# A phase 1, open-label multicenter, 3-period, fixed-sequence study to investigate the effect of vemurafenib on the pharmacokinetics of a single dose of acenocoumarol in patients with BRAFV600 mutation positive metastatic malignancy

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40270

**Source**
ToetsingOnline

**Brief title**
GO28397, vemurafenib, acenocoumarol

### Condition

- Other condition
- Skin neoplasms malignant and unspecified

**Synonym**

cancerous disease with BrafV600 specific mutation

**Health condition**

solid tumors

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Hoffmann-La Roche
**Source(s) of monetary or material Support:** Sponsor

## Intervention

**Keyword:** BrafV600 mutation-positive malignancies, Phase I, Verumafenib

## Outcome measures

**Primary outcome**

The following PK parameters for R* and S*acenocoumarol will be obtained using

non*compartmental analysis methods:

• Area under the plasma concentration-time curve (AUC) from Time 0 to last

measurable concentration timepoint (AUC0*T)

• AUC from Time 0 to infinity (AUC0**)

• Maximum plasma concentration (Cmax)

• Time to maximum plasma concentration (Tmax)

• Terminal half-life (t1/2)

• Apparent clearance (CL/F)

**Secondary outcome**

The safety outcome measures for this study are as follows:

• Incidence, nature, and intensity (severity) of AEs and SAEs, graded according

to the

NCI CTCAE (Version 4.0)

# Study description

### Background summary

A drug-drug interaction study (NP22676) using a CYP450 probe cocktail was conducted
in patients with metastatic melanoma to assess the effect of multiple doses of vemurafenib on single doses of five CYP450 probe substrates: caffeine-CYP1A2, warfarin-CYP2C9, omeprazole-CYP2C19, dextromethorphan-CYP2D6, and midazolam*CYP3A4). In the study, caffeine exposure was increased approximately 2.6*fold (geometric mean ratio [GMR]) and midazolam exposure was decreased by approximately 39% (GMR). Results suggested that vemurafenib might inhibit CYP1A2 activity and induce CYP3A4 activity in patients with melanoma. In the same clinical
study, although S- warfarin exposure was increased by approximately 18% by vemurafenib, the overall effect of vemurafenib on CYP2C9 activity was not considered
significant, as the 90% CI met the bioequivalence range of 80%-125% (see the Vemurafenib Package Insert for details).
Because of its narrow therapeutic index and the potential effects of vemurafenib on the
enzymes responsible for acenocoumarol metabolism, this study will evaluate the effect
of multiple doses of vemurafenib on acenocoumarol PK. Given acenocoumarol is administered as a racemic mixture, both R- and S- acenocoumarol plasma PK will be
monitored.
The risk associated with administering acenocoumarol to cancer patients as two single
4*mg doses taken 21 days apart is considered minimal. Because the dose administered
in this study will be only half of the suggested starting dose, patients in this study will not
derive any benefit from receiving acenocoumarol.
Patients with BRAFV600 mutations will be enrolled into this study. No unexpected adverse risks associated with the administration of vemurafenib to these patients are
anticipated. Some patients may derive some efficacy benefit from receiving vemurafenib
during this study and during the rollover study.

### Study objective

The primary objective of this study is to evaluate the effect of multiple oral doses of vemurafenib (960 mg BID) on the PK of a single oral dose of acenocoumarol (4 mg).
The secondary objective of this study is to assess the safety and tolerability of vemurafenib in the study population.

### Study design

This is a Phase I, open-label, multicenter, 3*period, fixed-sequence study to investigate
the effect of multiple doses of vemurafenib on the PK of acenocoumarol following oral
administration.
Enough patients will be enrolled to obtain at least 12 evaluable patients for PK analysis.
Additional patients may be enrolled if at least 12 evaluable patients are not available.

### Intervention

Following a screening period of up to 28 days, patients will receive acenocoumarol 4 mg
orally (PO) on Day 1 (Period A) under fasted conditions of at least 10 hours.
In Period B, patients will receive vemurafenib 960 mg PO BID for 20 days (Days 4*23).
In Period C, patients will receive acenocoumarol 4 mg PO on Day 23 (under fasted conditions of at least 10 hours) and vemurafenib 960 mg PO BID on Days 23*26.

### Study burden and risks

Because only patients are included for whom vemurafenib is an accepted standard of care or where there is no other generally accepted standard of care. And because The risk associated with administering acenocoumarol to cancer patients as two single 4*mg doses taken 21 days apart is considered minimal. In addition, some patients may derive some efficacy benefit from receiving vemurafenib during this study and during the rollover study.

## Contacts

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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 either unresectable Stage IIIc or Stage IV metastatic melanoma positive for the BRAFV600 mutation or other malignant tumor type, which harbors a V600-activating mutation of BRAF, as determined by the results of cobas 4800 BRAF V600 Mutation Test or a DNA sequencing method (e.g., Sanger), and who have no acceptable standard treatment options;• Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2;• Male or female patients between 18 and 70 years of age (inclusive);• Ability to participate and willingness to give written informed consent prior to any study related procedures and to comply with the study protocol;• Life expectancy >= 12 weeks;• Full recovery from the effects of any major surgery or significant traumatic injury at least 14 days prior to the first dose of study treatment;• Adequate hematologic and end organ function;• Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use 2 effective methods of contraception including at least 1 method with a failure rate of < 1% per year during the course of this study and for at least 6 months after completion of study treatment;• Negative serum or urine pregnancy test results within 7 days prior to commencement of dosing in women of childbearing potential; women not of childbearing potential may be included if they are either surgically sterile or have been naturally menopausal for >= 1 year. Women not of childbearing potential need not undergo pregnancy testing.;• Absence of any psychological, familial, sociological, or geographical condition that could potentially hamper compliance with the study protocol and follow-up schedule; such conditions should be discussed with the patient before trial entry.

## Exclusion criteria

• Prior treatment with vemurafenib or other BRAF inhibitor within 42 days of Day 1;• Prior anti-cancer therapy (e.g., biologic or other targeted therapy, chemotherapy, or hormonal therapy) within 28 days (6 weeks for nitrosoureas or mitomycin C, or 14 days for hormonal therapy or kinase inhibitors) before the first dose of study treatment in Period A, Day 1;• Palliative radiotherapy within 2 weeks prior to first dose of study drug treatment in Period A, Day 1
• Experimental therapy within 4 weeks prior to first dose of study drug treatment in Period A, Day 1;• History of clinically significant cardiac or pulmonary dysfunction, including: current uncontrolled Grade >= 2 hypertension or unstable angina;• Current Grade >= 2 dyspnea or hypoxia or need for supplemental oxygen;• History of symptomatic congestive heart failure of any New York Heart Association class or serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia;• History of myocardial infarction within 6 months prior to first dose of study treatment;• Current dyspnea at rest due to complications of advanced malignancy, or any requirement for supplemental oxygen to perform activities of daily living;• History of congenital long QT syndrome or corrected QT (QTc) > 450 msec;• Active central nervous system lesions (i.e., patients with radiographically unstable, symptomatic lesions);• Patients with VKORC1 mutatie (1639G*A, 1173C*T) in either one allele (heterozygoos) or two alleles (homozygous)
• Patients with CYP2C9*3 allele mutation in either one allele (heterozygoos) or two alleles (homozygous)
• Patients with a history of bleeding or coagulation disorders;• Allergy or hypersensitivity to vemurafenib or acenocoumarol formulation ;• Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease);• Inability or unwillingness to swallow pills;• History of malabsorption or other condition that would interfere with enteral absorption of study treatment;• History of clinically significant liver disease (including cirrhosis), current alcohol abuse, or known infection with human immunodeficiency virus (HIV) requiring antiretroviral treatment, acquired immune deficiency syndrome (AIDS)*related illness, or active heaptitis B or hepatitis C virus;• Uncontrolled ascites requiring weekly large-volume paracentesis for 3 consecutive weeks prior to enrollment;• Pregnancy, lactation, or breastfeeding;• Unwillingness or inability to comply with study and follow-up procedures;• Need to take a concomitant medication, dietary supplement, or food that is prohibited during the study

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |

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| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-07-2013 |
| Enrollment: | 6 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Sinthrome |
| Generic name: | Acenocoumarol |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Zelboraf |
| Generic name: | Vemurafenib |
| Registration: | Yes - NL intended use |

## Ethics review

Approved WMO

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|---|---|
| Date: | 26-03-2013 |
| Application type: | First submission |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

Approved WMO

| | |
|---|---|
| Date: | 26-06-2013 |
| Application type: | First submission |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

Approved WMO

| | |
|---|---|
| Date: | 16-07-2013 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

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|---|---|
| Approved WMO Date: | 02-08-2013 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 23-08-2013 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 09-01-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 21-01-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 12-06-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 15-07-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |
| Approved WMO Date: | 24-07-2014 |
| Application type: | Amendment |
| Review commission: | PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam) |

# 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 | EUCTR2012-003706-27-NL |
| CCMO | NL43460.031.13 |