Essai Clinique

Généré le 25 avr. 2024 à partir de

Titre	A Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients With FLT3/ITD AML
Protocole ID	2215-CL-0304
ClinicalTrials.gov ID	NCT02997202
Type(s) de cancer	Leucémie myéloïde aiguë (LMA)
Phase	Phase III
Type étude	Traitement
Médicament	Gilteritinib
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But étude	Participants with FLT3/ITD AML in first morphologic complete remission (CR1) undergoing allogeneic hematopoietic stem cell transplant (HCT) will be randomized to receive gilteritinib or placebo 30 to 90 days after HCT for a two year period. Participants will be stratified according to: 1) conditioning regimen intensity (myeloablative vs. reduced intensity/non-myeloablative), 2) time from first day of hematopoietic cell infusion to randomization (30-60 days vs. 61-90 days) and 3) presence vs absence of or unknown minimal residual disease (MRD) from the most recent pre-registration bone marrow (BM) aspirate.
Critères d'éligibilité	**Registration Inclusion Criteria** • Participant is considered a suitable candidate for HCT and has an acceptable source of allogeneic donor stem cells, as defined per institutional practice (allogeneic HCT for any donor source [matched sibling, unrelated donor (URD), mismatched URD, related haploidentical, or umbilical cord blood] and any graft source [umbilical cord, BM, peripheral blood (PB)], and any conditioning [myeloablative conditioning (MAC), reduced intensity conditioning (RIC), or non-myeloablative conditioning (NMA)] will be permitted). • Participant is considered a legal adult by local regulation at the time of signing informed consent form (ICF). • Participant consents to allow access to diagnostic BM aspirate or PB sample and/or the DNA derived from that sample, if available, that may be used to validate a companion diagnostic that is being developed in parallel with gilteritinib. • Participant has confirmed, morphologically documented AML in CR1. For the purposes of registration, CR1 will be defined as < 5% blasts in the BM with no morphologic characteristics of acute leukemia (e.g., Auer Rods) in the BM with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma. • Participant has not received more than 2 cycles of induction chemotherapy to achieve CR1. The induction cycles can be the same regimen or different regimens. The regimen(s) may contain conventional agents, investigational agents, or a combination of both. • Participants with CR with incomplete count recovery (CRp or CRi) are allowed. Incomplete platelet recovery (CRp) is defined as CR with platelet count < 100 x 109/L. Incomplete blood count recovery (CRi) is defined as CR with residual neutropenia < 1 x 109/L with or without

complete platelet recovery. Red blood cell count (RBC) and platelet transfusion independence is not required.
- The maximum time allowed from establishment of CR1 to registration is 12 months.
- Participant has presence of the FLT3/ITD activating mutation in the BM or PB as determined by the local institution at diagnosis.
- Participant must meet the following criteria as indicated on the clinical laboratory tests:
- Serum creatinine within normal range, or if serum creatinine outside normal range, then glomerular filtration rate (GFR) > 40 mL/min/1.73m2 as calculated with the Cockcroft-Gault equation with adjustment if total body weight is ≥ 125% of ideal body weight.
- Total bilirubin (TBL) ≤ 2.5 mg/dL, except for participants with Gilbert's syndrome.
- Serum AST and/or alanine aminotransferase (ALT) < 3 x institutional upper limit of normal (ULN).
- Participant has left ventricular ejection fraction at rest ≥ 40%.
- Participant has diffusing capacity of the lung for carbon monoxide (DLCO) (corrected for hemoglobin) ≥ 50% predicted and/or forced expiratory volume in 1 second (FEV1) ≥ 50% predicted.
- Female participants must either:
- Be of non-childbearing potential:
- postmenopausal (defined as at least 1 year without menses) prior to screening or
- documented as surgically sterilized (at least 1 month prior to the screening visit)
- Or, if of childbearing potential,
- Agree not to try to become pregnant during the study for 6 months after the final study drug administration
- And have a negative serum pregnancy test at screening
- And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after the final study drug administration.
- Female participants must agree not to breastfeed or donate ova throughout the study drug treatment period and for 6 months after the final study drug administration.
- Male participants (even if surgically sterilized), and partners who are women of childbearing potential must be using highly effective contraception in addition to a barrier method throughout the study drug treatment period and for 127 days after the final study drug administration.
- Male participants must not donate sperm throughout the study drug treatment period and for 127 days after the final study drug administration.
- Participant is able to take an oral medication.
- Participant agrees not to participate in another interventional study while on treatment.

Randomization Inclusion Criteria

- Participant is ≥ 30 days and ≤ 90 days from hematopoietic cell infusion.
- Participant has achieved engraftment. Engraftment is defined as ANC ≥ 500 cells/µL and platelets ≥ 20000/µL on 3 consecutive measurements (each occurring at least 1 day apart). The participant must not have had a platelet transfusion within 7 days prior to the first measurement.
- Participant has confirmed ongoing morphologically documented AML in CR1. For the purposes of randomization, CR1 will be defined as < 5% blasts with no morphologic characteristics of acute leukemia (e.g., Auer Rods) in the BM with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma.
- Participant meets the following criteria as indicated on the clinical laboratory tests:
- Serum creatinine within normal range, or if serum creatinine outside normal range, then GFR > 40 mL/min/1.73m2 as calculated with the Cockcroft-Gault equation with adjustment if total body weight is ≥ 125% of ideal body weight.
- TBL < 2.5 mg/dL, except for participants with Gilbert's syndrome.
- Serum AST and/or ALT < 3 x institutional ULN.
- Serum potassium and magnesium ≥ the institutional lower limit of normal (LLN).
- If the participant has developed overall grades II-IV acute GVHD, the following criteria must be met to be randomized:
- No requirement of > 0.5 mg/kg of prednisone (or equivalent) daily dose within 1 week of randomization
- No escalation of systemic immunosuppression in terms of increase of corticosteroids or addition of new agent / modality within 2 weeks of randomization. (Note that increasing calcineurin inhibitors or sirolimus to achieve therapeutic trough levels is allowed.) Topical skin and topical gastrointestinal steroids are allowed.
- Participant is able to take oral medication.

Critères d'exclusion

Registration Exclusion Criteria

- Participant has had a prior allogeneic transplant.
- Participant has Karnofsky performance status score < 70% .
- Participant requires treatment with concomitant drugs that are strong inducers of CYP3A within 14 days of start of study drug.
- Participant requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 (5HT1R) or 5-hydroxytryptamine receptor 2B (5HT2BR) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the participant.
- Participant has a Fridericia-corrected QT interval (QTcF) > 450 msec (average of triplicate determinations) per central read.

- Participant has long QT Syndrome at screening.
- Participant has a known infection with human immunodeficiency virus (HIV).
- Participant has active hepatitis B infection as determined by NAAT or surface antigen assay. Participants who have acquired immunity from past exposure (HBcAb positive / HBsAb positive / HBsAg negative) are eligible.
- Participant has active hepatitis C infection as determined by NAAT. NAAT must be performed if the participant has positive serology for hepatitis C. Participants who have had past exposure and have no detectable virus either through spontaneous clearance or treatment are eligible.
- Participant has an uncontrolled infection. If a bacterial or viral infection is present, the participant must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to registration. If a fungal infection is present, the participant must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to registration.
- Progressing infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection.
- Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
- Participant has had a myocardial infarction within 6 months prior to registration or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia.
- Participant has a serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- Participant is breast feeding or pregnant.
- Participant has prior malignancies, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ.
- Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.

Randomization Exclusion Criteria

- Participant requires treatment with concomitant drugs that are strong inducers of CYP3A within 14 days of starting study drug.
- Participant requires treatment with concomitant drugs that target serotonin 5HT1R or 5HT2BR or sigma nonspecific receptor with the exception of drugs that are considered by the investigator to be absolutely essential for the care of the participant and for which no acceptable alternative exists.
- Participant has a QTcF interval > 450 msec (average of triplicate determinations) by central read.
- Participant has a need for supplemental oxygen with the exception of using previously existing non-invasive continuous positive airway pressure (CPAP) at night.
- Participant has used investigational agents within 4 weeks of randomization.
- Participant has used experimental therapy for acute GVHD within 4 weeks of randomization. If unsure of the definition of "experimental", discussion with one of the protocol chairs is recommended.
- Participant has an uncontrolled infection. If a bacterial or viral infection is present, the participant must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to randomization. If a fungal infection is present, the participant must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to randomization.
- Progressing infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection.
- Persisting fever without other signs or symptoms will not be interpreted as progressing infection.