30 June 2026

Informationsgranskningsnämnden, IGN, LIF
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Att: Anders Öhlén

Response to IGN's Remark (IGN690)

Dear IGN,

We refer to IGN's comments concerning the promotional video for Vanflyta as of 22 June 2026 and set out below our response on behalf of Daiichi Sankyo Nordics's headquarter, Daiichi Sankyo Europe ("**DSE**") to the issues raised regarding the clinical data, the primary endpoint focus, and the minimum text displayed.

We have taken note of IGN's comments and wish to assist in ensuring a complete and accurate understanding of the factual circumstances surrounding the promotional video at the exhibition stand.

1 Regarding the Clinical Data and Primary Endpoint Focus

The Committee has raised concerns regarding the presentation of the clinical data in the promotional video. It is our position that the clinical data was presented in a balanced, scientifically accurate, and non-misleading manner. Furthermore, all statements presented in the video are derived directly from, and are fully consistent with, the approved SmPC and the QuANTUM-First study.

1.1 Primary Endpoint Focus

As expressly set out in Section 5.1 of the approved SmPC (attached as **Appendix 1**), the primary efficacy endpoint was overall survival (OS). The promotional video focuses exclusively on this approved primary endpoint and presents the corresponding efficacy data in a manner that is fully consistent with the approved SmPC.

1.2 Significant Efficacy

The promotional video presents the approved efficacy data demonstrating that quizartinib/kizartinib, in combination with standard chemotherapy, significantly improved overall survival compared with placebo in combination with standard chemotherapy, corresponding to a 22% reduction in the risk of death (hazard ratio [HR] vs placebo: 0.776; 95% CI: 0.615–0.979). These data are presented as approved in the SmPC and accurately reflect the exact efficacy results.

1.3 Context of Secondary Endpoints

The 39% reduction in the risk of relapse or death presented in the promotional video is a clinical finding from the peer-reviewed publication of the QuANTUM-First study (attached as **Appendix 2**, with the relevant passage highlighted on page 9). This forms part of the broader clinical evidence base supporting the efficacy profile of quizartinib/kizartinib. We acknowledge that, in accordance with Section 5.1 of the SmPC, the primary efficacy endpoint is overall survival (OS).

However, the referenced 39% reduction relates to a secondary efficacy endpoint assessed in the QuANTUM-First study. This figure corresponds to the event-free survival (EFS) analysis, which was included in the promotional video to provide a comprehensive and descriptive overview of the clinical trial results, consistent with established practice in the communication of clinical data.

We maintain that the inclusion of this information is fully aligned with the clinical evidence from the trial and does not conflict with the primary endpoint as defined in the SmPC.

Any references to secondary or exploratory endpoints in the promotional video were presented in the context of the statistically significant primary endpoint of overall survival. This was intended to ensure that the target audience was not misled and to support a balanced communication of the core clinical profile of the medicinal product, as defined in the approved SmPC.

1.4 Conclusion

We fully acknowledge the importance of ensuring that information is presented in a clear, balanced, and non-misleading manner. The relative risk reductions of

22% (overall survival) and 39% (event-free survival) were featured because they represent the statistically significant hazard ratios directly derived from the SmPC and the peer-reviewed publication of the QuANTUM-First study. As shown in the attached publication excerpt, the 39% reduction corresponds precisely to a hazard ratio of 0.61. Our intention was to accurately reflect the primary and key secondary efficacy findings as approved and published.

In light of the above, we respectfully request that IGN reconsider its assessment of the presentation of the clinical data and endpoints in the promotional video.

2 Regarding the Minimum Text

The Committee has expressed concerns that the minimum text displayed at the end of the promotional video was shown for such a short duration that it may not comply with Article 19, Chapter 1, Section 1 of the LER.

2.1 Interpretation of Article 19, 1, Section 1 of the LER

In our view, the assessment under Article 19 of the LER should be conducted in light with the overall manner in which the information was made available to the target audience.

This interpretation is supported by the IGN's own guidance on minimum information/mandatory text in relation to roll-ups and banners, in which the IGN states:

> "It depends on the overall impression of all the information in the exhibition stand. The basic rule is that minimum information should be on a roll-up/banner. In a manned stand, however, the minimum information does not have to be printed on a roll-up/banner, but it can be available in the stand, in printed or digital form. There must be a clear indication in a roll-up/banner or, for example, in a note/sign in the stand about where the minimum information is available."
>
> (attached as **Appendix 3**)

In our view, this guidance reflects a general principle that applies by analogy to a video screen at an exhibition stand. Roll-ups, banners and video screens serve the same function in the context of an exhibition stand. All tools are visual communication tools intended to attract attention and support the overall messaging at the exhibition stand. We find no legal basis for treating a video screen more strictly than a roll-up or banner in this regard, where both form part of the same staffed exhibition stand and do not operate as standalone advertisements outside their contextual setting.

Further, in the context of a staffed exhibition stand, minimum information does not necessarily need to be reproduced on each individual communication element, provided that the information is available elsewhere at the exhibition stand and that the overall presentation ensures clear access for the recipient.

Finally, the objective of the requirement for minimum information is to ensure that recipients are provided with the information necessary to assess the advertising message on a sound and balanced basis. This objective is fulfilled where the information at a staffed exhibition stand is clearly accessible in printed or digital form, and where the stand clearly indicates where such information can be found.

2.2 The Minimum Text Available in the Exhibition stand

In the present case, the video screen did not constitute an isolated or standalone advertising unit but rather formed an integral part of a staffed exhibition stand.

The mandatory text was visible upon entering the exhibition stand and was also displayed at several locations within the exhibition stand (pictures attached as **Appendix 4**). The overall layout of the exhibition stand was specifically designed to ensure immediate access to the mandatory information. A large, static, and fully legible panel containing the minimum text was prominently integrated into the exhibition stand architecture directly to the right of the main video screen. Furthermore, physical brochures containing the minimum text were readily available in the kiosk positioned in the immediate foreground, directly in the viewer's line of sight when looking at the screen.

The decisive factor should not be whether the mandatory text on the promotional video screen could be fully read within the time it was displayed in the video sequence. Rather, the decisive factor should be whether the recipients exposed to the exhibition stand had genuine and sufficient access to the minimum information, based on the stand’s overall layout and informational materials.

It should also be given weight that the exhibition stand was staffed with trained employees. The guidance expressly distinguishes between roll-ups/banners and staffed exhibition stands and accepts that minimum information in staffed stands may be provided in printed or digital form. That distinction is directly relevant to the present case.

In DSE’s staffed exhibition stand, the visitors could obtain further information, ask questions, and be directed to the relevant minimum information. The exhibition stand included the mandatory text displayed in multiple locations and was designed to provide immediate access to the SmPC.

This reduces any risk that the recipient relies solely on a single communication element, such as a video screen. The assessment should therefore be based on

the exhibition stand's overall information environment, rather than an isolated evaluation of the video screen.

2.3 Conclusion

We fully acknowledge the importance of ensuring that mandatory text is easily legible and that the text displayed in the promotional video alone is not sufficient in itself.

However, we respectfully request that IGN reconsider its assessment of the minimum text in the video in the specific context, in light of the concurrent and clearly visible placement of the mandatory text at the exhibition stand.

If IGN maintains its view that the requirements are not met, we would be grateful for further clarification in that respect. We remain, of course, at IGN's disposal to provide any further information or otherwise assist as needed.

Best regards,

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 17.7 mg film-coated tablets
VANFLYTA 26.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VANFLYTA 17.7 mg film-coated tablets

Each film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride).

VANFLYTA 26.5 mg film-coated tablets

Each film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

VANFLYTA 17.7 mg film-coated tablets

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

Yellow, round-shaped film-coated tablets, 10.2 mm in diameter and debossed with 'DSC 512' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment with VANFLYTA should be initiated by a physician experienced in the use of anti-cancer therapies.

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 alternate validated test.

ECGs should be performed, and electrolyte abnormalities should be corrected prior to initiation of treatment (see section 4.4).

Posology

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 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.

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.
Duration (28-day cycles)	Two weeks in each cycle	Two weeks in each cycle	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. It may be resumed after completion of the transplant based on white blood cell count (WBC) and at the discretion of the treating physician for patients with sufficient haematologic recovery and with ≤ Grade 2 graft-versus-host disease (GVHD), not requiring the initiation of new systemic GVHD therapy within 21 days, following the dosing recommendations described above.

Dose modifications
VANFLYTA should be initiated only if QTcF is ≤ 450 ms (see section 4.4).

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: Recommended dose modifications for adverse reactions

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.

Adverse reaction	Recommended action
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, and it is suspected to be associated with VANFLYTA. 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 and is suspected to be associated with VANFLYTA.
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: Dose adjustments by phase for adverse reactions and/or concomitant use with strong CYP3A inhibitors during treatment with VANFLYTA

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 populations

Elderly
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
The safety and efficacy of VANFLYTA in children and adolescents less than 18 years of age have not been established (see section 5.1). No data are available.

Method of administration

VANFLYTA is for oral use.
The tablets should be taken at approximately the same time each day with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Congenital long QT syndrome (see section 4.4).
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

QT interval prolongation

Quizartinib is associated with QT interval prolongation (see section 4.8). QT interval prolongation may increase the risk of ventricular arrhythmias or torsade de pointes. Patients with congenital long QT syndrome and/or a previous history of torsade de pointes were excluded from the quizartinib development programme. VANFLYTA must not be used in patients with congenital long QT syndrome.

VANFLYTA should be used with caution in patients who are at significant risk of developing QT interval prolongation. These include patients with uncontrolled or significant cardiovascular disease (e.g., history of second-or third-degree heart block (without pacemaker), myocardial infarction within 6 months, uncontrolled angina pectoris, uncontrolled hypertension, congestive heart failure, history of clinically relevant ventricular arrhythmias or torsade de pointes), and patients receiving concomitant medicinal products known to prolong the QT interval. Electrolytes should be maintained in the normal range (see section 4.2).

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 section 4.2).

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 section 4.5).

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 sections 4.2 and 4.5).

Infections in elderly patients

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. Patients older than 65 years of age 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 section 4.6).

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).

4.5 Interaction with other medicinal products and other forms of interaction

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

Effect of other medicinal products on VANFLYTA

Strong CYP3A/P-glycoprotein (P-gp) inhibitors
Co-administration of ketoconazole (200 mg twice daily for 28 days), a strong CYP3A/P-gp inhibitor, with a single dose of VANFLYTA increased quizartinib maximum plasma concentration (C_{max}) and area under the curve (AUC_{inf}) by 1.17-fold and 1.94-fold, respectively, and decreased AC886 C_{max} and AUC_{inf} by 2.5-fold and 1.18-fold, respectively, compared to VANFLYTA alone. At steady state, quizartinib exposure (C_{max} and AUC_{0-24h}) was estimated to be increased by 1.86-fold and 1.96-fold,

respectively, and AC886 exposure (C_{max} and AUC_{0-24h}) decreased by 1.22-fold and 1.17-fold, respectively. 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 section 4.2.

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 (200 mg twice daily for 28 days), a moderate CYP3A inhibitor, with a single dose of VANFLYTA increased quizartinib and AC886 C_{max} by 1.11-fold and 1.02-fold, respectively, and AUC_{inf} by 1.20-fold and 1.14-fold, respectively. This change was not considered clinically relevant. No dose modification is recommended.

Strong or moderate CYP3A inducers
Co-administration of efavirenz (lead-in treatment at 600 mg once daily for 14 days), a moderate CYP3A inducer, with a single dose of VANFLYTA decreased quizartinib C_{max} and AUC_{inf} by approximately 1.18-fold and 9.7-fold, respectively, compared to VANFLYTA alone. The C_{max} and AUC_{inf} of AC886 decreased by approximately 3.1-fold and 26-fold, respectively (see section 5.2).

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 section 4.4).

Gastric acid reducing agents
Proton pump inhibitor lansoprazole decreased quizartinib C_{max} by 1.16-fold and AUC_{inf} by 1.05-fold. This decrease in quizartinib absorption was not considered clinically relevant. No dose modification is recommended.

Effect of VANFLYTA on other medicinal products

P-glycoprotein (P-gp) substrates
Co-administration of quizartinib and dabigatran etexilate (a P-gp substrate) increased total and free dabigatran C_{max} by 1.12-fold and 1.13-fold, respectively, and increased total and free dabigatran AUC_{inf} by 1.13-fold and 1.11-fold, respectively (see section 5.2). Quizartinib is a weak P-gp inhibitor,

and no dose modification is recommended when P-gp substrates are co-administered with VANFLYTA.

Breast cancer resistance protein (BCRP) substrates
In vitro data indicate that quizartinib is an inhibitor of BCRP. The clinical relevance is currently not known. Caution should be used when quizartinib is co-administered with medicinal products that are substrates of BCRP.

4.6 Fertility, pregnancy and 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 section 5.3); 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 section 5.3).

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.

Breast-feeding

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 section 4.3).

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 section 5.3).

4.7 Effects on ability to drive and use machines

VANFLYTA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were increased alanine aminotransferase (58.9%), decreased platelet count (40.0%), decreased haemoglobin (37.4%), diarrhoea (37.0%), nausea (34.0%), abdominal pain (29.4%), headache (27.5%), vomiting (24.5%) and decreased neutrophil count (21.9%).

The most common Grade 3 or 4 adverse reactions were decreased platelet count (40%), decreased haemoglobin (35.5%), decreased neutrophil count (21.5%), increased alanine aminotransferase (12.1%), bacteraemia (7.2%) and fungal infections (5.7%). The most common serious adverse reactions in the VANFLYTA arm were neutropenia (3.0%), fungal infections (2.3%) and herpes infections (2.3%). Adverse reactions with fatal outcome were fungal infections (0.8%) and cardiac arrest (0.4%).

The most common adverse reactions associated with dose interruption of VANFLYTA were neutropenia (10.6%), thrombocytopenia (4.5%) and prolonged electrocardiogram QT interval (2.6%). The most common adverse reactions associated with dose reduction were neutropenia (9.1%), thrombocytopenia (4.5%) and prolonged electrocardiogram QT interval (3.8%).

The most common adverse reaction associated with permanent discontinuation of VANFLYTA was thrombocytopenia (1.1%).

Tabulated list of adverse reactions

The safety of VANFLYTA was investigated in QuANTUM-First, a randomised, double-blind, placebo-controlled study in adult patients with newly diagnosed FLT3-ITD positive AML.

Adverse reactions are listed according to MedDRA System Organ Class (SOC). Within each SOC, the adverse reactions are ranked by frequency with the most frequent reactions first, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse reactions

Adverse reaction	All grades %	Grade 3 or 4 %	Frequency category (All grades)
Infections and infestations			
Upper respiratory tract infections[a]	18.1	1.9	Very common
Fungal infections[b]	15.1	5.7	Very common
Herpes infections[c]	14.0	3.0	Very common
Bacteraemia[d]	11.3	7.2	Very common
Blood and lymphatic system disorders			
Thrombocytopenia[e]	40.0	40.0	Very common
Anaemia[e]	37.4	35.5	Very common
Neutropenia[e]	21.9	21.5	Very common
Pancytopenia	2.6	2.3	Common
Metabolism and nutrition disorders			
Decreased appetite	17.4	4.9	Very common
Nervous system disorders			
Headache[f]	27.5	0	Very common
Cardiac disorders			
Cardiac arrest[g]	0.8	0.4	Uncommon
Ventricular fibrillation[g]	0.4	0.4	Uncommon
Respiratory, thoracic and mediastinal disorders			
Epistaxis	15.1	1.1	Very common
Gastrointestinal disorders			
Diarrhoea[h]	37.0	3.8	Very common
Nausea	34.0	1.5	Very common
Abdominal pain[i]	29.4	2.3	Very common
Vomiting	24.5	0	Very common
Dyspepsia	11.3	0.4	Very common

Adverse reaction	All grades %	Grade 3 or 4 %	Frequency category (All grades)
Hepatobiliary disorders			
ALT increased[e]	58.9	12.1	Very common
General disorders and administration site conditions			
Oedema[j]	18.9	0.4	Very common
Investigations			
Prolonged electrocardiogram QT[k]	14.0	3.0	Very common

Standard chemotherapy = cytarabine (cytosine arabinoside) and anthracycline (daunorubicin or idarubicin).

[a] Upper respiratory tract infections include upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, tonsillitis, laryngopharyngitis, pharyngitis bacterial, pharyngotonsillitis, viral pharyngitis and acute sinusitis.

[b] 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, fungemia, systemic candida and systemic mycosis.

[c] Herpes infections include oral herpes, herpes zoster, herpes virus infections, herpes simplex, human herpesvirus 6 infection, genital herpes and herpes dermatitis.

[d] Bacteraemia includes bacteraemia, Klebsiella bacteraemia, Staphylococcal bacteraemia, Enterococcal bacteraemia, Streptococcal bacteraemia, device-related bacteraemia, Escherichia bacteraemia, Corynebacterium bacteraemia and Pseudomonal bacteraemia.

[e] Terms based on laboratory data.

[f] Headache includes headache, tension headache and migraine.

[g] One subject experienced two events (ventricular fibrillation and cardiac arrest).

[h] Diarrhoea includes diarrhoea and diarrhoea haemorrhagic.

[i] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.

[j] Oedema includes oedema peripheral, face oedema, oedema, fluid overload, generalised oedema, peripheral swelling, localised oedema and face swelling.

[k] Electrocardiogram QT prolonged includes electrocardiogram QT prolonged and electrocardiogram QT interval abnormal.

Description of selected adverse reactions

Cardiac disorders

Quizartinib prolongs the QT interval on ECG. Any grade QT interval prolongation treatment-emergent adverse reactions were reported in 14.0% of VANFLYTA-treated patients and 3.0% of patients experienced reactions of Grade 3 or higher severity. QT prolongation was associated with dose reduction in 10 (3.8%) patients, dose interruption in 7 (2.6%) patients, and discontinuation in 2 (0.8%) patients. QTcF > 500 ms occurred in 2.3% of patients based on central review of ECG data. Two (0.8%) patients treated with VANFLYTA experienced cardiac arrest with recorded ventricular fibrillation, one with a fatal outcome, both in the setting of severe hypokalaemia. 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 section 4.2.

Other special populations

Elderly

Fatal infections have occurred more frequently with quizartinib in elderly patients (i.e., older than 65 years), compared to younger patients (13% vs. 5.7%), especially in the early treatment period.

Patients older than 65 years of age should be closely monitored for the occurrence of severe infections during induction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX11

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.

Pharmacodynamic effects

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 and safety

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 with either daunorubicin on days 1, 2 and 3 or idarubicin on days 1, 2 and 3 and cytarabine for 7 days, followed by post remission therapy which consisted of up to 4 cycles of consolidation chemotherapy and/or HSCT. Consolidation chemotherapy consisted of cytarabine on days 1, 3 and 5. Patients who proceeded to HSCT stopped receiving study treatment 7 days before the start of a conditioning regimen. Please refer to the Summary of Product Characteristics 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.

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

The study demonstrated a statistically significant improvement in OS for the quizartinib arm (see Table 5 and Figure 1). The median follow-up time of the study was 39.2 months.

A difference was observed between the quizartinib arm vs. the placebo arm in the estimates of survival rates (95% CI) at the landmark timepoints of 12, 24, 36 and 48 months (see Table 5).

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.

Table 5: Efficacy results from QuANTUM-First (intent-to-treat population)

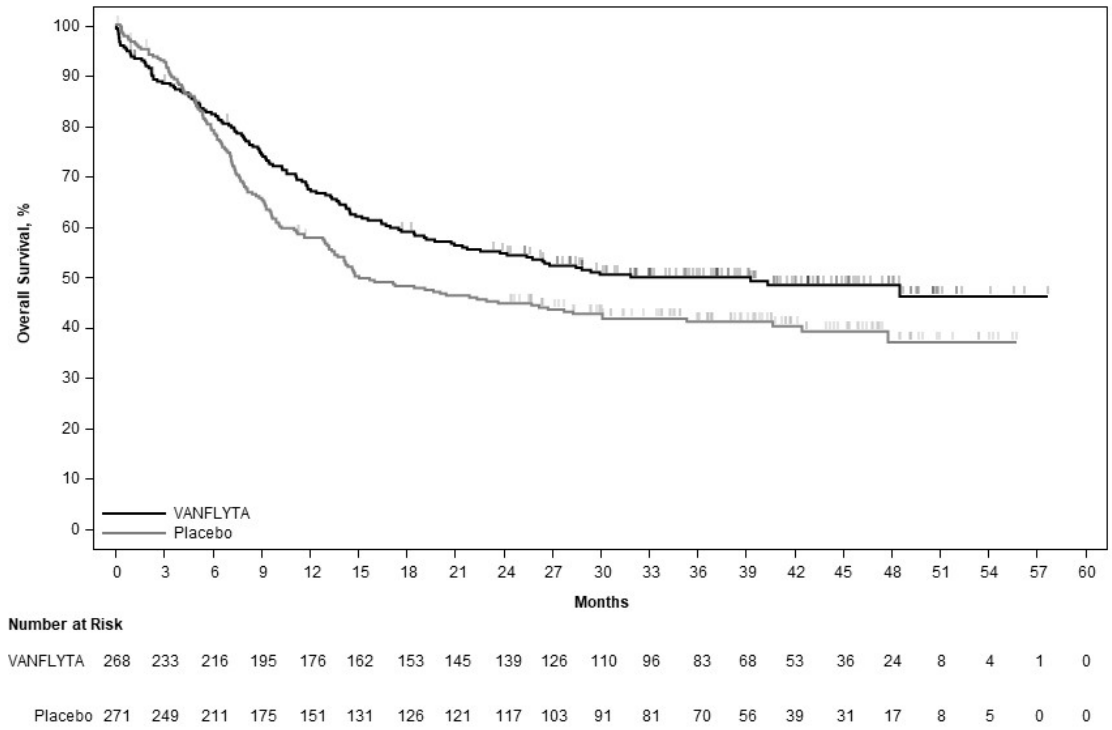
	Quizartinib N = 268	**Placebo N = 271**
OS (months)		
Median (95% CI)[a]	31.9 (21.0, NE)	15.1 (13.2, 26.2)
HR[b] relative to placebo (95% CI)	0.776 (0.615, 0.979)	
p-value (two-sided stratified log-rank test)	0.0324	
OS rate (%) (95% CI)[a]		
12 months	67.4 (61.3, 72.7)	57.7 (51.6, 63.4)
24 months	54.7 (48.4, 60.5)	44.7 (38.7, 50.6)
36 months	49.9 (43.7, 55.9)	41.1 (35.0, 47.0)
48 months	48.4 (41.9, 54.5)	37.0 (29.8, 44.2)

CI = confidence interval; NE = not estimable

[a] Kaplan-Meier estimate

[b] Hazard ratio (HR) was based on stratified Cox regression model.

Figure 1: Kaplan-Meier curves for overall survival in QuANTUM-First



Paediatric population

The European Medicines Agency 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 section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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. VANFLYTA can be administered with or without food.

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_{0-24h} 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%).

Biotransformation

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 relationships

Age (18 to 91 years), race, sex, body weight, 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.

Interaction studies with other medicinal products

Transporters
In vitro studies showed that quizartinib is a substrate for P-gp but not for BCRP, OATP1B1, OATP1B3, OCT1, OAT2, MATE1 or MRP2. AC886 is a substrate for BCRP but not for OATP1B1, OATP1B3, MATE1 or MRP2. However, the single-dose administration of quizartinib with ketoconazole, a strong inhibitor for both CYP3A and P-gp, increased quizartinib C_{max} by approximately 1.17-fold, 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.

Breast cancer resistance protein (BCRP) substrates
Quizartinib inhibits BCRP with an estimated *in vitro* IC50 of 0.813 μM. As no clinical data is available, it cannot be excluded that quizartinib could inhibit this transporter at the recommended doses.

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.

Special populations

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.

No dose adjustment is recommended in patients with mild or moderate hepatic impairment.

Patients with severe hepatic impairment (Child-Pugh Class C) were not included in the clinical studies; therefore, VANFLYTA is not recommended for use in these patients.

Renal impairment
A population pharmacokinetic analysis in AML patients with mild to moderate renal impairment (CLcr 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. No dose adjustment is recommended in patients with mild or moderate renal impairment.

Patients with severe renal impairment (CLcr < 30 mL/min) were not included in the clinical studies; therefore, VANFLYTA is not recommended for use in these patients.

5.3 Preclinical safety data

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.

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 recommended human dose (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.

Animal toxicology studies

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.

Environmental risk assessment studies have shown that quizartinib may pose a risk for the aquatic compartment.

In vitro and animal safety pharmacology studies

In cardiovascular safety pharmacology studies conducted in cynomolgus monkeys, quizartinib resulted in QT prolongation at doses approximately 2 times the RHD 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium perforated unit dose blisters.

VANFLYTA 17.7 mg film-coated tablets

Cartons containing 14 x 1 or 28 x 1 film-coated tablets.

VANFLYTA 26.5 mg film-coated tablets

Cartons containing 14 x 1, 28 x 1 or 56 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product may pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/23/1768/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 November 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1
85276 Pfaffenhofen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of VANFLYTA in each Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reinforcing the prescriber's and patient/caregiver's awareness about the risk of serious ADRs related to QTc interval prolongation, and the actions to be taken to minimise the occurrence of the risk in patients receiving VANFLYTA.

The MAH shall ensure that in each Member State where VANFLYTA is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe, dispense, and use VANFLYTA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals will contain the following key elements:

- Description of serious ADRs related to QTc interval prolongation that have occurred with quizartinib
- Detailed description of the recommended VANFLYTA dosing regimen: starting dose and dose escalation criteria
- Detailed description of VANFLYTA dose interruption, dose reduction, and treatment discontinuation based on QTc interval duration
- VANFLYTA dose modification for concomitant strong CYP3A inhibitors use
- Management of other co-medications that are known to cause QT prolongation
- Frequency of ECG monitoring
- Serum electrolyte monitoring and management

The patient information pack:

- Package leaflet
- Patient card

The Patient card will contain the following key elements:

- A warning message for healthcare professionals that VANFLYTA treatment may increase the risk of serious ADRs related to QTc interval prolongation
- Important information for healthcare professionals not involved in the regular care of the patient about patient management related to QTc prolongation
- Important information for patients/caregivers about signs or symptoms of serious ADRs related to QTc interval prolongation and when to seek attention from a healthcare professional
- Contact details of the VANFLYTA prescriber

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 17.7 mg film-coated tablets
quizartinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
81366 Munich, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1768/001 14 x 1 film-coated tablets
EU/1/23/1768/002 28 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vanflyta 17.7 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 17.7 mg tablets
quizartinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Daiichi-Sankyo (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 26.5 mg film-coated tablets
quizartinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 x 1 film-coated tablets
28 x 1 film-coated tablets
56 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
81366 Munich, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1768/003 14 x 1 film-coated tablets
EU/1/23/1768/004 28 x 1 film-coated tablets
EU/1/23/1768/005 56 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vanflyta 26.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

VANFLYTA 26.5 mg tablets
quizartinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Daiichi-Sankyo (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT CARD

PATIENT CARD

VANFLYTA

quizartinib

- Please keep this card with you at all times.
- This card contains important safety information that you should know before you take VANFLYTA and during treatment with VANFLYTA.
- Show this card to any doctor, pharmacist or surgeon before any medical intervention or treatment.

Patient information

Patient name:
Date of birth:

In case of emergency, please contact:
Name:
Phone number:

Treatment information
(To be completed by physician or patient)

VANFLYTA has been prescribed at a once-daily dose of: mg
Started on: /(mm/yy)

Prescriber information
(To be completed by physician or patient)

For more information or in case of emergency, please contact:
Physician's name:
Phone number:

Important information for the patient

VANFLYTA can cause an abnormal electrical activity in your heart called 'prolonged QT interval' which may lead to a life-threatening disturbances of the heart rhythm. Therefore, a regular check of the electrical activity in your heart with an electrocardiogram (ECG) is very important.

Contact your doctor immediately if:

- You are feeling dizzy, lightheaded or faint.
- You sense a change in heart rhythm, e.g., palpitations or an abnormality of your pulse. You may feel your heart is beating too fast, but you may also sense a more nonspecific or vague change.
- You have fainted or have been unconscious, even if it was only for a very short period of time, e.g., seconds.
- You suffer from diarrhoea or vomiting, or are unable to eat or drink fluids in sufficient amounts.
- You feel any other sudden change in your well-being.
- Your medicines are changed by a physician other than the prescribing physician for VANFLYTA.

Consult your doctor first before taking VANFLYTA with any other medicines, including medicines obtained without a prescription or supplementary products as these may increase the risk of you developing QT interval prolongation.

For more information, please read the package leaflet.

Important information for healthcare professionals

VANFLYTA is associated with QT interval prolongation, which may increase the risk of ventricular arrhythmias or torsade de pointes.

- Interrupt VANFLYTA if QTcF is ≥501 ms and permanently discontinue if associated with torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of life-threatening arrhythmia. VANFLYTA is contraindicated in patients with congenital long QT syndrome.
- During VANFLYTA treatment, check serum electrolytes and correct any hypokalaemia and hypomagnesaemia as needed.
- Avoid non-essential medicines that prolong the QT interval. If unavoidable, monitor ECG frequently.
- The dose of VANFLYTA should be reduced when used concomitantly with strong CYP3A inhibitors.

For more information, please see the Summary of Product Characteristics (SmPC).

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See the Patient Information Leaflet for how to report side effects.

Daiichi-Sankyo (logo)

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

VANFLYTA 17.7 mg film-coated tablets
VANFLYTA 26.5 mg film-coated tablets
quizartinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VANFLYTA is and what it is used for
2. What you need to know before you take VANFLYTA
3. How to take VANFLYTA
4. Possible side effects
5. How to store VANFLYTA
6. Contents of the pack and other information

1. What VANFLYTA is and what it is used for

What VANFLYTA is

VANFLYTA contains the active substance quizartinib. It is a type of cancer medicine called a 'protein kinase inhibitor'. The medicine is used along with chemotherapy to treat adults who have acute myeloid leukaemia (AML, a type of blood cancer), with a mutation (change) in the FLT3 gene called 'FLT3-ITD'. VANFLYTA treatment may be continued also after a bone marrow transplant when patients have sufficiently recovered.

Your doctor will test your cancer cells for changes in the FLT3 gene to look for FLT3-ITD mutations beforehand to make sure that VANFLYTA is right for you.

How VANFLYTA works

In AML, the body makes a large amount of abnormal white blood cells that do not mature to become healthy cells. VANFLYTA works by blocking the action of proteins called 'tyrosine kinases' in these abnormal cells. This slows down or stops the abnormal cells from dividing and growing uncontrollably, and helps immature cells grow into normal cells.

2. What you need to know before you take VANFLYTA

Do not take VANFLYTA

- if you are allergic to quizartinib or any of the other ingredients in this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

- if you were born with a heart problem called 'long QT syndrome' (abnormal electrical activity of the heart that affects its rhythm).
- if you are breast-feeding (see 'Pregnancy, breast-feeding and fertility').

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking VANFLYTA:
- if you have or have had any heart problems including arrhythmia (abnormal heart rhythm), myocardial infarction (heart attack) within 6 months, congestive heart failure (heart isn't pumping hard enough), uncontrolled angina pectoris (chest pain) or uncontrolled hypertension (blood pressure that's too high).
- if you have been told you have low blood levels of potassium or magnesium.
- if you are taking medicines that can prolong the QT interval (irregular heart rhythm; see 'Other medicines and VANFLYTA').
- if you are taking strong CYP3A inhibitors (see 'Other medicines and VANFLYTA').
- if you have or have had fever, cough, chest pain, shortness of breath, tiredness or pain when urinating.

Monitoring during treatment with VANFLYTA

Blood tests
Your doctor will perform regular blood tests during treatment with VANFLYTA to check your blood cells (white blood cells, red blood cells, and platelets) and electrolytes (salts such as sodium, potassium, magnesium, calcium, chloride and bicarbonate in blood). Your doctor will check your electrolytes more often if you are experiencing diarrhoea or vomiting.

Electrocardiogram
Before and during your treatment, your doctor will check your heart with an electrocardiogram (ECG) to make sure your heart is beating normally. ECGs will be done weekly initially and less often thereafter as decided by your doctor. Your doctor will check your heart more often if you are taking other medicines that prolong the QT interval (see 'Other medicines and VANFLYTA').

Infections in patients older than 65 years
Elderly patients are at increased risk for very serious infections when compared to younger patients, especially in the early treatment period. If you are older than 65 years of age you will be closely monitored for the occurrence of severe infections during induction.

Children and adolescents

Do not give this medicine to children or adolescents below 18 years of age because there is not enough information about its use in this age group.

Other medicines and VANFLYTA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, vitamins, antacids (medicines for heartburn and stomach acidity) and herbal supplements. This is because some medicines can affect how VANFLYTA works.

In particular, the following medicines may increase the risk of side effects with VANFLYTA by increasing the levels of this medicine in the blood:
- certain medicines used to treat fungal infections – such as itraconazole, posaconazole or voriconazole;
- certain antibiotics – such as clarithromycin or telithromycin;
- nefazodone, a medicine used to treat major depression.

The following medicines may reduce the effectiveness of VANFLYTA:
- certain medicines used to treat tuberculosis – such as rifampicin;
- certain medicines used to treat seizures or epilepsy – such as carbamazepine, primidone, phenobarbital or phenytoin;
- certain medicines to treat prostatic cancer – such as apalutamide and enzalutamide;
- mitotane – a medicine used for the treatment of symptoms of tumours of the adrenal glands;
- bosentan – a medicine used to treat high blood pressure in the lungs (pulmonary arterial hypertension);
- St. John's Wort (*Hypericum perforatum*) – an herbal product used for anxiety and mild depression.

Certain medicines use 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.

QT interval prolonging medicinal products
Co-administration of VANFLYTA with other medicinal products that prolong the QT interval may further increase the risk 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.

Pregnancy, breast-feeding and fertility

Pregnancy
You should not take VANFLYTA during pregnancy. This is because it may harm your unborn baby. Women who are able to become pregnant should have a pregnancy test within 7 days before taking this medicine.

Women should use effective contraception during treatment with VANFLYTA and for at least 7 months after stopping treatment. Men should use effective contraception during treatment with VANFLYTA and for at least 4 months after stopping treatment.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Breast-feeding
Do not breast-feed during treatment with VANFLYTA, and for at least 5 weeks after stopping treatment. This is because it is not known if VANFLYTA passes into your breast milk (see 'Do not take VANFLYTA').
If you are breast-feeding, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Fertility
VANFLYTA may reduce fertility in women and men. You should discuss this with your doctor before starting treatment.

Driving and using machines

VANFLYTA is unlikely to affect your ability to drive or use machines.

3. How to take VANFLYTA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much VANFLYTA to take

Your doctor or pharmacist will tell you exactly how much VANFLYTA to take. Do not change your dose or stop taking VANFLYTA without talking to your doctor first.

Usually you will start by taking 35.4 mg (two 17.7 mg tablets) once daily for 2 weeks during each cycle of chemotherapy. The maximum recommended dose is 53 mg once daily.

Your doctor may start you on a lower dose of one 17.7 mg tablet once daily if you are taking certain other medicines.

After your chemotherapy is completed your doctor may change your dose to one 26.5 mg tablet once daily for 2 weeks and then increase your dose to 53 mg (two 26.5 mg tablets) once daily going forward depending on how you respond to VANFLYTA.

Your doctor may temporarily interrupt treatment or change your dose based on blood tests, side effects or other medicines you may be taking.

Your doctor will discontinue your treatment if you are having a stem cell transplant. Your doctor will tell you when to stop taking your medicine and when to restart it.

Taking this medicine

- Take VANFLYTA by mouth - either with or without food.
- Take VANFLYTA at about the same time each day. This will help you remember to take your medicine.
- If you vomit after you take this medicine, do not take any more tablets until your next scheduled dose.

How long to take VANFLYTA

Continue taking VANFLYTA for as long as your doctor tells you. Your doctor will regularly monitor your condition to check that the treatment is continuing to work.

If you have any questions about how long to take VANFLYTA, talk to your doctor or pharmacist.

If you take more VANFLYTA than you should

If you accidentally take more tablets than you should, or if someone else accidentally takes your medicine, talk to a doctor straightaway or go to a hospital and take this package leaflet with you. Medical treatment may be necessary.

If you forget to take VANFLYTA

If you forget to take VANFLYTA, take it as soon as possible on the same day. Take your next dose at your usual time on the next day.

Do not take an extra dose (two doses on the same day) to make up for a forgotten dose.

If you stop taking VANFLYTA

Stopping your treatment with VANFLYTA may cause your condition to become worse. Do not stop taking your medicine unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor, pharmacist or nurse immediately if you notice the following side effects:
- feeling dizzy, lightheaded or faint. These could be signs of a heart problem called 'prolonged QT interval' (abnormal electrical activity of the heart that affects its rhythm).
- fever, cough, chest pain, shortness of breath, tiredness or pain when urinating. These could be signs of an infection or febrile neutropenia (low white blood cell counts with fever).

Very common side effects
(may affect more than 1 in 10 people)
- Increase in alanine aminotransferase (abnormal liver enzyme results)
- Thrombocytopenia (low levels of blood platelets)
- Anaemia (low levels of red blood cells)
- Neutropenia (low levels of neutrophils, a type of white blood cell)
- Diarrhoea
- Nausea (feeling sick)
- Abdominal (stomach) pain
- Headache
- Vomiting
- Oedema (swelling of the face, arms and legs)
- Upper respiratory tract infections (nose and throat infections)
- Decreased appetite
- Epistaxis (severe nosebleeds)
- Fungal infections
- Herpes infections
- Dyspepsia (indigestion)
- Bacteraemia (bacteria in the blood)

Common side effects
(may affect up to 1 in 10 people)
- Pancytopenia (low levels in all types of blood cells)

Uncommon side effects
(may affect up to 1 in 100 people)
- Cardiac arrest (heart stops beating)
- Ventricular fibrillation (dangerous, irregular and uncoordinated contractions of the lower chambers of the heart)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VANFLYTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What VANFLYTA contains

- The active substance is quizartinib.
  VANFLYTA 17.7 mg: Each film-coated tablet contains 17.7 mg quizartinib (as dihydrochloride).
  VANFLYTA 26.5 mg: Each film-coated tablet contains 26.5 mg quizartinib (as dihydrochloride).
- The other ingredients are:
  VANFLYTA 17.7 mg:
  Tablet core: Hydroxypropylbetadex, microcrystalline cellulose, magnesium stearate
  Film-coating: Hypromellose, talc, triacetin, titanium dioxide
  VANFLYTA 26.5 mg:
  Tablet core: Hydroxypropylbetadex, microcrystalline cellulose, magnesium stearate
  Film-coating: Hypromellose, talc, triacetin, titanium dioxide, yellow iron oxide

What VANFLYTA looks like and contents of the pack

VANFLYTA 17.7 mg film-coated tablets (tablets) are white, round and with ‘DSC 511’ on one side, and available in cartons containing 14 x 1 or 28 x 1 film-coated tablets in aluminium/aluminium perforated unit dose blisters.

VANFLYTA 26.5 mg film-coated tablets (tablets) are yellow, round and with ‘DSC 512’ on one side, and available in cartons containing 14 x 1, 28 x 1 or 56 x 1 film-coated tablets in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Quizartinib plus chemotherapy in newly diagnosed patients with *FLT3*-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Patients with acute myeloid leukaemia (AML) positive for internal tandem duplication (ITD) mutations of *FLT3* have poor outcomes. Quizartinib, an oral, highly potent, selective, type 2 FLT3 inhibitor, plus chemotherapy showed antitumour activity with an acceptable safety profile in patients with *FLT3*-ITD-positive newly diagnosed AML. The aim of the study was to compare the effect of quizartinib versus placebo on overall survival in patients with *FLT3*-ITD-positive newly diagnosed AML aged 18–75 years.

Methods We conducted a randomised, double-blind, placebo-controlled, phase 3 trial comparing quizartinib and placebo in combination with chemotherapy in induction and consolidation, followed by quizartinib or placebo single-agent continuation, in patients with *FLT3*-ITD-positive newly diagnosed AML at 193 hospitals and clinics in 26 countries in Europe; North America; and Asia, Australia, and South America. Patients aged 18–75 years were eligible. Patients were randomly assigned (1:1) to the quizartinib group or the placebo group by an independent biostatistician through an interactive web and voice response system, stratified by region, age, and white blood cell count at diagnosis. Patients, investigators, funders, and contract research organisations were masked to treatments assigned. Induction therapy comprised a standard 7+3 induction regimen of cytarabine 100 mg/m² per day (or 200 mg/m² per day allowed if institutional or local standard) by continuous intravenous infusion from day 1 to day 7 and anthracycline (daunorubicin 60 mg/m² per day or idarubicin 12 mg/m² per day) by intravenous infusion on days 1, 2, and 3, then quizartinib 40 mg orally or placebo once per day, starting on day 8, for 14 days. Patients with complete remission or complete remission with incomplete neutrophil or platelet recovery received standard consolidation with high-dose cytarabine plus quizartinib (40 mg per day orally) or placebo, allogeneic haematopoietic cell transplantation (allo-HCT), or both as consolidation therapy, followed by continuation of single-agent quizartinib or placebo for up to 3 years. The primary outcome was overall survival, defined as time from randomisation until death from any cause and assessed in the intention-to-treat population. Safety was evaluated in all patients who received at least one dose of quizartinib or placebo. This study is registered with ClinicalTrials.gov (NCT02668653).

Findings Between Sept 27, 2016, and Aug 14, 2019, 3468 patients with AML were screened and 539 patients (294 [55%] male patients and 245 [45%] female patients) with *FLT3*-ITD-positive AML were included and randomly assigned to the quizartinib group (n=268) or placebo group (n=271). 148 (55%) of 268 patients in the quizartinib group and 168 (62%) of 271 patients in the placebo group discontinued the study, primarily because of death (133 [90%] of 148 in the quizartinib group *vs* 158 [94%] of 168 in the placebo group) or withdrawal of consent (13 [9%] of 148 in the quizartinib group *vs* 9 [5%] of 168 in the placebo group). Median age was 56 years (range 20–75, IQR 46·0–65·0). At a median follow-up of 39·2 months (IQR 31·9–45·8), median overall survival was 31·9 months (95% CI 21·0–not estimable) for quizartinib versus 15·1 months (13·2–26·2) for placebo (hazard ratio 0·78, 95% CI 0·62–0·98, p=0·032). Similar proportions of patients in the quizartinib and placebo groups had at least one adverse event (264 [100%] of 265 in the quizartinib group and 265 [99%] of 268 in the placebo group) and one grade 3 or higher adverse event (244 [92%] of 265 in the quizartinib group and 240 [90%] of 268 in the placebo group). The most common grade 3 or 4 adverse events were febrile neutropenia, hypokalaemia, and pneumonia in both groups and neutropenia in the quizartinib group.

Interpretation The addition of quizartinib to standard chemotherapy with or without allo-HCT, followed by continuation monotherapy for up to 3 years, resulted in improved overall survival in adults aged 18–75 years with *FLT3*-ITD-positive newly diagnosed AML. Based on the results from the QuANTUM-First trial, quizartinib provides a new, effective, and generally well tolerated treatment option for adult patients with *FLT3*-ITD-positive newly diagnosed AML.

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Introduction

Acute myeloid leukaemia (AML) is a genetically heterogeneous disease with poor clinical outcomes.[1–4] Mutations in *FLT3* are among the most frequently reported genetic alterations in AML.[1,5–7] Approximately 25% of patients with newly diagnosed AML have *FLT3* internal tandem duplication (ITD) mutations; approximately 7% have point mutations in the tyrosine kinase domain (TKD).[1,8] *FLT3*-ITD is associated with poor prognosis, including increased risk of relapse and shorter overall survival versus wild-type *FLT3* and *FLT3*-TKD.[1,8–14]

Standard treatments for *FLT3*-ITD-positive AML include chemotherapy and allogeneic haematopoietic cell transplantation (allo-HCT).[15] Furthermore, several FLT3-targeted agents, including multikinase inhibitors, have been investigated in patients with *FLT3*-mutated AML.[16–24] In 2017, the multikinase inhibitor midostaurin, plus standard chemotherapy, gained US Food and Drug Administration (FDA) and European Medicines Agency approval for the treatment of newly diagnosed AML with either ITD or TKD mutations on the basis of data from the RATIFY trial.[22]

Quizartinib is an oral, once per day, highly potent, selective, second-generation, type 2 FLT3 inhibitor.[16,25–27] In phase 1/2 trials, quizartinib plus chemotherapy showed antileukaemic activity with an acceptable safety profile[28–30] and as a single agent after allo-HCT[31] in patients with *FLT3*-ITD-positive newly diagnosed AML.

Research in context

Evidence before this study

Standard treatments for acute myeloid leukaemia (AML) with internal tandem duplication (ITD) mutations of *FLT3* include chemotherapy and allogeneic haematopoietic cell transplantation (allo-HCT). Several *FLT3*-targeted agents, including multikinase inhibitors, have been investigated in patients with *FLT3*-mutated AML. In 2017, the multikinase inhibitor midostaurin was approved by the US Food and Drug Administration and the European Medicines Agency for newly diagnosed *FLT3*-mutation-positive AML in combination with standard chemotherapy on the basis of data from the RATIFY trial. Midostaurin is a type 1 inhibitor, essentially ATP-mimetic, that inhibits both internal tandem duplication and tyrosine kinase domain mutations. Despite advances in the past 6 years, there is need for continued improvement of outcomes for patients with *FLT3*-ITD-positive newly diagnosed AML due to the high rate of relapse. We searched PubMed for clinical studies of patients with newly diagnosed *FLT3*-mutated AML using the search terms "AML", "Acute Myeloid Leukemia", "Acute Myeloblastic Leukemia", "Acute myelogenous leukemia", and "*FLT3*". We included all English language articles published from database inception to Sept 27, 2016. We searched the American Society of Hematology, European Hematology Association, American Society of Clinical Oncology, and European Society for Medical Oncology congresses for the years 2015 and 2016. The phase 3 RATIFY trial of standard chemotherapy and midostaurin in patients with newly diagnosed *FLT3*-mutated AML showed that the addition of midostaurin to standard chemotherapy for 1 year of maintenance therapy significantly improved event-free survival and overall survival.

Added value of this study

Our trial (QuANTUM-First) is the first trial to evaluate the efficacy and safety of the potent and selective FLT3-ITD type 2 inhibitor quizartinib in patients aged 18–75 years with *FLT3*-ITD-positive newly diagnosed AML alongside standard induction and consolidation chemotherapy, including allo-HCT, then single-agent continuation therapy for up to 3 years. QuANTUM-First is also the first large global phase 3 study of newly diagnosed AML to use *FLT3*-ITD measurable residual disease (MRD) assessment to show the effects of a reduction in *FLT3*-ITD MRD by an FLT3 inhibitor at the end of induction, highlighting it as a powerful tool in this heterogeneous disease. QuANTUM-First showed superior overall survival of quizartinib to placebo in patients with *FLT3*-ITD-positive newly diagnosed AML. Clinically meaningful improvements in relapse-free survival, reduced cumulative incidence of relapse, increased duration of complete remission, and reduction in MRD underpin the overall survival benefit. Quizartinib had a generally manageable safety profile, with no new safety signals identified.

Implications of all the available evidence

The findings from QuANTUM-First show the potential to provide a novel and well tolerated treatment option for adult patients with *FLT3*-ITD-positive newly diagnosed AML. To our knowledge, the survival improvement in QuANTUM-First is the first reported evidence of treatment benefit with a potent and specific FLT3 inhibitor for patients with *FLT3*-ITD-positive newly diagnosed AML, including patients who are older than 60 years. These patients were excluded from the RATIFY study, which enrolled patients up to age 59 years. The survival benefit observed in RATIFY could primarily be attributed to the 35% reduced risk of death in the *FLT3*-TKD population versus the 20% reduction in the *FLT3*-ITD population. The findings from QuANTUM-First represent important progress in the management of patients older than 60 years with *FLT3*-ITD-positive newly diagnosed AML.

Furthermore, quizartinib monotherapy improved overall survival versus salvage chemotherapy in the relapsed or refractory setting in the phase 3 QuANTUM-R trial.[17] To date, QuANTUM-First is the first trial to evaluate the efficacy and safety of a selective FLT3 inhibitor, quizartinib, in patients aged 18–75 years with *FLT3*-ITD-positive newly diagnosed AML alongside standard induction and consolidation chemotherapy, including allo-HCT, then single-agent continuation therapy for up to 3 years. This study aimed to assess the effect of quizartinib versus placebo on overall survival in patients with *FLT3*-ITD-positive newly diagnosed AML. We hypothesised that quizartinib would extend overall survival in these patients.

Methods

Study design and patients

QuANTUM-First, a randomised, double-blind, placebo-controlled, global phase 3 study (appendix p 10), was conducted at 193 hospitals and clinics in 26 countries in Europe, Asia, North America, South America, and Australia in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines outlined by the International Council for Harmonization. Institutional review boards or independent ethics committees approved the protocol at each participating site (appendix p 2). Patients provided written informed consent before enrolment (appendix p 24).

Patients aged 18–75 years with morphologically documented primary newly diagnosed AML, or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm, with an *FLT3*-ITD mutation identified by central laboratory assessment in bone marrow or peripheral blood at screening and able to receive standard induction chemotherapy were eligible. Investigators prospectively screened patients for eligibility at clinics and hospitals after their presentation with an initial diagnosis of AML. Information, data, and medical records of each patient were reviewed by investigators. Furthermore, necessary tests were conducted and the results were reviewed by the investigators to assess the eligibility of patients. Patients had to have a variant allelic frequency (VAF; *FLT3*-ITD divided by total *FLT3*) of 3% or more; an Eastern Cooperative Oncology Group performance status of 0–2; and adequate cardiac, renal, and hepatic function at randomisation. Patients diagnosed with acute promyelocytic leukaemia with t(15;17), *BCR-ABL1*-positive leukaemia, or AML secondary to previous chemotherapy or radiotherapy were excluded (appendix pp 3–5). Sex data were self-reported by patients; the options were male or female.

Randomisation and masking

Patients were randomly assigned (1:1) to the quizartinib group or the placebo group. Randomisation was stratified by region (Europe; North America; or Asia, Australia, and South America), age (<60 years and ≥60 years), and white blood cell count at diagnosis (<40×10^9/L and ≥40×10^9/L).[32] Randomisation was managed by an independent biostatistician through an interactive web and voice response system using a stratified permuted block procedure. The investigators enrolled patients, were fully responsible for the management of patients during the trial, and were responsible for the data. Patients, investigators, funders, and contract research organisations were masked to treatments assigned. Masking was achieved as placebo tablets matched the appearance of the quizartinib tablets. The success of blinding was not assessed. In an emergency, unmasking information was restricted to designated study centre staff or personnel providing immediate care to the patient.

Procedures

See Online for appendix

During the first induction cycle, all patients received a standard 7+3 induction regimen with cytarabine 100 mg/m² per day (200 mg/m² per day allowed if institutional or local standard) by continuous intravenous infusion from day 1 to day 7 and anthracycline (daunorubicin 60 mg/m² per day or idarubicin 12 mg/m² per day) by intravenous infusion on days 1, 2, and 3. Patients were randomly assigned on day 7 to receive quizartinib or placebo. On day 8, patients started quizartinib 40 mg or placebo orally once per day for 14 days. On day 21 (up to day 28), a bone marrow aspirate specimen was collected for local and central morphology assessment. Investigators made treatment decisions on the basis of local results. If required, the bone marrow aspirate was repeated upon count recovery or up to day 56 (plus or minus 3 days), for reliable assessment of response at the end of induction. Patients with persistent leukaemia after the first cycle could receive a second cycle of induction chemotherapy with either 7+3 or 5+2 regimens plus quizartinib or placebo, according to institutional standard practice (appendix p 5).

Patients with complete remission or with complete remission with incomplete neutrophil or platelet recovery during induction (appendix p 5) could proceed to consolidation, consisting of treatment with high-dose cytarabine plus quizartinib (40 mg/day) or placebo (up to four cycles), allo-HCT alone (from end of induction to within 3 months of starting continuation), or treatment with high-dose cytarabine plus quizartinib (40 mg/day) or placebo then allo-HCT (appendix p 5). High-dose cytarabine was administered by intravenous infusion every 12 h on days 1, 3, and 5 for a total of six doses. Patients younger than 60 years received cytarabine 3 g/m² per dose, whereas patients aged 60 years or older received 1·5 g/m² per dose. Quizartinib or placebo was then administered orally once per day for 14 days from day 6 to day 19. For patients concomitantly receiving a strong CYP3A4 inhibitor, the dose was reduced to 20 mg/day. Each consolidation cycle could last up to

60 days to allow blood count recovery. A bone marrow aspirate specimen was collected for local and central morphology assessment in cycle 1 of consolidation and in the last cycle of consolidation upon count recovery between days 21 and 56.

Quizartinib or placebo continuation therapy began after induction and consolidation therapy (including allo-HCT) upon blood count recovery (absolute neutrophil count [ANC] >500 mm³ and platelet count >50 000 mm³ without a platelet transfusion within 24 h of taking blood samples). Patients who had allo-HCT could start continuation therapy any time between 30 and 180 days after the transplantation. During continuation, patients received quizartinib (starting at 30 mg per day then increased to 60 mg per day if the mean QT interval corrected with Fridericia's formula [QTcF] of the triplicate echocardiogram was ≤450 ms on cycle 1, day 15) or placebo for up to 36 28-day cycles (3 years; appendix pp 5–6). For patients concomitantly receiving a strong CYP3A4 inhibitor, the dose of study drug on cycle 1, days 1–15, was 20 mg/day. On cycle 1 day 16, the dose was to be increased to 30 mg/day if the mean QTcF of the triplicate electrocardiogram (ECG) was 450 ms or less on cycle 1 day 15. If the dose of study drug could not be increased on cycle 1 day 16, the dose could be increased on cycle 2 day 2 if the mean QTcF of the triplicate ECG was 450 ms or less on cycle 2 day 1. Patients had to have their blood counts monitored at least every 4 weeks and a bone marrow examination every 12 weeks for 48 weeks and then every 24 weeks until week 96.

Dose modifications were implemented for QTcF prolongation, other non-haematological toxicities, myelosuppression, and concomitant administration of strong CYP3A inhibitors (appendix pp 6–7). Antibiotics (eg, quinolones), antifungals, and antivirals were used as standard of care for the prevention or treatment of infections. The fourth phase of the study was a long-term follow-up, which included patients who completed 36 cycles of quizartinib or placebo in the continuation phase and patients who permanently discontinued quizartinib or placebo in any phase (appendix p 7). The follow-up visit to assess adverse events occurred 30 days (up to 37 days) after the last dose of quizartinib or placebo once a patient permanently discontinued or completed the study. This was a telephone visit, unless the patient did not have an event-free survival event or any assessment had to be repeated for resolution of treatment-related adverse events. In these cases, an in-person visit was scheduled. Patients who did not have an event-free survival event were followed up every 4 weeks; these patients would attend the medical center for testing (eg, blood tests) and assessment of relapse or survival.

At each visit during induction, consolidation, and continuation, adverse events were directly observed by the investigator or reported by the patient. Patients with adverse events were followed up by an investigator until the adverse event had resolved or the condition of the patient had stabilised. For unresolved adverse events, including substantial atypical laboratory values at the end of study assessment, patients were followed up until adverse-event resolution or until the adverse event became clinically not relevant. Adverse events were graded with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Outcomes

The primary efficacy outcome was overall survival, defined as the time from randomisation until death from any cause and assessed in the intention-to-treat (ITT) population. Patients alive or lost to follow-up at the time of analysis were considered censored at the date when they were last known to be alive. Secondary efficacy outcomes, assessed in the ITT population, were based on independent review committee assessment and included event-free survival (defined as the time from randomisation to lack of complete remission based on independent review committee assessment, relapse, or death from any cause, whichever occurred first), rates of complete remission, composite complete remission (defined as complete remission or complete remission with incomplete neutrophil or platelet recovery), complete remission with *FLT3*-ITD measurable residual disease (MRD) negativity (assessed with next-generation sequencing and based on a cutoff of 10^{-4} leukaemia cells), and composite complete remission with *FLT3*-ITD MRD negativity (appendix p 7). The secondary outcome of pharmacokinetics will be published elsewhere. Exploratory outcomes included relapse-free survival and duration of complete remission by independent review committee. The primary outcome was analysed in all patients who were randomly assigned. The exploratory outcome of quality of life will be published elsewhere.

All safety analyses were based on the safety analysis population (ie, all patients who received at least one dose of the study drug; appendix p 8) and included the frequency and severity of adverse events. Adverse events recorded more than 30 days after the last dose of quizartinib or placebo were not considered unless they were thought to be drug related. If a patient had more than one adverse event, that patient was counted only once.

Statistical analysis

536 patients, with an expected 287 events, were estimated to be required to give the trial 84% power to detect a hazard ratio (HR) for death of 0·7 up to 30 months and of 1 after 30 months with a two-sided log-rank test at the 0·05 significance level. The findings from the midostaurin RATIFY study[22] were used in the design of QuANTUM-First. For overall survival, a plateau effect was observed after 30 months of treatment in the control group of the RATIFY study, with landmark survival rates in the *FLT3*-ITD-positive group of 42% at 30 months

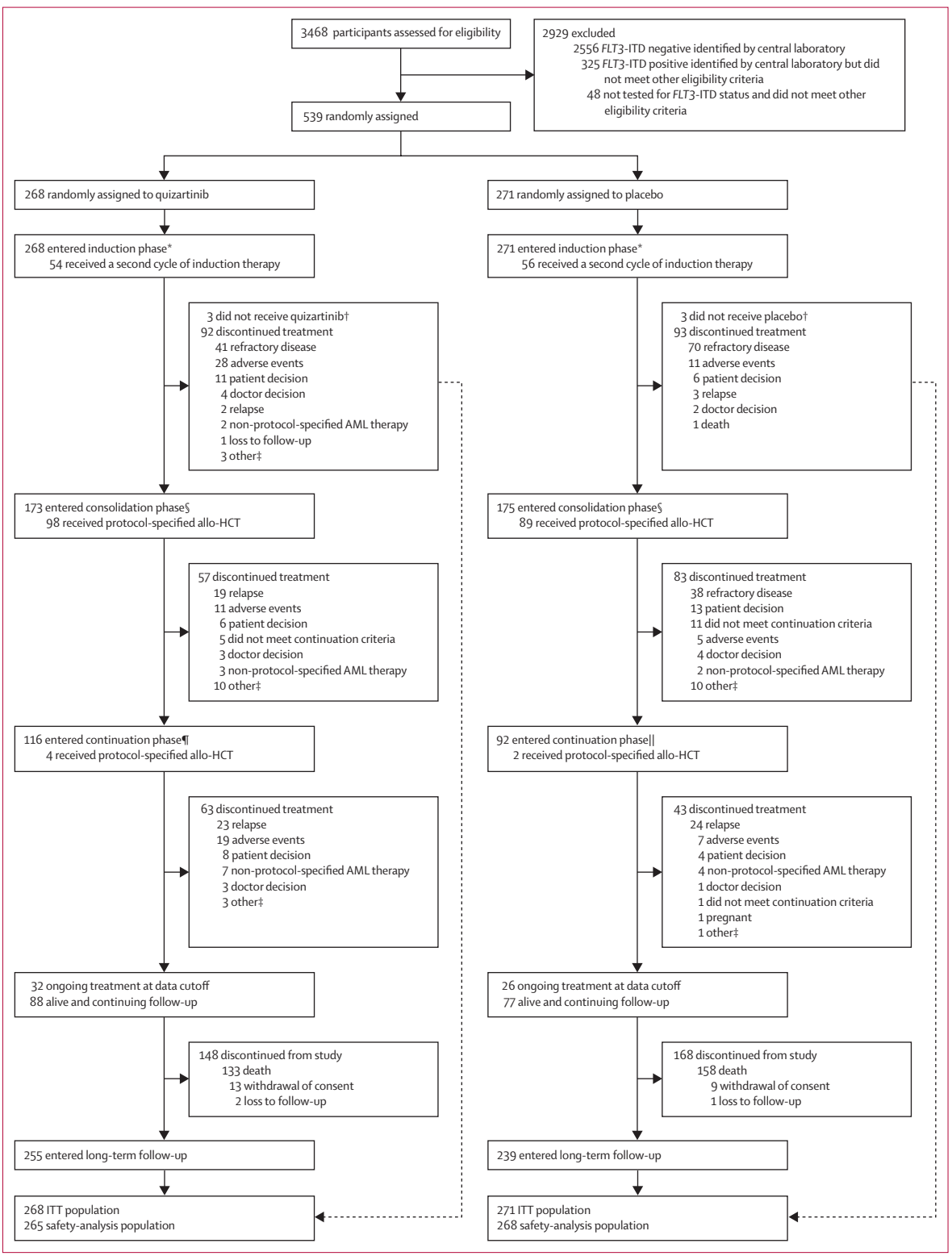

Figure 1: **Trial profile**
Allo-HCT=allogeneic haematopoietic cell transplantation. AML=acute myeloid leukaemia. *FLT3*-ITD=fms-related receptor tyrosine kinase 3–internal tandem duplication. ITT=intention-to-treat. *Median number of cycles of induction was 1 (range 1–2). †Not included in safety-analysis population. ‡Other reasons for exclusion are provided in the appendix (p 22). §Median number of cycles of consolidation was 2 (range 1–4). ¶Median number of cycles of continuation was 16 (range 1–36). ||Median number of cycles of continuation was 17 (range 1–36).

	Quizartinib (n=268)*	Placebo (n=271)*
Age, years		
Median (IQR)	56·0 (44·5–65·0)	56·0 (47·0–64·0)
Range	23–75	20–75
≥60 years	107 (40%)	109 (40%)
Sex		
Male	124 (46%)	121 (45%)
Female	144 (54%)	150 (55%)
Race		
Asian	80 (30%)	78 (29%)
Black or African American	2 (1%)	5 (2%)
American Indian or Alaska Native	0	1 (<1%)
White	159 (59%)	163 (60%)
Other	27 (10%)	24 (9%)
Region		
Europe	163 (61%)	163 (60%)
Asia or other regions	89 (33%)	90 (33%)
North America	16 (6%)	18 (7%)
ECOG performance status†		
0	87 (32%)	98 (36%)
1	134 (50%)	136 (50%)
2	47 (18%)	36 (13%)
AML type		
De novo AML	243 (91%)	255 (94%)
Secondary AML	25 (9%)	16 (6%)
Cytogenetic risks‡		
Favourable	14 (5%)	19 (7%)
Intermediate	197 (74%)	193 (71%)
Unfavourable	19 (7%)	27 (10%)
Unknown	38 (14%)	31 (11%)
Missing	0	1 (<1%)
Mutated *NPM1*§	142 (53%)	140 (52%)
Mutated *CEBPA*§¶	61 (23%)	65 (24%)
VAF‖		
≥3% to ≤25%	94 (35%)	98 (36%)
>25% to ≤50%	143 (53%)	138 (51%)
>50%	30 (11%)	35 (13%)
WBC count at diagnosis of AML		
<40 × 10⁹/L	135 (50%)	137 (51%)
≥40 × 10⁹/L	133 (50%)	134 (49%)

Data are n (%), median (IQR), or range. The intention-to-treat population includes all patients who were randomly assigned. AML=acute myeloid leukaemia. ECOG=Eastern Cooperative Oncology Group. *FLT3*-ITD=fms-related receptor tyrosine kinase 3–internal tandem duplication. VAF=variant allelic frequency. WBC=white blood cell. *Three patients in the intention-to-treat population were randomly assigned but not treated in each group. †One patient in the placebo group was missing an ECOG score. ‡Favourable: inv(16), t(16;16), t(8;21), or t(15;17); intermediate: normal, 8, 6, or –Y; unfavourable: del(5q), –5, del(7q), –7, or complex karyotype. §Based on the Navigate BioPharma central data. ¶In a post-hoc analysis, 18 (7%) of 268 patients in the quizartinib group and 20 (7%) of 271 patients in the placebo group had *CEBPA* single mutations; nine (3%) of 268 patients in the quizartinib group and four (1%) patients of 271 patients in the placebo group had *CEBPA* double mutations. ‖Variant allele frequency was assessed by central laboratory testing; one patient in the quizartinib group was enrolled on the basis of positive *FLT3*-ITD (VAF) per local laboratory testing, which was not confirmed by central laboratory testing due to lack of availability of screening sample; therefore, this one patient is classified as unknown *FLT3*-ITD (VAF) by central laboratory testing.

Table 1: **Demographics and baseline characteristics of the intention-to-treat population**

(corresponding to a hazard rate of 0·03) and 38% at 60 months (corresponding to a hazard rate of 0·003). A piecewise exponential model was considered to account for the plateau effect in the simulations to establish sample size and power.

Overall survival was analysed in the ITT population, consisting of all randomly assigned patients with a minimum 24 months of follow-up after the last randomly assigned patient. HR with 95% CI was estimated with a stratified Cox proportional hazards model. Median overall survival was calculated based on Kaplan-Meier estimates, with corresponding 95% CIs.[33] A sensitivity analysis of overall survival, censored for allo-HCT conducted at any time during the study, and subgroup analyses of overall survival were done (appendix pp 7–8).

Event-free survival was analysed in the ITT population with the stratified log-rank test and stratified Cox proportional hazards model. The primary analysis of event-free survival was based on lack of induction treatment success (defined as not having complete remission) during a 42-day period from the start of the last induction cycle (as defined in US FDA AML guidance).[34] Sensitivity and supplementary analyses of event-free survival used different definitions of lack of induction treatment success, such as not having composite complete remission (original protocol definition) or not having complete remission by the end of induction (including an optional second cycle) until blood count recovery up to day 56.

To control for the family-wise type 1 error rate for primary and secondary efficacy outcomes, serial, hierarchically ordered gatekeeping strategies were used. If the primary assessment of overall survival was significant, event-free survival was evaluated, then other secondary outcomes (appendix pp 8–9). Deviations from the protocol are provided in the appendix (p 9).

All statistical analyses were conducted with SAS version 9.4. An independent data monitoring committee, comprised of doctors and scientists who were not investigators in the study and were not otherwise directly associated with the funder, periodically reviewed unmasked safety or efficacy data in this study. This study is registered with ClinicalTrials.gov (NCT02668653).

Role of the funding source

Daiichi Sankyo and the study steering committee designed the study. Data were collected by the investigators and monitored by Daiichi Sankyo. Daiichi Sankyo and all authors were responsible for data analysis and interpretation, and for writing this Article.

Results

Between Sept 27, 2016, and Aug 14, 2019, 3468 patients with AML were screened and 539 patients (294 [55%] female patients and 245 [45%] male patients) with *FLT3*-ITD-positive AML were included in this study and randomly assigned to the quizartinib group (n=268) or the

placebo group (n=271). Of 3468 patients screened, 2929 (84%) were not eligible for inclusion. 2556 (87%) of 2929 were *FLT3*-ITD negative; 48 (2%) were not tested by the central laboratory (figure 1). One patient in the quizartinib group was enrolled on the basis of positive *FLT3*-ITD VAF by local laboratory testing that was not confirmed by central laboratory testing because of a lack of availability of screening sample. 864 (25%) of 3468 screened patients were *FLT3*-ITD-positive and 539 (16%) patients were randomly assigned (325 [9%] patients were *FLT3*-ITD-positive but excluded because they did not meet other eligibility criteria). 192 (72%) of 268 patients in the quizartinib group and 176 (65%) of 271 patients in the placebo group had composite complete remission after one or two cycles of induction. Of these, 167 (87%) in the quizartinib group and 164 (93%) in the placebo group proceeded to consolidation, and 114 (59%) in the quizartinib group and 87 (49%) in the placebo group entered continuation. Of the 533 patients randomly assigned and treated, 110 (21%; 54 in the quizartinib group and 56 in the placebo group) received a second induction cycle. In total, 348 patients (65%; 173 in the quizartinib group and 175 in the placebo group) proceeded to consolidation and 116 (44%) of 265 treated with quizartinib versus 92 (34%) of 268 treated with placebo entered continuation. At the time of data cutoff (Aug 13, 2021), 32 (12%) of 268 in the quizartinib group and 26 (10%) of 271 in the placebo group were still receiving study treatment.

The demographics and disease characteristics of patients were balanced between the treatment groups and were generally reflective of the patient population with *FLT3*-ITD-positive AML (table 1). Median age was 56 years (range 20–75, IQR 46·0–65·0). At a median follow-up of 39·2 months in both the quizartinib group (IQR 32·2–45·4) and placebo group (31·4–46·0), median overall survival was 31·9 months (95% CI 21·0–not estimable [NE]) for quizartinib versus 15·1 months (13·2–26·2) for placebo, with an HR for death of 0·78 (95% CI 0·62–0·98, p=0·032; figure 2A). A prespecified overall-survival sensitivity analysis that censored patients who received allo-HCT at any time was consistent with the primary analysis (HR 0·75, 0·56–1·01; appendix p 11). An improvement in overall survival favouring quizartinib was observed across most prespecified subgroups (appendix p 12). In a post-hoc subgroup analysis by age, the HR for overall survival was 0·68 (0·49–0·95) in patients younger than 60 years and 0·91 (0·66–1·26) in patients aged 60 years or older (appendix p 19).

The main analysis of the secondary outcome of event-free survival, based on the definition of lack of induction treatment success as not having complete remission within 42 days from the start of the last induction cycle, showed an HR of 0·92 (95% CI 0·75–1·11, p=0·24; appendix p 13). However, an event-free survival benefit favouring quizartinib was observed with the original protocol definition of lack of induction treatment success

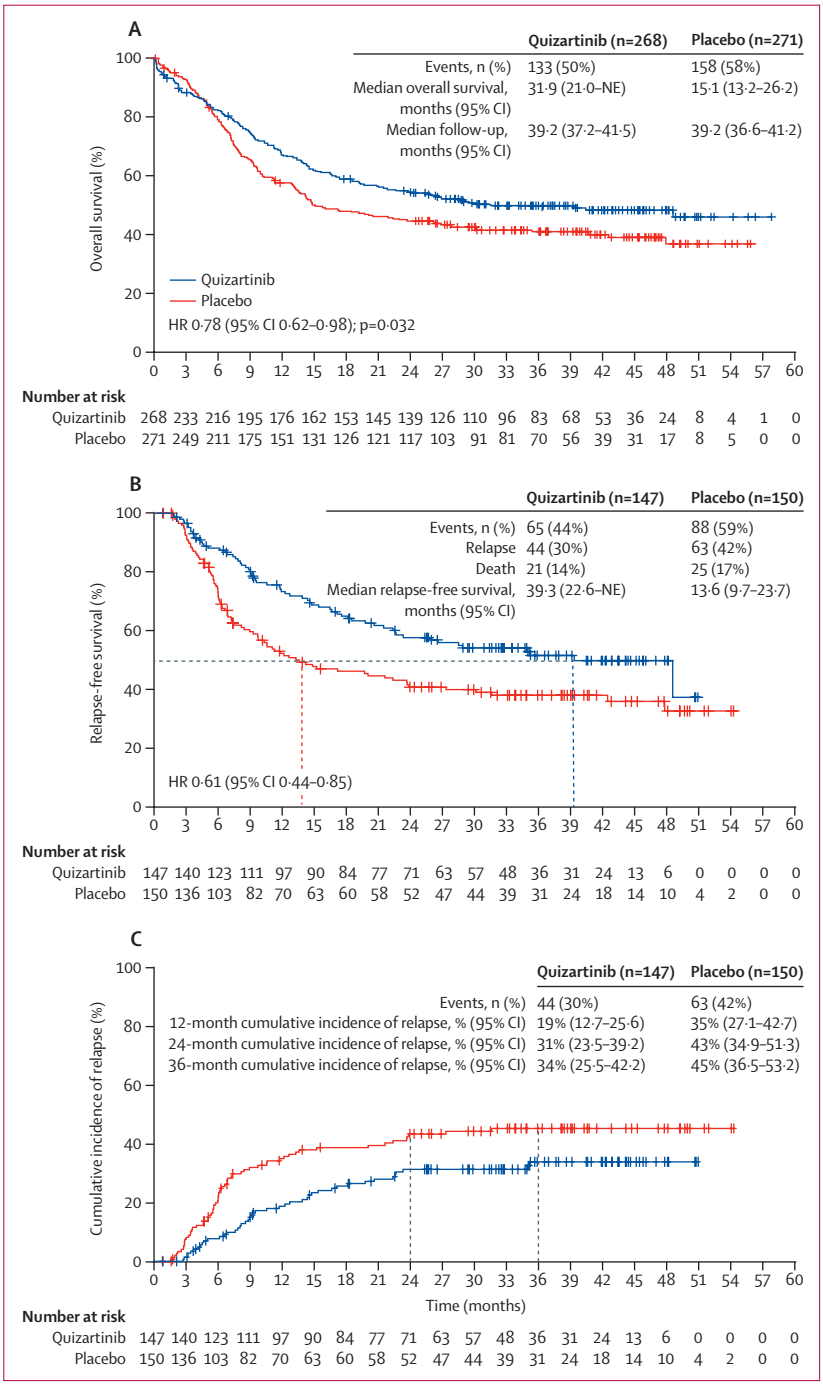

Figure 2: **Overall survival, relapse-free survival, and cumulative incidence of relapse**
(A) Overall survival in the ITT population. Overall survival was time from randomisation to death from any cause. (B) Relapse-free survival for patients with complete remission during induction per independent review committee assessment (exploratory outcome). Relapse-free survival was time from randomisation for patients with complete remission during induction until the date of documented relapse or death from any cause, whichever occurred first. (C) Cumulative incidence of relapse in patients with complete remission during induction per independent review committee assessment (post-hoc analysis). Plus symbols indicate censored data. ITT=intention-to-treat. NE=not estimable.

as not having composite complete remission by the end of induction up to day 56 (0·73, 0·59–0·90, $p_{nominal}$=0·0031; appendix p 13) or lack of induction treatment success as not having complete remission by the end of induction up to day 56 (0·82, 0·67–1·00, $p_{nominal}$=0·032; appendix p 13). Because the main analysis of event-free survival was not statistically significant, formal hierarchical testing on other secondary endpoints was stopped; their results are provided descriptively.

	Quizartinib (n=265)	Placebo (n=268)
Adverse events*	264 (100%)	265 (99%)
Drug-related adverse events†	160 (60%)	97 (36%)
Grade ≥3 adverse events (including grade 5)	244 (92%)	240 (90%)
Drug-related grade ≥3 adverse events† (including grade 5)	118 (45%)	65 (24%)
Adverse events associated with fatal outcome	30 (11%)	26 (10%)
Grade 5 infections and infestations	20 (8%)	12 (4%)
Drug-related adverse events associated with fatal outcome†	4 (2%)	4 (1%)
Serious adverse events	143 (54%)	123 (46%)
Serious adverse events occurring in ≥3% of patients in either group		
Febrile neutropenia	29 (11%)	22 (8%)
Pneumonia	17 (6%)	15 (6%)
Septic shock	11 (4%)	8 (3%)
Sepsis	10 (4%)	14 (5%)
Pyrexia	8 (3%)	5 (2%)
Thrombocytopenia	2 (1%)	8 (3%)
Drug-related serious adverse events†	41 (15%)	29 (11%)
Grade 3 or 4 pancytopenia*	6 (2%)	1 (<1%)
Grade 3 or 4 myelosuppression*	4 (2%)	0
Time to haematological recovery from C1D1 in patients with complete remission with onset of neutropenia or thrombocytopenia during induction, days		
Time to recovery of neutropenia (absolute neutrophil count ≥1000 cells per mm³)	36 (29–44)	29 (27–38)
Time to recovery of thrombocytopenia (platelet count ≥100 000 cells per mm³)	31 (28–40)	29 (26–34)
Transfusions	263 (99%)	266 (99%)
Platelets	261 (98%)	263 (98%)
Packed red blood cells	260 (98%)	260 (97%)
Immunostimulants	125 (47%)	121 (45%)
Filgrastim	92 (35%)	87 (32%)
G-CSF	22 (8%)	13 (5%)
Lenograstim	15 (6%)	15 (6%)
Dose modifications‡		
Adverse events associated with discontinuation*	54 (20%)§	23 (9%)
Adverse events associated with dose interruption*	90 (34%)	54 (20%)
Adverse events associated with dose reduction*	50 (19%)	17 (6%)
Dose reductions due to QT prolongation	10 (4%)	1 (<1%)
Summary of early deaths¶		
Deaths within 30 days of study drug initiation	15 (6%)	9 (3%)
Deaths within 60 days of study drug initiation	20 (8%)	13 (5%)

Data are n (%) or median (IQR). The safety-analysis population includes all patients who received at least one dose of quizartinib or placebo. Three patients in each group were not treated and are not included in the safety-analysis population. If a patient had more than one event, that patient was counted only once. C1D1=cycle 1 day 1. G-CSF=granulocyte colony stimulating factor. *Treatment emergent adverse events regardless of causality. †Based on investigator-reported causality. ‡Patients might be included in more than one category. §Four patients are not included as the adverse events were not considered treatment-emergent because they started either before first study drug administration or more than 30 days after the last study drug administration. ¶During induction, 20 patients died in the quizartinib group and 13 patients died in the placebo group.

Table 2: **Summary of overall safety of the safety-analysis population**

Rates of complete remission, composite complete remission, complete remission with incomplete neutrophil or platelet recovery, complete remission with MRD negativity, and composite complete remission with MRD negativity by independent review committee at the end of induction were similar between treatment groups (appendix p 20).

Median study drug exposure was 10·71 weeks (IQR 2·29–70·86) for quizartinib and 9·50 weeks (2·14–42·14) for placebo. Three patients in each group were not treated and are not included in the safety-analysis population. Similar proportions of patients in the quizartinib and placebo groups had at least one adverse event and one grade 3 or worse adverse event, with more frequent serious adverse events and adverse events associated with dose modifications in the quizartinib group than the placebo group (table 2). The most common grade 3 or 4 adverse events (in ≥10% of patients) were febrile neutropenia, hypokalaemia, and pneumonia in both groups and neutropenia in the quizartinib group (table 3). Among patients with complete remission, median time to recovery of neutropenia (ANC ≥1000 cells per mm³) was 36 days (IQR 29–44) in the quizartinib group and 29 days (27–38) in the placebo group. Median time to recovery of thrombocytopenia (platelet count ≥100 000 cells/mm³) was 31 days (28–40) in the quizartinib group and 29 days (26–34) in the placebo group (table 2). Myelosuppression and cytopenias were managed by transfusion, growth factor support, and dose modifications. QT prolongation adverse events were more frequent with quizartinib than placebo. Most QT prolongation adverse events were manageable, from the clinical perspective, with quizartinib dose modification and correction of electrolyte atypicalities. QTcF prolongation of more than 500 ms on ECG was uncommon (six [2%] of 265 in the quizartinib group and two [1%] of 268 in the placebo group). There were no cases of torsade de pointes; two patients in the quizartinib group (none in placebo) had cardiac arrest with recorded ventricular fibrillation on ECG (appendix p 21). The incidence of serious haemorrhages was low and similar between the quizartinib and placebo groups. Seven (3%) of 265 patients treated with quizartinib and eight (3%) of 268 patients treated with placebo had serious bleeding events. Adverse events associated with a fatal outcome occurred in 30 (11%) of 265 patients in the quizartinib group and 26 (10%) of 268 of the patients in the placebo group (table 2), with infections being the most common. More deaths occurred within the first 30 days of treatment in the quizartinib group than in the placebo group, primarily due to infections (table 2).

Median duration of complete remission was longer with quizartinib than with placebo (38·6 months, 95% CI 21·9–NE *vs* 12·4 months, 8·8–22·7; HR 0·62,

0·45–0·86; appendix p 14). In patients with complete remission during induction, relapse-free survival was longer with quizartinib versus placebo (HR 0·61, 0·44–0·85), with a median relapse-free survival of 39·3 months (22·6–NE) for quizartinib and 13·6 months (9·7–23·7) for placebo (figure 2B; appendix p 15). A 12-percentage-point decrease in cumulative incidence of relapse at 24 months versus placebo was also observed. We did a post-hoc analysis to analyse the cumulative incidence of relapse in patients with complete remission (figure 2C) or composite complete remission (appendix p 16) during induction. Reduced cumulative incidences of relapse were observed in patients with complete remission treated with quizartinib versus those treated with placebo (18·7% [95% CI 12·7–25·6] *vs* 34·9% [27·1–42·7] at 12 months and 31·2% [23·5–39·2] *vs* 43·3% [34·9–51·3] at 24 months; figure 2C).

A post-hoc analysis of *FLT3*-ITD MRD was done in 308 (84%) of the 368 patients with composite complete remission after induction (157 patients in the quizartinib group and 151 patients in the placebo group) with samples collected at the time of response assessment during induction, before any further therapy. Among the 157 patients with composite complete remission treated with quizartinib after induction, 66 (42%) had MRD less than 10^{-4} leukaemia cells at the time of complete remission or complete remission with incomplete neutrophil or platelet recovery. Among the 151 patients with composite complete remission treated with placebo after induction, 58 (38%) had MRD less than 10^{-4} leukaemia cells at the time of complete remission or complete remission with incomplete neutrophil or platelet recovery. Patients with composite complete remission with MRD less than 10^{-4} had improved overall survival compared with those with composite complete remission with MRD 10^{-4} or more, regardless of treatment, when combining the two randomised groups (HR 0·57, 0·40–0·80; appendix p 17). The proportion of patients with composite complete remission with *FLT3*-ITD MRD less than 10^{-4} was similar across groups (66 [25%] of 268 in the quizartinib group *vs* 58 [21%] of 271 in the placebo group; appendix p 20), whereas the proportion of patients with composite complete remission with undetectable MRD (by use of the 0 cutoff) was larger with quizartinib (37 [14%] of 268 *vs* 20 [7%] of 271). Among patients with composite complete remission after induction, the median *FLT3*-ITD VAF was three times lower with quizartinib (0·01%, IQR 0·00–0·182) than with placebo (0·03%, 0·00–0·26; appendix p 18).

	Quizartinib (n=265)		Placebo (n=268)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse events*	264 (100%)	214 (81%)	265 (99%)	214 (80%)
Haematological adverse events				
Febrile neutropenia	117 (44%)	115 (43%)	113 (42%)	110 (41%)
Neutropenia	54 (20%)	48 (18%)	27 (10%)	23 (9%)
Thrombocytopenia	30 (11%)	21 (8%)	30 (11%)	26 (10%)
Anaemia	29 (11%)	15 (6%)	19 (7%)	14 (5%)
Neutrophil count decreased	27 (10%)	23 (9%)	12 (4%)	9 (3%)
Non-haematological adverse events				
Pyrexia	112 (42%)	12 (5%)	109 (41%)	13 (5%)
Diarrhoea	98 (37%)	10 (4%)	94 (35%)	10 (4%)
Hypokalaemia	93 (35%)	50 (19%)	96 (36%)	44 (16%)
Nausea	90 (34%)	4 (2%)	84 (31%)	5 (2%)
Headache	73 (28%)	0	53 (20%)	2 (1%)
Rash	69 (26%)	8 (3%)	66 (25%)	3 (1%)
Vomiting	65 (25%)	0	53 (20%)	4 (1%)
Stomatitis	57 (22%)	12 (5%)	56 (21%)	8 (3%)
Constipation	56 (21%)	1 (<1%)	69 (26%)	0
Cough	50 (19%)	1 (<1%)	44 (16%)	0
Abdominal pain	46 (17%)	3 (1%)	38 (14%)	3 (1%)
Decreased appetite	46 (17%)	13 (5%)	36 (13%)	5 (2%)
Alanine aminotransferase increase	42 (16%)	12 (5%)	27 (10%)	13 (5%)
Epistaxis	40 (15%)	3 (1%)	29 (11%)	1 (<1%)
Pneumonia	39 (15%)	30 (11%)	41 (15%)	30 (11%)
Insomnia	37 (14%)	0	30 (11%)	0
Electrocardiogram QT prolongation	36 (14%)	8 (3%)	11 (4%)	3 (1%)
Pruritus	35 (13%)	2 (1%)	40 (15%)	0
Dyspepsia	30 (11%)	1 (<1%)	23 (9%)	2 (1%)
Oedema peripheral	30 (11%)	1 (<1%)	37 (14%)	3 (1%)
Hypomagnesemia	30 (11%)	1 (<1%)	30 (11%)	1 (<1%)
Hypertension	29 (11%)	13 (5%)	33 (12%)	18 (7%)
Upper abdominal pain	29 (11%)	3 (1%)	25 (9%)	2 (1%)
Arthralgia	29 (11%)	1 (<1%)	35 (13%)	2 (1%)
Fatigue	29 (11%)	1 (<1%)	23 (9%)	0
Aspartate aminotransferase increase	28 (11%)	7 (3%)	19 (7%)	3 (1%)
Hypophosphataemia	27 (10%)	18 (7%)	24 (9%)	16 (6%)
Oropharyngeal pain	27 (10%)	0	18 (7%)	1 (<1%)
Hypocalcaemia	26 (10%)	2 (1%)	29 (11%)	8 (3%)
Back pain	19 (7%)	0	28 (10%)	2 (1%)
Sepsis	15 (6%)	11 (4%)	28 (10%)	24 (9%)

Data are n (%). Only treatment-emergent adverse events that occurred in ≥10% of patients in the safety-analysis population of either group are presented. The safety analysis population includes all patients who received at least one dose of quizartinib or placebo. Three patients in each group were not treated and are not included in the safety-analysis population. If a patient had more than one event, that patient was counted only once. *Adverse events regardless of causality.

Table 3: **Summary of treatment-emergent adverse events**

Discussion

In this randomised, double-blind, placebo-controlled, phase 3 trial of adults aged 18–75 years with *FLT3*-ITD-positive newly diagnosed AML, quizartinib plus standard induction and consolidation therapy and up to 3 years of continuation with quizartinib monotherapy resulted in a statistically significant overall survival advantage. Median overall survival was longer with quizartinib compared with standard therapy in the placebo group, resulting in a 16·8-month extension of median overall survival and a significant reduction in the risk of

death (HR 0·78, 95% CI 0·62–0·98). As allo-HCT is the recommended consolidation therapy for patients with *FLT3*-ITD-positive AML in first composite complete remission,[1,3,15] we did an overall-survival sensitivity analysis by censoring for allo-HCT, which was consistent with the primary overall-survival analysis in favour of quizartinib. The significant improvement in overall survival is clinically relevant because of the high risk of relapse and poor prognosis of the study population. The effect of allo-HCT on overall survival with quizartinib versus placebo will be published elsewhere. The main event-free survival analysis, based on a lack of induction treatment success definition according to US FDA AML guidance,[34] showed no statistically significant difference between groups. However, additional prespecified event-free survival sensitivity and supplementary analyses, based on lack of induction treatment success definitions consistent with current AML guidelines,[35–37] showed a clear event-free survival benefit favouring quizartinib, probably because the period up to day 56 allowed patients to recover from quizartinib's myelosuppressive effects. Among patients with complete remission during induction, the median duration of complete remission was longer with quizartinib than with placebo, with sustained separation of the curves for up to 3 years. When MRD was assessed as detectable versus not detectable (at a cutoff of 0), differences between quizartinib and placebo were observed, suggesting the use of quizartinib in combination with chemotherapy leads to deeper responses. Detection of *FLT3*-ITD with next-generation sequencing allowed for the evaluation of *FLT3*-ITD presence at levels lower than what is routinely detected with the use of flow cytometry for a more sensitive measure of this aspect of the disease. Because quizartinib targets *FLT3*-ITD-positive AML, *FLT3*-ITD MRD is an important variable for evaluation in this patient population. Additional molecular data should continue to be evaluated to further elucidate a more comprehensive understanding of the molecular mechanisms owing to the benefit of quizartinib in patients with *FLT3*-ITD-positive AML in the first-line setting. In the meantime, these data suggest that there might be an advantage of being able to effectively target and reduce *FLT3*-ITD MRD in patients with AML who then have an overall survival benefit. The effect of *FLT3*-ITD MRD on overall survival will be published elsewhere. Furthermore, in patients with complete remission during induction, median relapse-free survival was three times longer with quizartinib than placebo, with a significant reduction of relapse or death favouring quizartinib (HR 0·61, 95% CI 0·44–0·85). This relapse-free survival benefit was maintained over time. A 12-percentage-point decrease in cumulative incidence of relapse at 24 months versus placebo was also observed, suggesting that quizartinib might prevent or delay relapses. The long-term survival benefits conferred by quizartinib might, in part, derive from an early and deeper reduction of the *FLT3*-ITD MRD burden compared with placebo.

In the phase 3, placebo-controlled RATIFY study, which enrolled younger patients than QuANTUM-First (aged 18–59 years), including 162 (23%) of 717 patients with *FLT3*-TKD-positive newly diagnosed AML and 555 (77%) of 717 patients with *FLT3*-ITD-positive newly diagnosed AML, the HR for reduction in risk of death for midostaurin was 0·65 (95% CI 0·39–1·08) in the *FLT3*-TKD-positive population, 0·80 (0·57–1·12) in the *FLT3*-ITD-positive population with a high ratio of mutant alleles to wild-type alleles (>0·7), and 0.81 (0·60–1·11) in the *FLT3*-ITD-positive population with a low ratio of mutant alleles to wild-type alleles (0·05–0·7).[22] The rate of cumulative incidence of relapse with midostaurin was approximately 40% at 2 years.[22] Therefore, despite advances in the past 6 years, new treatments are needed to improve outcomes for patients with *FLT3*-ITD-positive newly diagnosed AML. Other FLT3 inhibitors (eg, gilteritinib and crenolanib) are under evaluation with intensive chemotherapy for patients with *FLT3*-mutated newly diagnosed AML.[23,38] By contrast, QuANTUM-First enrolled patients at high risk of relapse aged 18–75 years (216 patients aged 60–75 years, representing 40% of the study population) with *FLT3*-ITD-positive newly diagnosed AML who were fit for intensive chemotherapy and still showed a robust reduction in risk of death with quizartinib. In the post-hoc subgroup analyses by age, the HR for overall survival was 0·68 (0·49–0·95) in patients younger than 60 years and 0·91 (0·66–1·26) in patients aged 60 years or older (appendix p 19). However, these subgroup analyses were not powered to detect treatment differences in each of the subgroups. The significant survival improvement in the overall population (age 18–75 years) is the first reported evidence of treatment benefit of an FLT3 inhibitor for patients at high risk of relapse with newly diagnosed AML and *FLT3*-ITD mutations, including patients who are aged 60 years or older (these patients were excluded from the RATIFY study).[22] The overall survival benefit was statistically significant and clinically meaningful in this population who have poor prognosis. At the time of the QuANTUM-First study, no data from other randomised studies were available for patients in this age group. To our knowledge, the QuANTUM-First study provides the first data for this subgroup, representing important progress in the management of patients aged 60 years or older with *FLT3*-ITD-positive newly diagnosed AML.

Quizartinib had a generally manageable safety profile, similar to that expected for patients with newly diagnosed AML receiving standard intensive chemotherapy alone or chemotherapy and midostaurin. Adverse events were managed through monitoring and dose modifications, with no new safety signals identified.[2,17] QT prolongation, myelosuppression, cytopenias, and infections were the main safety risks. Overall, the incidence of serious infections and cytopenias was generally well balanced between treatment groups, consistent with the use of induction and consolidation chemotherapy in the study.

Cytopenias and infections occurred predominantly during induction and consolidation. The most frequent adverse event occurring during single-agent continuation was neutropenia, which was manageable by dose reduction or interruption. Quizartinib is associated with QT prolongation in a dose-dependent and concentration-dependent manner.[39] Although the incidence of QT prolongation was higher with quizartinib than placebo, most events were asymptomatic and grade 1 or 2, and the incidence of grade 3 or worse QTcF prolongation overall was low, showing that QT prolongation with quizartinib is manageable with dose modification and correction of electrolyte atypicalities. The early death rates (within 30 days) from start of study drug (6% in the quizartinib group *vs* 3% in the placebo group) were in line with reported early mortality rates in patients with newly diagnosed AML treated with chemotherapy alone[40,41] or chemotherapy and an FLT3 inhibitor.[22] The most common reason for these early deaths was infection. The role of long-term quizartinib continuation therapy after chemotherapy will be reported elsewhere.

The placebo comparator group is one limitation of QuANTUM-First, considering that midostaurin plus chemotherapy has been the standard of care since 2017. However, when QuANTUM-First began in 2016, no *FLT3* inhibitor was approved for *FLT3*-mutated newly diagnosed AML, and there was a lack of randomised data in people aged 60 years or older. Therefore, at that time, chemotherapy plus placebo was chosen as the appropriate comparator. Furthermore, the data monitoring committee reviewed the RATIFY data[22] and recommended continuing the QuANTUM-First study as originally designed, maintaining the placebo group. Another limitation is the low enrolment in North America, probably because midostaurin received US approval 7 months after the start of QuANTUM-First, whereas it received EU approval 12 months after the start of QuANTUM-First. Enrolment in the EU was not affected as much as enrolment in the USA, probably because in some EU countries, reimbursement for midostaurin was granted by health technology assessment agencies up to 3 years after its approval.

QuANTUM-First showed overall survival improvement in patients with *FLT3*-ITD-positive newly diagnosed AML. Clinically meaningful improvements in relapse-free survival, reduced cumulative incidence of relapse, increased duration of complete remission, and reduction in MRD underlie the overall survival benefit. Safety of quizartinib was generally manageable, with no new safety signals identified. The findings from QuANTUM-First show the potential to provide an effective and well tolerated treatment option for patients aged 18–75 years with *FLT3*-ITD-positive newly diagnosed AML.

Contributors

Daiichi Sankyo and the study steering committee (including HPE, PM, EP, JC, AEP, MAS, HD, SA, JW, MJL, and RFS) designed the study. All authors contributed to critical review and revision of the Article and approved the decision to submit for publication. Data were collected by the investigators and monitored by Daiichi Sankyo. All authors had full access to all the data in the study. LL and HPE directly accessed and verified the data. HPE, RFS, and MJL wrote the first draft of this Article with professional medical writing and editing support. Daiichi Sankyo and all authors were responsible for data analysis and interpretation.

Declaration of interests

HPE reports research grants from AbbVie, Agios Pharmaceuticals, ALX Oncology, Amgen, Ascentage, Celgene, Daiichi Sankyo, Forma Therapeutics, Forty Seven, Gilead, GlycoMimetics, ImmunoGen, Jazz Pharmaceuticals, Kura Oncology, MacroGenics, Novartis, PTC Therapeutics, Servier, and Sumitomo Dainippon Pharma; consulting fees for participation on advisory boards for AbbVie, Agios Pharmaceuticals, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Genentech, GlycoMimetics, ImmunoGen, Incyte, Jazz Pharmaceuticals, Kura Oncology, MacroGenics, Novartis, Pfizer, Servier, Syros Pharmaceuticals, Takeda, and Trillium Therapeutics; payment for speakers bureaus from AbbVie, Agios Pharmaceuticals, Bristol Myers Squibb, Celgene, Incyte, Jazz Pharmaceuticals, Novartis, and Servier; and has served as a steering committee member for GlycoMimetics, as chair of the Myeloid Neoplasms Repository study for Bristol Myers Squibb and Celgene, and as chair of the independent review committee of the VIALE A and VIALE C studies for AbbVie. PM reports research grants from AbbVie, Bristol Myers Squibb, Jazz Pharmaceuticals, Menarini, Stemline Therapeutics, Novartis, Pfizer, and Takeda; consulting fees from AbbVie, Astellas, BeiGene, Bristol Myers Squibb, Gilead, Incyte, Jazz Pharmaceuticals, Kura Oncology, Menarini, Stemline Therapeutics, Nerviano Medical Sciences, Novartis, Otsuka Pharmaceutical, Pfizer, Ryvu Therapeutics, and Takeda; and payment for speakers bureaus from AbbVie, Astellas, Bristol Myers Squibb, Gilead, Jazz Pharmaceuticals, and Pfizer. H-JK reports research grants from BL&H; consulting fees from AbbVie, AIMS BioScience, Amgen, AMLHub, Astellas, Aston BioSciences, Bristol Myers Squibb, Celgene, Boryung Pharmaceutical, Daiichi Sankyo, Handok, Ingenium, Janssen, LG Chem, Novartis, Pfizer, Sanofi Genzyme, SL VaxiGen, and VigenCell; is on a data safety monitoring board or advisory board for AbbVie, the Asia Pacific Leukemia Consortium, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Handok, Janssen, Novartis, Pfizer, and Sanofi Genzyme; and is a leader in other board, society, committee, or advocacy groups for AMLHub, the Asia Pacific Leukemia Consortium, the Asia Pacific Blood and Marrow Transplantation Group, and the Korean Society of Blood and Marrow Transplantation. EP reports consulting fees from KCR US; payment for lectures from Amgen, Angelini, Astellas, Novartis, Pfizer, and Servier; and support for attending meetings from Angelini, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Pfizer, and Servier. RV reports consulting fees from AbbVie, Astellas, Pfizer, and PharmaS; and payment for lectures from AbbVie, Astellas, Merck Sharp & Dohme, Novartis, Pfizer, PharmaS, Servier, and Teva. JC reports research grants from AbbVie, Daiichi Sankyo, Novartis, Sun Pharma, and Pfizer; consulting fees from AbbVie, Bio-Path, Daiichi Sankyo, Gilead, Forma Therapeutics, Novartis, Pfizer, and Takeda; payment for lectures from Novartis, Pfizer, and Takeda; and has stock options with Bio-Path. AEP reports research grants from AbbVie, Actinium Pharmaceuticals, Astellas, Bayer, BioMed Valley Discoveries, and Daiichi Sankyo; personal fees from Actinium Pharmaceuticals, Agios Pharmaceuticals, Astellas, Daiichi Sankyo, Forma Therapeutics, Jazz Pharmaceuticals, Leukemia & Lymphoma Society (Beat AML Master Clinical Trial), Loxo Oncology, NewLink Genetics, Novartis, and Takeda; and non-financial support from Arog Pharmaceuticals, Astellas, Jazz Pharmaceuticals, NewLink Genetics, Novartis, and Takeda. MAS reports consulting fees from Bristol Myers Squibb, Kurome Therapeutics, and Novartis; and has stock options with Kurome Therapeutics. HD reports personal fees from Incyte and Servier. JW reports payment for participation on an advisory board from Abbvie and for participation on a data safety monitoring committee from AstraZeneca. MJL reports research grants from Astellas and FujiFilm Pharmaceuticals; consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, Menarini, Pfizer, and Takeda; and payment for lectures from Astellas. RFS reports consulting fees from Daiichi Sankyo for participation on a steering

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Data sharing

Anonymised individual participant data from completed studies and applicable supporting clinical study documents are available upon request at https://vivli.org/. Data sharing access is provided through the Vivli data sharing portal (https://vivli.org/ourmember/daiichi-sankyo/) after approval of a research proposal and signed data agreement from the research, legal, and intellectual property reviewers of the funder of this study and an independent review panel from the Vivli platform. If clinical study data and supporting documents are provided pursuant to company policies and procedures, Daiichi Sankyo will continue to protect the privacy of the company and clinical study participants.

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This statement should be seen as a recommendation and not an advance ruling that exempts companies from any conviction by IGN or NBL, as one always needs to take a position on the overall impression of the stand and on the special conditions that apply in each individual case.

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▼Detta läkemedel är föremål för utökad övervakning. Detta kommer att göra det möjligt att snabbt identifiera ny säkerhetsinformation.
Hälso- och sjukvårdspersonal uppmanas att rapportera varje misstänkt biverkning.
Vanflyta (kizartinib) 17,7 mg och 26,5 mg filmdragerade tabletter. Rx, Ef. Antineoplastiska medel, proteinkinashämmare (L01EX11). Indikation: Vanflyta är indicerat i kombination med standardmässig induktionsbehandling med cytarabin och antracyklin och standardmässig konsolideringskemoterapi med cytarabin, följt av underhållsbehandling med Vanflyta som enda läkemedel för vuxna patienter med nydiagnostiserad akut myeloisk leukemi (AML) som är FLT3-ITD-positiv. Kontraindikationer: Överkänslighet mot aktiv substans eller mot något hjälpämne. Medfött långt QT-syndrom. Amning. Varningar och försiktighet: Behandling ska sättas in av en läkare med erfarenhet av cancerbehandlingar. Innan behandling måste FLT3-ITD-positiv AML ha bekräftats med en CE-märkt medicinteknisk produkt för in vitro-diagnostik (IVD) med motsvarande avsett syfte. Om en sådan produkt inte är tillgänglig ska FLT3-ITD-positiv AML bekräftas med ett alternativt validerat test. Rekommenderas inte till patienter med svårt nedsatt leverfunktion (Child-Pugh klass C) eller svårt nedsatt njurfunktion (CICr < 30 ml/min, beräknad enligt Cockcroft-Gaults formel). Kizartinib förknippas med förlängt QT-intervall. Ska användas med försiktighet till patienter som löper stor risk för att utveckla förlängt QT-intervall. Elektrolyter ska hållas inom normalintervallet. Påbörja inte behandling om QTcF-intervallet är längre än 450 ms. Under induktion och konsolidering ska EKG utföras före insättning och därefter en gång i veckan under behandlingen, eller oftare när det är kliniskt indicerat. Under underhållsbehandling ska EKG utföras före insättning och sedan en gång i veckan under den första månaden efter dosinsättning och -höjning och därefter när det är kliniskt indicerat. Vanflyta ska sättas ut permanent hos patienter som utvecklar förlängt QT-intervall med tecken och symtom på livshotande arytmi. EKG-övervakning av QT-intervallet bör utföras oftare hos patienter som löper betydande risk att utveckla förlängt QT-intervall och torsade de pointes. Hypokalemi och hypomagnesemi ska övervakas och korrigeras före och under behandling. Elektrolyter och EKG ska kontrolleras oftare vid diarré eller kräkningar. Patienter ska övervakas oftare med EKG vid samtidig administrering av läkemedel som är kända för att förlänga QT-intervallet. Dödliga infektioner har förekommit oftare hos äldre, patienter över 65 års ålder ska övervakas noga avseende svåra infektioner under induktionsfasen. De vanligaste biverkningarna var ökat alaninaminotransferas, minskat trombocytantal, minskat hemoglobin, diarré, illamående, buksmärta, huvudvärk, kräkningar och minskat antal neutrofila granulocyter. Interaktioner: Om samtidig användning av starka CYP3A-hämmare inte kan undvikas ska dosen av Vanflyta minskas. Samtidig administrering av starka eller måttliga CYP3A-inducerare ska undvikas. Försiktighet ska iakttas vid samtidig administrering av läkemedel som är substrat för BCRP. Graviditet och amning: Fertila kvinnor ska lämna graviditetstest inom sju dagar innan de påbörjar behandling. Fertila kvinnor ska använda effektiv preventivmetod under behandling och under minst sju månader efter den sista dosen. Manliga patienter med fertila kvinnliga partners ska använda en effektiv preventivmetod under behandling och under minst fyra månader efter den sista dosen. Ska inte användas under graviditet eller till fertila kvinnor som inte använder preventivmedel, såvida inte kvinnans kliniska tillstånd kräver behandling. Kvinnor ska undvika att amma under behandling och under minst fem veckor efter den sista dosen. Effekter på förmågan att framföra fordon och använda maskiner: Ingen eller försumbar effekt. Innehavare av godkännande för försäljning: Daiichi Sankyo Europe GmbH, Zieblatttstrasse 48, 81379 München, Tyskland.
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För ytterligare information, se www.fass.se.
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26 months
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