# A phase I, multicenter, open-label study of oral LGH447 in patients with acute myeloid leukemia or high risk myelodysplastic syndrome (CLGH447X2102)

Published: 24-12-2013
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Primary: To determine the MTD and/or RDE of LGH447 with or without midostaurin. Secondary: 1. To characterize the safety and tolerability of LGH447 with or without midostaurin at the MTD and/or RDE.2. To assess any observed antitumor activity of...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Haematological disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44931

**Source**
ToetsingOnline

**Brief title**
CLGH447X2102

### Condition

- Haematological disorders NEC

**Synonym**
acute myeloid leukemia and high risk myelodysplastic syndrome

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Novartis Pharma BV
**Source(s) of monetary or material Support:** Novartis Pharma BV

## Intervention

**Keyword:** AML, LGH447, MDS, midostaurin

## Outcome measures

### Primary outcome

Incidence rate of dose limiting toxicities during the first cycle of LGH447

with or without midostaurin treatment.

### Secondary outcome

Clinical response, adverse events, dose interruptions, dose reductions, and

dose intensity.

# Study description

### Background summary

Currently, treatment of patients with AML includes intensive remission induction and consolidation therapies, including stem cell transplantation. Approximately 60-70% of adults with AML can be expected to attain complete remission following appropriate induction therapy. More than 25% of adults with AML can be expected to survive 3 or more years and may be cured. Remission rates in adult AML are inversely related to age. Data suggest that once attained, duration of remission may be shorter in older patients. Despite the improvements in standard chemotherapy and supportive case, more effective therapeutic modalities to improve the survival of patients with AML are needed. MDS are a heterogenous group of chronic myeloid disorders that involve persistent peripheral blood cytopenias and an increased prevalence of leukemic transformation. Patients are grouped into five risk categories based prognostic factors. As the disease evolves to AML, AML-based therapies are utilized. However, similar to patients with relapsed AML, patients with transformed MDS respond poorly to standard therapeutic regimens and additional treatment options are needed for MDS.
Elevated levels of PIM1 and PIM2 are seen in various hematologic malignancies.

Deregulation of PIM gene expression is frequently associated with commonly occurring genetic alterations and it is thought that the resulting increased PIM kinase activity contributes to disease progression. There are indications that PIM2 is significantly over-expressed in hematological malignancies relative to the levels in solid tumors.
The PIM kinase gene family encodes three Serine/Threonine protein kinases that have roles in cell cycle progression and survival.
LGH447 is a potent, selective, and orally bioavailable inhibitor of the PIM kinase. In vitro, LGH447 demonstrates inhibition of proliferation in cell lines derived from a variety of hematological malignancies, including multiple myeloma, AML, and B-Cell NHL. In vivo, LGH447 is efficacious in mouse models of MM and AML.
In September 2016 a protocol amendement has been issued. Sofar 41 subjects iwth AML or MDS have been included in the study.
The objective of this amendement is to assess whether combined targeting of Pim kinase and FMS-like tyrosine kinase 3 (FLT3) signaling patheways promotes greater sustained reduction in tumor burden compared with either monotherapy in patients with AML. this amendement will evaluate the combination of LGH447 with the multi-kinase inhibitor midostaurin in patients with AML. To better understand whether the combination of LGH447 and midostaurin exhibits immunomodulatory activity in AML blood samples and tumor samples will be evaluated for immunomodulation.

**Study objective**

Primary:
To determine the MTD and/or RDE of LGH447 with or without midostaurin.

Secondary:
1. To characterize the safety and tolerability of LGH447 with or without midostaurin at the MTD and/or RDE.
2. To assess any observed antitumor activity of LGH447 with or without midostaurin.
3. To assess pharmacodynamics effects of LGH447 with or without midostaurin.
4. To evaluate the pharmacokinetics of LGH447 with or without midostaurin and its metabolites if appropriate.

**Study design**

The study includes a phase 1 dose escalation portion to define the MTD/RDE for LGH447 with or without midostaurin, followed by an expansion at the MTD/RDE to further characterize the safety and efficacy of LGH447 with or without midostaurin.
41 subjects have been included in the monotherapy part and 52 will be included in the combination therapy part (12 in dose escalation and 40 in dose expansion).

### Intervention

Treatment with LGH447 with or without midostaurin.

### Study burden and risks

Risk:
Adverse events of LHG447. The drug is still in a very early stage of development
Burden:
Cycle 1-2: 5 visits, thereafter 2 visits/cycle. 2 visits after termination of study medication.
Physical examination1-3x per cycle.
Blood draws approx. 5 ml screening, every visit during cycle 1 and 2, therafter twice.
2 days with long PK sampling up to 8 h after administration of LGH447.
Bone aspirate/-biopsy screening, once during cycle 1 and once during the next cycles.
Pregnancy test screening and startin in cycle 2 once every cycle..
ECG (3 registrations with an interval of 5-10 min.) screening and cycle 1-6 once per cycle.
CT-/MRI-scan in case of extramedullary disease during screening and to be repeated if indicated.

## Contacts

**Public**
Novartis Pharma BV

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NL
**Scientific**
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## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Male or female patients *18 years.with refractory/relapsed AML (see protocol page 44 for details).
2. Patients with active CNS disease are eligible and may be treated concurrently with intrathecal (or intra Ommaya) chemotherapy.
3. Patients are eligible as long as previous and concomitant medications are in line with the with the list of approved concomitant medications (see protocol appendix 5 for details).
4. ECOG performance status 0-2.

## Exclusion criteria

1. Systemic antineoplastic therapy or any experimental therapy within 7 days or 5 half-lives, whichever is longer, before the first dose of LGH447 with or without midostaurin (see protocol page 45 for further details).
2. Radiotherapy with a wide field of radiation within 28 days or radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of LGH447 with or without midostaurin.
3. CNS irradiation for meningeal leukemia, except if radiotherapy occurred > 3 months previously.
4. Ongoing systemic therapy with corticosteroids greater than 10 mg of prednisone or its equivalent
per day.
5. Uncontrolled cardiovascular condition within the past 6 months.
6. Active infection requiring systemic therapy or other severe infection with 2 weeks before the first dose of LGH447.
7. Currently receiving hydroxyurea to control peripheral blood leukemic
blasts that cannot be discontinued for at least 48 hours prior to obtaining PD biomarkers at screening/baseline and during the study.
8. Other prohibited medications (see protocol page 27 for details).
9. Pregnancy, lactation.
10. Inadequate contraception for women of childbearing potential (see protocol page 46 for details).

11 Sexually active males must use a condom during intercourse while taking the drug and for 96 days after stopping treatment and should not father a child in this period.

# Study design

## Design

**Study type:** Interventional

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 20-03-2014 |
| Enrollment: | 5 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | LGH447 |
| Generic name: | LGH477 |
| Product type: | Medicine |
| Brand name: | Midostaurin |
| Generic name: | Midostaurin |

# Ethics review

Approved WMO

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|---|---|
| Date: | 24-12-2013 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

Approved WMO

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|---|---|
| Date: | 06-03-2014 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-11-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 13-02-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-04-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 02-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 27-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

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|---|---|
| Date: | 01-03-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-06-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 29-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 30-11-2018 |
| 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 |
|---|---|
| Other | clinicaltrials.gov; registratienummer n.n.b. |
| EudraCT | EUCTR2013-003756-20-NL |
| CCMO | NL46781.029.13 |