen) [c]	**Starting on day 6**	**First day of maintenance therapy**
Dose	35.4 mg once daily	35.4 mg once daily	• Starting dose of 26.5 mg once daily for two weeks if QTcF is ≤ 450 ms. • After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg once daily. • Maintain the 26.5 mg once daily dose if QTcF greater than 500 ms was observed during induction or consolidation.
Duration (28-day cycles)	Two weeks in each cycle (day 8 to 21)	Two weeks in each cycle (day 6 to 19)	Once daily with no break between cycles for up to 36 cycles.

[a] Patients can receive up to 2 cycles of induction.

[b] Patients can receive up to 4 cycles of consolidation.

[c] For 5 + 2 regimen as the second induction cycle, VANFLYTA will be started on day 6.

Haematopoietic stem cell transplantation

For patients who proceed to haematopoietic stem cell transplantation (HSCT), VANFLYTA should be stopped 7 days before the start of a conditioning regimen.

Dose modifications

VANFLYTA should be initiated only if QTcF is ≤ 450 ms (see see “Warnings and precautions”).
For recommended dose modifications due to adverse reactions, see Table 2. For dose adjustments due to adverse reactions and/or concomitant use with strong CYP3A inhibitors, see Table 3.

Table 2: Recommendation for dose reduction in case of adverse effects

Adverse reaction	Recommended action
QTcF 450-480 ms (Grade 1)	• Continue VANFLYTA dose.
QTcF 481-500 ms (Grade 2)	• Reduce VANFLYTA dose (see Table 3) without interruption. • Resume VANFLYTA at the previous dose in the next cycle if QTcF has decreased to < 450 ms. Monitor the patient closely for QT prolongation for the first cycle at the increased dose.
QTcF ≥ 501 ms (Grade 3)	• Interrupt VANFLYTA. • Resume VANFLYTA at a reduced dose (see Table 3) when QTcF returns to < 450 ms. • Do not escalate to 53 mg once daily during maintenance if QTcF > 500 ms was observed during induction and/or consolidation. Maintain the 26.5 mg once daily dose.
Recurrent QTcF ≥ 501 ms (Grade 3)	• Permanently discontinue VANFLYTA if QTcF > 500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (e.g., serum electrolyte abnormalities, concomitant QT prolonging medicinal products).
Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of life-threatening arrhythmia (Grade 4)	• Permanently discontinue VANFLYTA.
Grade 3 or 4 non-haematologic adverse reactions	• Interrupt VANFLYTA. • Resume treatment at the previous dose if adverse reaction improves to ≤ Grade 1. • Resume treatment at a reduced dose (see Table 3) if adverse reaction improves to < Grade 3. • Permanently discontinue if Grade 3 or 4 adverse reaction persists beyond 28 days.
Persistent Grade 4 neutropenia or thrombocytopenia without active bone marrow disease	• Reduce the dose (see Table 3).

Grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

Dose adjustments for adverse reactions and/or concomitant use with strong CYP3A inhibitors

Table 3: Recommendation for dose reduction with concomitant use of strong CYP3A inhibitors

Phase of treatment	Full dose	Dose Reductions		
		Adverse reaction	Concomitant strong CYP3A inhibitors	Adverse reaction and concomitant strong CYP3A inhibitors
Induction or Consolidation	35.4 mg	26.5 mg	17.7 mg	Interrupt
Maintenance (first two weeks)	26.5 mg	Interrupt	17.7 mg	Interrupt
Maintenance (after two weeks)	53 mg	35.4 mg	26.5 mg	17.7 mg

Missed dose or vomiting

If a dose of VANFLYTA is missed or not taken at the usual time, the patient should take the dose as soon as possible on the same day and return to the usual schedule the following day. The patient should not take two doses on the same day.

If the patient vomits after taking VANFLYTA, the patient should not take an additional dose that day but take the next dose the following day at the usual time.

Special dosage instructions

Elderly patients

No dose adjustment is required in the elderly.

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. VANFLYTA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C), as safety and efficacy have not been established in this population.

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. VANFLYTA is not recommended for use in patients with severe renal impairment (CLcr < 30 mL/min, estimated by Cockcroft-Gault), as safety and efficacy have not been established in this population.

Paediatric population

VANFLYTA is not authorised for use in the paediatric population.

Mode of administration

VANFLYTA is for oral use.
The film-coated tablets should be taken at approximately the same time each day with or without food. The film-coated tablets should be taken whole, without splitting, crushing or dissolving.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section "Composition".
- Congenital long QT syndrome (see "Warnings and precautions").
- Breast-feeding (see "Pregnancy, lactation").
- Severe hypokalemia, severe hypomagnesemia, or patients with a history of ventricular arrhythmias or torsades de pointes (see section "Warnings and Precautions").

Warnings and precautions

QT interval prolongation

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, IKs, as compared to all other medications that prolong the QTc interval, which is via the rapid delayed rectifier potassium current, IKr. Therefore, the level of QTc prolongation with VANFLYTA that predicts the risk of cardiac arrhythmias is unclear. Inhibition of IKs and IKr may leave patients with limited reserve leading to a higher risk of QT prolongation and serious cardiac arrhythmias, including fatal outcomes (see section "Pharmacodynamics"). 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%, including 0.4% with a fatal outcome, and 0.1% of patients experienced ventricular fibrillation (see section "Undesirable Effects"). 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 (e.g., NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome). Therefore, avoid use in patients who are at risk of developing torsades

de pointes, including uncontrolled or significant cardiac disease (e.g., history of second-or third-degree heart block [without pacemaker], recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, tachyarrhythmias, uncontrolled hypertension, high-degree atrioventricular block, severe aortic stenosis), uncontrolled hypothyroidism, and patients receiving concomitant medicinal products known to prolong the QT interval. Electrolytes should be maintained in the normal range (see “Dosage/Administration”).
VANFLYTA must not be used in patients with congenital long QT syndrome.
Do not start treatment with VANFLYTA if the QTcF interval is greater than 450 ms.
During induction and consolidation, ECGs should be performed prior to initiation and then once weekly during quizartinib treatment or more frequently as clinically indicated.
During maintenance, ECGs should be performed prior to initiation and then once weekly for the first month following dose initiation and escalation, and thereafter as clinically indicated. The maintenance starting dose should not be escalated if the QTcF interval is greater than 450 ms (see Table 1).
Permanently discontinue VANFLYTA in patients who develop QT interval prolongation with signs or symptoms of life-threatening arrhythmia (see “Dosage/Administration”).
ECG monitoring of the QT interval should be performed more frequently in patients who are at significant risk of developing QT interval prolongation and torsade de pointes.
Monitoring and correction of hypokalaemia and hypomagnesaemia should be performed prior to and during treatment with VANFLYTA. More frequent monitoring of electrolytes and ECGs should be performed in patients who experience diarrhoea or vomiting.

ECG monitoring with QT interval prolonging medicinal products

Patients should be monitored more frequently with ECG if co-administration of VANFLYTA with medicinal products known to prolong the QT interval is required (see “Interactions”).

Co-administration with strong CYP3A inhibitors

The dose of VANFLYTA should be reduced when used concomitantly with strong CYP3A inhibitors as they may increase quizartinib exposure (see “Dosage/Administration”and “Interactions”).

Increased mortality due to infections

In the study Quantum-First, an increased mortality mainly during the initial 60 days has been observed under quizartinib, compared to the control arm. Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients especially in the early treatment period.
This imbalance was due to the grade 5 infections, mainly sepsis and septic shock (see “*Undesirable effects”*).
Patients should be closely monitored for the occurrence of severe infections during induction.

Women of childbearing potential/Contraception in males and females

Based on findings in animals, quizartinib may cause embryo-foetal harm when administered to a pregnant woman. Women of childbearing potential should undergo pregnancy testing within 7 days before starting treatment with VANFLYTA. Women of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 7 months after the last dose. Male patients with female partners of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 4 months after the last dose (see “Pregnancy, lactation”).

Patient card

The prescriber must discuss the risks of VANFLYTA therapy with the patient. The patient will be provided with the patient card with each prescription (included in the medicinal product pack).

Interactions

Quizartinib and its active metabolite AC886 are primarily metabolised by CYP3A.

Effect of other medicinal products on VANFLYTA

Strong CYP3A/P-glycoprotein (P-gp) inhibitors

Co-administration of ketoconazole, a strong CYP3A/P-gp inhibitor, with a single dose of VANFLYTA increased quizartinib exposure and decreased AC886 exposure compared to VANFLYTA alone (Table 4). Increased quizartinib exposure may increase the risk of toxicity.
The dose of VANFLYTA should be reduced as shown in the table below if concomitant use with strong CYP3A inhibitors cannot be avoided. For more details regarding dose adjustments, see Table 3 in “Dosage/Administration”.

Full dose	**Dose reductions for concomitant use with strong CYP3A inhibitors**
26.5 mg	17.7 mg
35.4 mg	
53 mg	26.5 mg

Examples of strong CYP3A/P-gp inhibitors include itraconazole, posaconazole, voriconazole, clarithromycin, nefazodone, telithromycin and antiretroviral medicinal products (Certain medicines used to treat HIV may either increase the risk of side effects (e.g., ritonavir) or reduce the effectiveness (e.g., efavirenz or etravirine) of VANFLYTA).

Moderate CYP3A inhibitors

Co-administration of fluconazole, a moderate CYP3A inhibitor, with a single dose of VANFLYTA only had a minor effect on the quizartinib and AC886 exposure (Table 4), which is not considered clinically relevant. No dose modification is recommended.

Strong or moderate CYP3A inducers

Co-administration of efavirenz, a moderate CYP3A inducer, with a single dose of VANFLYTA lead to a strong decrease of quizartinib and A886 exposure, compared to VANFLYTA alone (Table 4) (see “Properties/Effects”).
Decreased quizartinib exposure may lead to reduced efficacy. Co-administration of VANFLYTA with strong or moderate CYP3A inducers should be avoided.
Examples of strong CYP3A4 inducers include apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin and certain herbal medicinal products such as St. John’s Wort (also known as *Hypericum perforatum*). Examples of moderate CYP3A4 inducers include efavirenz, bosentan, etravirine, phenobarbital and primidone.

QT interval prolonging medicinal products

Co-administration of VANFLYTA with other medicinal products that prolong the QT interval may further increase the incidence of QT prolongation. Examples of QT prolonging medicinal products include but are not limited to antifungal azoles, ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine and tacrolimus. Caution should be used when co-administering medicinal products that prolong the QT interval with VANFLYTA (see “Warnings and precautions”).

Gastric acid reducing agents

Proton pump inhibitor lansoprazole slightly decreased quizartinib exposure (Table 4). This decrease in quizartinib absorption was not considered clinically relevant. No dose modification is recommended.

P-gp Inhibitoren

In vitro studies showed that quizartinib is a substrate for P-gp. However, the single-dose administration of quizartinib with ketoconazole, a strong inhibitor for both CYP3A and P-gp, increased quizartinib C_{max} only slightly, suggesting that the effect of P-gp is minimal. As dose adjustment is required for concomitant strong CYP3A inhibitors, many of which also inhibit P-gp, no specific dose adjustment is required for P-gp inhibitors alone.

Additional transporters

In vitro studies showed that quizartinib is not a substrate for BCRP, OATP1B1, OATP1B3, OCT1, OAT2, MATE1 or MRP2. AC866 is a substrate for BCRP, but not for OATP1B1, OATP1B3, MATE1 or MRP2.

Effect of VANFLYTA on other medicinal products

P-glycoprotein (P-gp) substrates

Co-administration of quizartinib and dabigatran etexilate (a P-gp substrate) slightly increased exposure of total and free dabigatran (see table 4 and “Properties/Effects”). Quizartinib is a weak P-gp inhibitor, and no dose modification is recommended when P-gp substrates are co-administered with VANFLYTA.

Uridine diphosphate glucuronosyltransferases (UGT)1A1 substrates

Quizartinib inhibits UGT1A1 with an estimated *in vitro* Ki of 0.78 µM. Based on a physiologically based pharmacokinetic (PBPK) analysis, quizartinib was predicted to increase the C_{max} and AUC_{inf} of raltegravir (a UGT1A1 substrate) by 1.03-fold which was not considered clinically relevant.

Table 4 indicates the geometric mean ratio (GMR) of the pharmacokinetic parameters in case of use with/without concomitant medication along with the 90% confidence intervals (CI).

Table 4: Interactions between quizartinib and AC886 with other medicines

Active substance according to therapeutic area **(dosage recommendation)**	**Effect on medicines concentration** **GMR (90%-KI)** **(potential interaction mechanism)**
Ketoconazol (200 mg b.i.d. for 28 days), Quizartinib (30 mg single dose)	Quizartinib: AUC_{inf}: 1.94 (1.69, 2.23) C_{max}: 1.17 (1.05, 1.30) AC886: AUC_{inf}: 0.85 (0.68, 1.05) C_{max}: 0.40 (0.31, 0.51) (strong inhibition of CYP3A)
Fluconazol (200 mg b.i.d. for 28 days), Quizartinib (30 mg single dose)	Quizartinib: AUC_{inf}: 1.20 (1.04, 1.38) C_{max}: 1.11 (1.00, 1.24) AC886: AUC_{inf}: 1.14 (0.93, 1.40) C_{max}: 1.02 (0.80, 1.31)

	(moderate inhibition of CYP3A)
Efavirenz (600 mg q.d. for 14 days), Quizartinib (60 mg single dose)	Quizartinib: AUC_{inf}: 0.10 (0.08, 0.14) C_{max}: 0.55 (0.45, 0.67) AC886: AUC_{inf}: 0.04 (0.03, 0.05) C_{max}: 0.32 (0.24, 0.44) (Induction von CYP3A)
Lansoprazol (60 mg for 4 days), Quizartinib (30 mg single dose)	Quizartinib: AUC_{inf}: 0.95 (0.80, 1.13) C_{max}: 0.86 (0.78, 0.95) AC886: AUC_{inf}: 0.82 (0.68, 0.99) C_{max}: 0.77 (0.57, 1.04) (increase of gastric pH value)
Dabigatranetexilat (150 mg single dose), Quizartinib (60 mg single dose)	total Dabigatran: AUC_{inf}: 1.13 (0.79, 1.61) C_{max}: 1.12 (0.78, 1.61) free Dabigatran: AUC_{inf}: 1.11 (0.77, 1.60) C_{max}: 1.13 (0.77, 1.65) (inhibition of P-gp)

AUC_{inf} = Area under the plasma concentration-time curve from time point zero until infinity; b.i.d. = twice a day; CI = confidence interval; C_{max} = maximum measured plasma concentration; GMR = geometric mean ratio of the pharmacokinetic parameters in case of use with/without concomitant medication

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should undergo pregnancy testing within 7 days before starting treatment with VANFLYTA.

Quizartinib may cause embryo-foetal harm when administered to pregnant women (see “Preclinical data”); therefore, women of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 7 months after the last dose.

Male patients with female partners of childbearing potential should use effective contraception during treatment with VANFLYTA and for at least 4 months after the last dose.

Pregnancy

There are no data on the use of quizartinib in pregnant women. Based on findings in animals, quizartinib may cause embryo-foetal toxicity when administered to pregnant women (see “Preclinical data”).

VANFLYTA should not be used during pregnancy and in women of childbearing potential not using contraception, unless the clinical condition of the woman requires treatment. Pregnant women should be advised of the potential risk to the foetus.

Lactation

It is unknown whether quizartinib or its active metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Because of the potential for serious adverse reactions in breast-fed children, women must not breast-feed during treatment with VANFLYTA and for at least 5 weeks after the last dose (see “Contraindications”).

Fertility

There are no human data on the effect of quizartinib on fertility. Based on findings in animals, female and male fertility may be impaired during treatment with VANFLYTA (see “Preclinical data”).

Effects on ability to drive and use machines

VANFLYTA has a potential influence on the ability to drive and use machines. Occurrence of life-threatening ventricular tachycardia can result in impairment of the patient's ability to drive or operate machinery.

Undesirable effects

Summary of the safety profile

The pooled safety population has been evaluated for patients who received at least one dose of quizartinib, 30-60 mg (n = 669) across multiple clinical studies.
The most common adverse reactions in this population (n=669) were infections and infestations (70.7%), decreased lymphocyte count (68.6%), decreased white blood cell count (58.9%), decreased hemoglobin (55.2%), decreased platelet count (53.8%), increased alanine aminotransferase (51.0%), increased alkaline phosphatase (46.5.%), decreased potassium (45.4%), bleeding events (45.1%), decreased neutrophil count (45.0%), increased aspartate aminotransferase (43.5%), nausea (40.8%), febrile neutropenia (38.9%), pyrexia (38.9%), diarrhoea (32.9%), decreased magnesium (30.9%), increased bilirubin (30.5%), vomiting (29.1%), abdominal pain (25.4%), oedema (24.1%), headache (23.5%), and fatigue (20.6%).
The most common Grade 3 or 4 adverse reactions were decreased lymphocyte count (56.1%), decreased white blood cell count (54.4%), decreased platelet count (49.5%), decreased haemoglobin (45.4%), decreased neutrophil count (42.3%), infections and infestations (40.4%), febrile neutropenia (37.2%), decreased potassium (15.2%), pneumonia (12.9%), sepsis (9.9%), bleeding events (8.2%), increased alanine aminotransferase (7.5%), bacteraemia (6.4%), increased bilirubin (5.1%), pyrexia (3.9%), increased aspartate aminotransferase (3.7%), decreased appetite (3.7%), electrocardiogram QT prolonged (3.1%), urinary tract infection (3.0%), and fungal infections (3.0%).

The most common serious adverse reactions were Infections and infestations (34.7%), febrile neutropenia (15.8%), pneumonia (11.1%), sepsis (9.0%), bleeding events (6.6%), pyrexia (3.9%), bacteraemia (2.8%), septic shock (2.8%), neutropenia (2.4%) and urinary tract infection (2.1%).
Adverse reactions with fatal outcome were Infections and infestations (6.6%), sepsis (1.9%), pneumonia (1.9%), septic shock (1.6%), bleeding events (1.3%), fungal infections (0.4%), cardiac arrest (0.3%), febrile neutropenia (0.3%), upper respiratory tract infection (0.1%) and thrombocytopenia (0.1%) .
The most common adverse reactions associated with dose interruption of VANFLYTA were Infections and infestations (9.9%), neutropenia (6.0%), pneumonia (3.3%), febrile neutropenia (3.1%), thrombocytopenia (3.0%) and prolonged electrocardiogram QT interval (3.1%).
The most common adverse reactions associated with dose reduction were prolonged electrocardiogram QT interval (5.7%), neutropenia (5.4%) thrombocytopenia (3.1%) and Infections and infestations (2.1%).
The most common adverse reaction associated with permanent discontinuation of VANFLYTA were Infections and infestations (6.1%), bleeding events (1.9%), septic shock (1.5%), pneumonia (1.3%), sepsis (1.3%), neutropenia (0.9%), thrombocytopenia (0.6%), electrocardiogram QT prolonged (0.6%), febrile neutropenia (0.6%).

Tabulated list of adverse reactions

The adverse reactions are presented by system organ class according to MedDRA. The frequencies are according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (based predominantly on spontaneous reports from market surveillance, exact frequency cannot be estimated on the basis of the available data).

Table 5: Adverse reactions

System organ class Adverse reaction	**All grades (%)**	**Grade 3 or 4 (%)**	**Frequency category (All grades)**
Infections and infestations			
Pneumonia[a]	19.1	12.9	Very common
Upper respiratory tract infections[b]	19.0	3.1	Very common
Sepsis[c]	12.7	9.9	Very common
Fungal infections[d]	10.6	3.0	Very common
Herpes infections[e]	10.3	1.8	Very common
Bacteraemia[f]	8.5	6.4	Common
Urinary tract infection[g]	7.2	3.0	Common
Septic shock	3.0	1.3	Common
All other infections[h]	49.5	21.4	Very common
Blood and lymphatic system disorders			
Lymphocytopenia[i]	68.6	56.1	Very common

Leukopenia[i]	58.9	54.4	Very common
Anaemia[i]	55.2	45.4	Very common
Thrombocytopenia[i]	53.8	49.5	Very common
Neutropenia[i]	45.0	42.3	Very common
Febrile neutropenia	38.9	37.2	Very common
Pancytopenia	2.5	2.4	Common
Metabolism and nutrition disorders			
Decreased appetite	18.2	3.7	Very common
Nervous system disorders			
Headache[j]	23.5	0.4	Very common
Dysgeusia	6.0	0	Common
Cardiac disorders			
Cardiac arrest	0.4	0.1	Uncommon
Ventricular fibrillation	0.1	0.1	Uncommon
Vascular disorders			
Bleeding events[k]	45.1	8.2	Very common
Gastrointestinal disorders			
Nausea	40.8	2.5	Very common
Diarrhoea	32.9	2.8	Very common
Vomiting	29.1	2.4	Very common
Abdominal pain[l]	25.4	1.9	Very common
Stomatitis	16.6	2.5	Very common
Dyspepsia	9.7	0.3	Common
Hepatobiliary disorders			
ALT increased[i]	51.0	7.5	Very common
ALP increased[i]	46.5	1.5	Very common
AST increased[i]	43.5	3.7	Very common
Bilirubin increased[i]	30.5	5.1	Very common
Skin and subcutaneous tissue disorder			
Rash	19.3	1.6	Very common
General disorders and administration site conditions			
Pyrexia	38.9	3.9	Very common
Oedema[m]	24.1	0.7	Very common
Fatigue	20.6	2.7	Very common
Investigations			
Potassium decreased[i]	45.4	15.2	Very common
Magnesium decreased[i]	30.9	1.3	Very common
Prolonged electrocardiogram QT[n]	20.0	3.1	Very common
Weight decreased	6.3	0.3	Common

Standard chemotherapy = cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin).
[a] Pneumonia include Pneumonia, Pneumonia fungal, Pneumonia respiratory syncytial viral, Atypical pneumonia, Pneumonia klebsiella, Pneumonia pseudomonal, Pneumonia staphylococcal, Pneumonia bacterial, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia streptococcal, Organising pneumonia, Pneumonia aspiration.
[b] Upper respiratory tract infections include Upper respiratory tract infection, Nasopharyngitis, Sinusitis, Rhinitis, Tonsillitis, Laryngopharyngitis, Pharyngitis bacterial, Pharyngotonsillitis, Viral pharyngitis, Acute sinusitis, Pharyngitis, Viral upper respiratory tract infection, Laryngitis, Tonsillitis bacterial.
[c] Sepsis include Sepsis, Neutropenic sepsis, Klebsiella sepsis, Staphylococcal sepsis, Escherichia sepsis, Bacterial sepsis, Enterococcal sepsis, Streptococcal sepsis, Candida sepsis, Enterobacter sepsis, Urosepsis, Clostridial sepsis, Fungal sepsis, Haemophilus sepsis, Pneumococcoal sepsis, Pseudomonal sepsis, Pulmonary sepsis.
[d] Fungal infections include Oral candidiasis, Bronchopulmonary aspergillosis, Fungal infection, Vulvovaginal candidiasis, Aspergillus infection, Lower respiratory tract infection fungal,Oral fungal infection, candida infection, Fungal skin infection, Mucormycosis, Oropharyngeal candidiasis, Aspergillosis oral, Hepatic infection fungal, Hepatosplenic candidiasis, Onychomycosis, Fungaemia, Systemic candida, Systemic mycosis.
[e] Herpes infections include Oral herpes, Herpes zoster, Herpes virus infections, Herpes simplex, Human herpesvirus 6 infection, Genital herpes, Herpes dermatitis.
[f] Bacteremia includes Bacteraemia, Klebsiella bacteraemia, Staphylococcal bacteraemia, Enterococcal bacteraemia, Streptococcal bacteraemia, Device related bacteraemia, Escherichia bacteraemia, Corynebacterium bacteraemia, Pseudomonal bacteraemia.
[g] Urinary tract infection include Urinary tract infection, Urinary tract infection bacterial, Escherichia urinary tract infection, Urinary tract infection enterococcal, Urinary tract infection fungal.
[h] All other infections include all PTs under SOC 'Infections and infestations' that occur at a frequency ≥ 1.0 % which include bronchitis, cellulitis, skin infection, cystitis, vascular device infection, folliculitis, conjunctivitis, clostridium difficile infection, influenza, device related infection, staphylococcal infection, respiratory tract infection, clostridium difficile colitis, gingivitis, catheter site infection, escherichia infection, pseudomonas infection, anal abscess, respiratory syncytial virus infection, paronychia, cytomegalovirus infection, Klebsiella infection, bacterial infection, and cytomegalovirus infection reactivation
[i] Terms are based on laboratory data.
[j] Headache includes Headache, Tension headache, Migraine.
[k] Bleeding events include; epistaxis, petechiae, contusion, gingival bleeding, haematuria, hematoma, intracranial hemorrhage and other bleeding.
[l] Abdominal pain includes Abdominal pain, Abdominal pain upper, Abdominal discomfort, Abdominal pain lower, Gastrointestinal pain.
[m] Oedema includes Oedema peripheral, Face oedema, Oedema, Fluid overload, Generalised oedema, Peripheral swelling, Localized oedema, Swelling face.
[n] Electrocardiogram QT prolonged include Electrocardiogram QT prolonged, Electrocardiogram QT interval abnormal.

Description of selected adverse reactions and additional information

Cardiac disorders

Quizartinib prolongs the QT interval on ECG. Any grade QT interval prolongation treatment-emergent adverse reactions were reported in 20% of VANFLYTA-treated patients and 3.1% of patients experienced reactions of Grade 3 or higher severity. QT prolongation was associated with dose reduction in 38 (5.7%) patients, dose interruption in 21 (3.1%) patients, and discontinuation in 4 (0.6%) patients. QTcF > 500 ms occurred in 2.5% of patients based on central review of ECG data. Three (0.4%) patients treated with VANFLYTA experienced cardiac arrest, two of the three patients had a fatal outcome, one of which also had a recorded ventricular fibrillation. Two of the events of cardiac arrest occurred in the setting of severe hypokalaemia and the other cardiac arrest was a direct result of blood loss caused by oesophageal erosions due to an invasive fungal infection. Electrocardiograms, monitoring and correction of hypokalaemia and hypomagnesemia should be performed prior to and during treatment with VANFLYTA. For dose modification for patients with QT interval prolongation, see “Dosage/Administration”.

Increased mortality due to infections,

Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients (<60 years; 13% vs. 5.7%) especially in the early treatment period of the Quantum-First study. The most frequent fatal infections in order of decreasing frequency

were septic shock (7.2%), Klebsiella sepsis (4.3%), and sepsis (1.4%) in the elderly patients, and in the younger patients they were sepsis, septic shock, Mucormycosis (1.3% each), and pneumonia (0.6%).
Patients should be closely monitored for the occurrence of severe infections during induction.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no known antidote for overdoses of VANFLYTA. For a substantial overdose, supportive measures should be provided as necessary, with interruption of treatment, evaluation of haematology and ECG monitoring as well as attention to serum electrolytes and concomitant medicinal products that may predispose patients to QT interval prolongation and/or torsade de pointes. Patients should be managed with symptomatic and supportive care (see “Dosage/Administration” and “Warnings and precautions”).

Properties/Effects

ATC code

L01EX11
Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors

Mechanism of action

Quizartinib is an inhibitor of the receptor tyrosine kinase FLT3. Quizartinib and its major metabolite AC886 competitively bind to the adenosine triphosphate (ATP) binding pocket of FLT3 with high affinity. Quizartinib and AC886 inhibit FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-ITD-dependent cell proliferation.

Pharmacodynamics

Cardiac electrophysiology
The exposure-response analysis of QuANTUM-First predicted a concentration-dependent QTcF interval prolongation of 24.1 ms [upper bound of two-sided 90% confidence interval (CI): 26.6 ms] at the steady-state C_{max} of quizartinib (53 mg) during maintenance therapy.

Clinical efficacy

The efficacy and safety of quizartinib vs. placebo was investigated in a randomised, double-blind, placebo-controlled, phase III study, QuANTUM-First. The study enrolled 539 adult patients between 18 and 75 years of age (25% were 65 years or older), who were newly diagnosed with FLT3-ITD

positive AML, as determined prospectively by a clinical study assay. Patients were randomised (1:1) to receive VANFLYTA 35.4 mg once daily (n = 268) or placebo (n = 271) for two weeks in each cycle in combination with standard chemotherapy (induction followed by consolidation for responding patients) followed by single-agent maintenance therapy with VANFLYTA (26.5 mg once daily for two weeks and 53 mg once daily thereafter) or placebo for up to 36 cycles (28 days/cycle).

Patients received up to 2 cycles of induction chemotherapy: 35.4 mg orally once daily on Days 8-21 of 7 + 3 (cytarabine [100 or 200 mg/m^2/day] on Days 1 to 7 plus daunorubicin [60 mg/m^2/day] or idarubicin [12 mg/m^2/day] on Days 1 to 3) and on Days 8-21 or 6-19 of an optional second induction (7 + 3 or 5 + 2 [5 days cytarabine plus 2 days daunorubicin or idarubicin], respectively), followed by post remission therapy which consisted of up to 4 cycles of consolidation chemotherapy and/or HSCT. Consolidation chemotherapy: 35.4 mg orally once daily on Days 6-19 of high-dose cytarabine (1.5 to 3 g/m^2 every 12 hours on Days 1, 3 and 5) for up to 4 cycles. Patients who proceeded to HSCT stopped receiving study treatment 7 days before the start of a conditioning regimen. Please refer to the Information for healthcare professionals for daunorubicin, idarubicin and cytarabine dosing recommendations.

The two randomised treatment groups were well balanced with respect to baseline demographics, disease characteristics and stratification factors. Of the 539 patients, the median age was 56 years (range 20-75 years), 26.1% of patients in the quizartinib arm and 24% of patients in the placebo arm were 65 years or older; 54.5% were female and 45.5% were male; 59.7% were White, 29.3% were Asian, 1.3% were Black or African American, and 9.7% were other races. Eighty-four percent of patients had an Eastern Cooperative Oncology Group (ECOG) baseline performance status of 0 or 1. The majority of the patients (72.4%) had intermediate cytogenetics risk status at baseline. FLT3-ITD variant allele frequency (VAF) was 3-25% in 35.6% of patients, greater than 25-50% in 52.1% of patients and greater than 50% in 12.1% of patients.

Among the patients who entered maintenance, 64% completed at least 12 cycles, 36% completed at least 24 cycles, and 16% completed all 36 planned cycles of maintenance. Twenty-nine percent (157/539) of the patients underwent HSCT in first complete remission (CR). The overall rate of HSCT (including the following settings: first CR, induction failure, or salvage after relapse) was 54% (144/268) in the VANFLYTA plus standard chemotherapy arm versus 47% (128/271) in the placebo plus standard chemotherapy arm. All patients were followed for survival.

The primary efficacy measure was overall survival (OS) defined as the time from randomisation until death from any cause.

The median follow-up time of the study was 39.2 months. Primary analysis has been conducted after a minimum follow-up time of 24 months after randomisation of the last patients.The study demonstrated a statistically significant improvement in OS for the quizartinib arm [hazard ratio (HR) 0.78; 95% CI: 0.62, 0.98; 2-sided p=0.0324]. The median OS (95% CI) was 31.9 (21.0, not estimable

[NE]) months in the quizartinib arm compared with 15.1 (13.2, 26.2) months in the control arm, resulting in a 16.8 month prolongation of median OS.
The survival rates (95% CI) at 12 and 24 months were 67.4% and 54.7% respectively in the quizartinib arm and 57.7% and 44.7%, respectively in the control arm.
In the subgroup analysis of while blood cell (WBC) count at the time of diagnosis of AML, for patients with WBC count ≥40x10^9/L (n=272), the OS HR was 0.62 (95% CI: 0.45, 0.86), with median OS (95% CI) as 31.9 (18.5, NE) months in the quizartinib arm compared with 12.9 (9.2, 15.7) months in the control arm; for patients with WBC count <40x10^9/L (n=267), the OS HR was 0.96 (95% CI: 0.69, 1.34), with median OS (95% CI) as 39.3 (16.5, NE) months in the quizartinib arm compared with 28.3 (14.7, NE) months in the control arm.
In an exploratory subgroup analysis of the 89/208 (43%) of patients who received maintenance therapy with VANFLYTA or placebo following consolidation chemotherapy, the OS HR was 0.40 (95% CI: 0.19, 0.84). Of 119/208 (57%) of patients who received maintenance therapy with VANFLYTA or placebo following HSCT, the OS HR was 1.62 (95% CI: 0.62, 4.22).
The complete remission (CR) rate [95% CI] for quizartinib was 54.9% (147/268) [48.7, 60.9] vs. 55.4% (150/271) [49.2, 61.4] for placebo.

Paediatric population

Swissmedic has deferred the obligation to submit the results of studies with VANFLYTA in one or more subsets of the paediatric population in the treatment of acute myeloid leukaemia (see “Dosage/Administration” for information on paediatric use).

Pharmacokinetics

The pharmacokinetics of quizartinib and its active metabolite AC886, were evaluated in healthy adult subjects (single dose) and in patients with newly diagnosed AML (steady state).

Absorption

The absolute bioavailability of quizartinib from the tablet formulation was 71%. After oral administration under fasted conditions in healthy subjects, time to peak concentration (median t_{max}) of quizartinib and AC886 measured post dose was approximately 4 hours (range 2 to 8 hours) and 5 to 6 hours (range 4 to 120 hours), respectively.
The administration of quizartinib with food, in healthy subjects, decreased quizartinib C_{max} by 1.09-fold, increased AUC_{inf} by 1.08-fold and t_{max} was delayed by two hours. These changes in exposure are not considered clinically relevant.
Based on population pharmacokinetic modelling in newly diagnosed AML patients, at 35.4 mg/day, steady state during induction therapy, the geometric mean (%CV) C_{max} of quizartinib and AC886 was estimated to be 140 ng/mL (71%) and 163 ng/mL (52%), respectively, and the geometric mean (%CV) $AUC_{0\text{-}24h}$ was 2 680 ng•h/mL (85%) and 3 590 ng•h/mL (51%), respectively.

During consolidation therapy at 35.4 mg/day, steady state, the geometric mean (%CV) C_{max} of quizartinib and AC886 was estimated to be 204 ng/mL (64%) and 172 ng/mL (47%), respectively, and the geometric mean (%CV) AUC_{0-24h} was 3 930 ng•h/mL (78%) and 3 800 ng•h/mL (46%), respectively.
During maintenance therapy at 53 mg/day, steady state, the geometric mean (%CV) C_{max} of quizartinib and AC886 was estimated to be 529 ng/mL (60%) and 262 ng/mL (48%), respectively, and the geometric mean (%CV) AUC_{0-24h} was 10 200 ng•h/mL (75%) and 5 790 ng•h/mL (46%), respectively.

Distribution

In vitro binding of quizartinib and AC886 to human plasma proteins is greater than or equal to 99%. The blood-to-plasma ratio of quizartinib and AC886 are concentration dependent, indicating saturation of the distribution to erythrocytes. At clinically relevant plasma concentrations, the blood-to-plasma ratio is approximately 1.3 for quizartinib and approximately 2.8 for AC886. Blood-to-plasma ratio of AC886 is also dependent on haematocrit, with a trend of increasing at higher haematocrit levels.
The geometric mean (%CV) volume of distribution of quizartinib in healthy subjects was estimated to be 275 L (17%).

Metabolism

Quizartinib is primarily metabolised by CYP3A4 and CYP3A5 *in vitro* via oxidative pathways which produces the active metabolite AC886, which is then further metabolised by CYP3A4 and CYP3A5. The steady-state AC886-to-quizartinib AUC_{0-24h} ratio during maintenance therapy was 0.57.

Elimination

The mean (SD) effective half-lives ($t_{1/2}$) for quizartinib and AC886 are 81 hours (73) and 136 hours (113), respectively, in patients with newly diagnosed AML. The mean (SD) accumulation ratios (AUC_{0-24h}) for quizartinib and AC886 were 5.4 (4.4) and 8.7 (6.8), respectively.
Quizartinib and its metabolites are primarily eliminated by the hepatobiliary route with excretion mainly via faeces (76.3% of the orally administered radioactive dose). Unchanged quizartinib represented approximately 4% of the orally administered radioactive dose in faeces. Renal excretion is a minor route of elimination of the administered radioactive dose (< 2%).
The geometric mean (%CV) total body clearance (CL) of quizartinib in healthy subjects was estimated to be 2.23 L/hour (29%).

Linearity/non-linearity

Quizartinib and AC886 showed linear kinetics in the dose range of 26.5 mg to 79.5 mg in healthy subjects and 17.7 mg to 53 mg in AML patients.

Pharmacokinetic/pharmacodynamic relationship(s)

Age (18 to 91 years), race (White 65%, Asian 18%, Black or African American 9%), sex, body weight (range 37 to 153 kg), or renal impairment (CLcr 30 to 89 mL/min, estimated by Cockcroft-Gault) did not have a clinically relevant effect on quizartinib and AC886 exposure based on a population pharmacokinetic analysis.

Kinetics in specific patient groups

Hepatic impairment

In a single-dose (26.5 mg) phase 1 study, the pharmacokinetics of quizartinib and AC886 were assessed in subjects with mild hepatic impairment (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) and compared to subjects with normal hepatic function. The exposure (C_{max} and AUC_{inf}) of quizartinib and AC886 were similar (≤ 30% difference) across all groups. Protein binding of quizartinib and AC886 is not affected by impaired hepatic function. Therefore, hepatic impairment did not have a clinically relevant effect on quizartinib and AC886 exposure.
Patients with severe hepatic impairment (Child-Pugh Class C) were not included in the clinical studies.

Renal impairment

A population pharmacokinetic analysis in AML patients with mild to moderate renal impairment (CrCl 30 to 89 mL/min) showed that renal function did not affect quizartinib and AC886 clearance. Therefore, mild and moderate renal impairment did not have a clinically relevant effect on quizartinib and AC886 exposure.
Patients with severe renal impairment (CrCl< 30 mL/min) were not included in the clinical studies.

Preclinical data

Safety pharmacology

In cardiovascular safety pharmacology studies conducted in cynomolgus monkeys, quizartinib resulted in QT prolongation at doses approximately 2 times the RHD (*recommended human dose*) of 53 mg/day based on C_{max}. The NOAEL was approximately 0.4 times the RHD based on C_{max}. Quizartinib primarily inhibited I_{Ks} with a maximum inhibition of 67.5% at 2.9 µM. The maximum inhibition of I_{Ks} by AC886 was 26.9% at 2.9 µM. Quizartinib and AC886 at 3 µM statistically significantly inhibited hERG currents by 16.4% and 12.0%, respectively. Neither quizartinib nor AC886 inhibited I_{Na}, I_{Na-L} and I_{Ca-L} at any concentration tested.

Repeated dose toxicity

In repeat dose toxicity studies, haematopoietic and lymphoid organ toxicity were observed including decreased peripheral blood cells and bone marrow hypocellularity; liver toxicity including elevated

aminotransferases, hepatocellular necrosis and birefringent crystal deposition (dogs); and kidney toxicity including tubular basophilia and birefringent crystal deposition (male rats). These changes were noted at approximately 0.4 times, 0.4 times and 9 times the RHD based on AUC, respectively. The corresponding NOAELs were approximately 0.1 times, 0.1 times and 1.5 times the RHD based on AUC, respectively.

Genotoxicity

In genotoxicity studies, quizartinib was mutagenic in a bacterial reverse mutation assay, but not in a mammalian cell mutation assay (mouse lymphoma thymidine kinase) or in an *in vivo* transgenic rodent mutation assay. Quizartinib was not clastogenic and did not induce polyploidy in a chromosome aberration assay and was not clastogenic or aneugenic in a single-dose rat bone marrow micronucleus assay. An *in vivo* bone marrow micronucleus assay in rats was equivocal after 28 days repeated dosing. After a single higher dose, the result was negative.

Carcinogenicity

No studies have been conducted to determine the carcinogenic potential of quizartinib.

Reproductive toxicity

Fertility studies in animals have not been conducted with quizartinib. However, adverse findings in male and female reproductive systems were observed in repeat dose toxicity studies in rats and monkeys. In female rats, ovarian cysts and vaginal mucosal modifications were observed at doses approximately 10 times the RHD based on AUC. Findings in female monkeys included atrophy of the uterus, ovary and vagina, observed at doses approximately 0.3 times the RHD based on AUC. The corresponding no observed adverse effect levels (NOAELs) for these changes were 1.5 times and 0.1 times the RHD, respectively, based on AUC. In male rats, testicular seminiferous tubular degeneration and failure of sperm release were observed at approximately 8 times the RHD based on AUC. Findings in male monkeys included germ cell depletion in the testes; observed at approximately 0.5 times the RHD based on AUC. The corresponding NOAELs for these changes were 1.4 times and 0.1 times the RHD, respectively, based on AUC. After a four-week recovery period, all these findings except the vaginal mucosal modifications in the female rats were reversible.

In embryo-foetal toxicity studies, embryo-foetal lethality and increased post-implantation loss were observed at maternally toxic doses. Foetotoxicity (lower foetal weights, effects on skeletal ossification) and teratogenicity (foetal abnormalities including oedema) were observed at doses approximately 3 times the RHD based on AUC. The NOAEL was 0.5 times the RHD based on AUC. Quizartinib is considered to be potentially teratogenic.

Toxicity tests with juvenile animals

In a 9-week juvenile rat toxicology study, juvenile SD rats were administered Quizartinib at daily doses of 0.3, 3 or 10 mg/kg from post-natal day 10 to 70 with a 6-week recovery period through post-natal day 113. Results were as follows:

- Early mortality at 10 mg/kg/day attributed to severe bone marrow toxicity which is approximately 9 times greater for Quizartinib and 11 times greater for the AC886 metabolite compared to the RHD based on AUC.
- At 3 mg/kg/day, reductions in peripheral neutrophils, lymphocytes, red blood cells and reticulocytes, as well as a decrease in myeloid:erythroid ratio in the bone marrow at approximately the same AUC exposure for Quizartinib and AC886 as the adult human exposure at the RHD.
- At 3 mg/kg/day, organ weight decreases in seminal vesicles, kidneys, spleen, thyroid/parathyroids and thymus. Organ weight decreases also noted in the testes and epididymides correlated with degeneration/atrophy in the testes and secondary degereneration in the epididymides which all were noted at approximately the same AUC exposure for Quizartinib and AC886 as the exposure at the RHD.
- The NOAEL for male and female rats was 0.3 mg/kg/day at approximately 0.07 and 0.08 times the AUC exposure for Quizartinib and AC886 respectively compared to AUC exposure at the RHD.
- After a 6-week recovery period, all findings reversed or partially reversed.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Handling Instructions

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69710 (Swissmedic).

Packs

VANFLYTA 17.7 mg, film-coated tablets: Cartons containing 14 x 1 or 28 x 1 film-coated tablets in aluminium/aluminium perforated unit dose blisters. (A)
VANFLYTA 26.5 mg, film-coated tablets: Cartons containing 14 x 1, 28 x 1 or 56 x 1 film-coated tablets in aluminium/aluminium perforated unit dose blisters. (A)

Marketing authorisation holder

DAIICHI SANKYO (Schweiz) AG, Zürich

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