# A phase II, multicentre study of oral LBH589 in patients with chronic phase chronic myeloid leukemia with resistant disease following treatment with at least two BCR-ABL tyrosine kinase inhibitors

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Primary1. To assess the major (complete/partial) cytogenetic response (MCyR) rateSecondary1. To determine the duration of MCyR2. To determine the complete hematologic response (CHR) rate3. To determine the complete cytogenetic response (CCyR) rate4...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Leukaemias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON30720

**Source**
ToetsingOnline

**Brief title**
Oral LBH589 for treatment of TKI inhibitor resistant chronic phase CML

### Condition

- Leukaemias

**Synonym**
Chronic myeloid leukemia (CML)

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Novartis
**Source(s) of monetary or material Support:** Financiering door de sponsor (Novartis pharma)

## Intervention

**Keyword:** CML Chronic phase, LBH589, Resistant

## Outcome measures

### Primary outcome

The primary objective is to assess the major cytogenetic response (MCyR) rate in patients with chronic phase CML when they are treated with oral LBH589. Efficacy measurements will be the bone marrow assessments for cytogenetic response (CyR), peripheral blood sampling for marrow response (MR) and complete hematological response (CHR) and by assessment of extramedullary disease.

### Secondary outcome

CHR rate, overall and complete cytogenetic response rate, major molecular response rate, and complete molecular response rate will be calculated. In addition median progression-free survival time and median duration of major cytogenetic response will be estimated.

Safety will be evaluated using assessment of adverse events and laboratory data. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that are new or worsening based on the CTCAE Grade.

# Study description

### Background summary

Imatinib mesylate (Glivec, Gleevec) is a highly effective BCR-ABL kinase-domain inhibitor and is recognized as the standard of care for patients with CML. Approximately 85 * 90% of patients with chronic phase CML treated with imatinib in the first-line setting will achieve a major cytogenetic response. In this setting approximately 16% of patients will have disease progression or relapse at 42 months. The primary mechanism of resistance to imatinib is the development of one or more imatinib-resistant mutations. New second generation BCR-ABL kinase inhibitors (e.g., nilotinib (AMN107), dasatinib) have demonstrated efficacy in the treatment of imatinib-resistant refractory CML. However not all patients respond to these second-generation inhibitors. Patients with resistant disease due
to the T315I mutation have demonstrated insensitivity to imatinib, nilotinib and dasatinib.
LBH589 is an orally-administered histone deacetylase (HDAC) inhibitor belonging to a novel class of compounds. Treatment of imatinib-resistant primary CMLcells with LBH589 induced apoptosis in these cells either as single agent or in combination with nilotinib.

### Study objective

Primary
1. To assess the major (complete/partial) cytogenetic response (MCyR) rate
Secondary
1. To determine the duration of MCyR
2. To determine the complete hematologic response (CHR) rate
3. To determine the complete cytogenetic response (CCyR) rate
4. To determine the overall (complete/partial/minor/minimal) cytogenetic response rate
5. To determine the major and complete molecular response rates
6. To characterize BCR-ABL mutations of patients at study entry and, in responding patients, at the time of disease progression
7. To estimate progression-free survival time
8. To characterize the population pharmacokinetics
9. To monitor the QTc interval in patients receiving oral LBH589
10. To evaluate the safety and tolerability profile of oral LBH589 when given at 20 mg p.o. Mon, Wed, Fri weekly

### Study design

This is a phase II, open label, multicentre, study of oral LBH589 in patients with chronic phase (CP) CML with resistant disease following treatment with at

least two BCR-ABL tyrosine kinase inhibitors . Patients who have stable disease, partial or complete response will
continue on treatment until disease progression.
This will be a three-stage statistical design.

### Intervention

This is an open label study. All of the patients will be receiving the same treatment regimen.
LBH589 will be administered orally, 20mg once-a-day on MWF, every week.

### Study burden and risks

Possible side effects of LBH589.
There will be additional visits and ECG assessments during the first 4 weeks of treatment. These additional assessments and ECG monitoring is for reasons of safety and monitoring efficacy. Afer the 1st treatment period a weekly ECG monitoring will be continued.
Bloodsamples will be drawn for pharmacokinetic evaluation.
However in the event that only an aspirate is performed and it is not sufficient for efficacy assessment, a biopsy must be performed.
Taking blood may cause pain, bleeding, and/or bruising. When a bone marrow aspirate or a bone marrow aspirate is taken bleeding and pain.

## Contacts

**Public**
Novartis

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**Scientific**
Novartis

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## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- Patients with diagnosis of Ph+ chronic phase CML (CP-CML)
- No evidence of extramedullary leukemic involvement with the exception of liver or spleen involvement
- Patients with CP-CML must have received treatment with at least two BCR-ABL kinase inhibitors and have demonstrated resistance to the most recent BCR-ABL kinase inhibitor
*Patients with a history of intolerance to one or two BCR-ABL kinase inhibitors are eligible if they demonstrate resistance to their most recent BCR-ABL kinase inhibitor
* Patients who are intolerant of at least 2 BCR-ABL kinase inhibitors must also demonstrate resistance to or intolerance of interferon-alpha (IFN-*) / cytarabine
- Patients must meet the following laboratory criteria:
* Serum albumin > 3g/dL
* AST/SGOT and ALT/SGPT * 2.5 x upper limit of normal (ULN) ) or * 5.0 x ULN if the transaminase elevation is due to leukemic involvement
* Serum bilirubin * 1.5 x ULN
* Serum creatinine * 1.5 x ULN or 24-hour creatinine clearance * 50 ml/min
* Serum potassium, phosphorus, total calcium, magnesium * LLN
* TSH and free T4 within normal limits (thyroid hormone replacement is allowed)
- Baseline MUGA or ECHO must demonstrate LVEF * lower limit normal.
- ECOG Performance Status of * 2

## Exclusion criteria

1. A candidate for stem cell transplantation (with appropriate donor)
2. Prior treatment with an HDAC inhibitor
3. A prior history of accelerated phase or blast crisis CML
4. Impaired cardiac function including :Screening ECG with a QTc > 450 msec, congenital long QT syndrome, history of sustained ventricular tachycardia, history of ventricular fibrillation or torsades de pointes, bradycardia (< 50 beats per minute), myocardial infarction or unstable angina within 6 months of studyentry, congestive heart failure (NYHA class III or IV), right bundle branch block and left anterior hemiblock, uncontrolled hypertension
5. Concomitant use of drugs with a risk of causing torsades de pointes

6. Concomitant use of CYP3A4 inhibitors
7. Patients with unresolved diarrhea > CTCAE grade 1
8. Impairment of gastrointestinal (GI) function that may significantly alter the absorption of oral LBH589
9. Other concurrent severe and/or uncontrolled medical conditions
10. Chemotherapy, any investigational drug or major surgery < 4 weeks prior to starstudy drug
11. BCR-ABL kinase inhibitor * 1 week of first treatment with LBH589
12. Concomitant use of any anti-cancer therapy or radiation therapy. Hydroxyurea, Agrylin (anagrelide) or leukaphereses is permitted at the investigators discretion
13. Active bleeding diathesis or on any treatment with therapeutic doses of sodium warfarin or any other anti-vitamin K drug.
14. HIV positiv or hepatitis C;

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Start date (anticipated): | 05-03-2007 |
| Enrollment: | 5 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Niet van toepassing |
| Generic name: | Niet van toepassing |

# Ethics review

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| Approved WMO Date: | 05-02-2007 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-10-2007 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 15-04-2008 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2006-000881-35-NL |
| CCMO | NL15457.029.06 |