# A phase I study assessing the safety and performance of VB5-845D-800CW, an anti-Epcam fluorescent agent, for the intraoperative detection of gastrointestinal cancer

Published: 09-08-2018
Last updated: 12-04-2024

Part A: healthy volunteers Primary objective- To determine safety and tolerability of a single dose of VB5-845D-800CW in healthy volunteers.Secondary objective- To determine the pharmacokinetics of VB5-845D-800CW by measuring fluorescence in blood…

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48830

**Source**
ToetsingOnline

**Brief title**
Intra-operative imaging of gastrointestinal cancer using VB5-845D-800CW

### Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

**Synonym**
esophageal/gastric- or colorectal cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** LUMC grant

## Intervention

**Keyword:** Fluorescence, Gastrointestinal cancer, Intraoperative detection, VB5-845D-800CW

## Outcome measures

### Primary outcome

Safety and tolerability endpoints

- Treatment-emergent (serious) adverse events ((S)AEs).

- Concomitant medication

- Clinical laboratory tests

o Haematology

o Chemistry

o Coagulation

o Urinalysis

- Vital signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

o Body temperature

o Peripheral oxygen saturation

o Respiratory rate

- Clinical examination, including assessment of injection site

- ECG

o Heart Rate (HR) (bpm), PR, QRS, QT, QTC

**Secondary outcome**

Efficacy endpoints

Dosing endpoints

- The optimal dose of VB5-845D-800CW will be based on the mean difference in fluorescent signal (mean fluorescence intensity) between the tumor and surrounding tissue, also known as the tumor-to-background ratio (TBR).

Other endpoints

- Expression of EpCAM in the lesions.

- Concordance rate between the pathology results with respect to the presence of cancer, EpCAM expression and the imaging signal.

- Immunohistochemistry will be scored on intensity using a 3-point score: 0 is no expression, 1 minimal expression, 2 moderate expression and 3 strong expression.

Pharmacokinetics endpoints

The following endpoints will be determined for VB5-845D-800CW following each treatment. They will be derived by non-compartimental analysis (NCA) of the serum concentration-time data:

- The area under the serum concentration-time curve from zero to infinity(AUC0-inf);

- The maximum serum concentration (Cmax);

- The area under the serum concentration-time curve from zero to t of the last

measured concentration above the limit of quantification (AUC0-last);

- The time to reach maximum plasma concentration (tmax);

- The terminal disposition rate constant (*z) with the respective half-life

(t*).

- Other parameters, including Vz/F, CL/F, and other parameters as appropriate,

as well as dose adjusted parameters, may be determined.

For the urine samples, the cumulative urine excretion of VB5-845D-800CW,

expressed as the percentage of the injected dose will be determined.

# Study description

**Background summary**

According to international guidelines, surgery is the primary care for achieving curation in many cancer types. During surgery, the surgeon mainly has to rely on pre-operative imaging modalities to predict the localization of the tumor and the extension of (tumor)tissue that has to be resected. Due to the new era of neo-adjuvant therapies, such as chemotherapy and radiotherapy, downstaging of tumors has become more common before surgery1,2. Consequently, intra-operative detection of tumors and tumor margins has become even more challenging for the surgeon since differentiation between vital tumor cells and chemotherapy induced necrosis or fibrosis can be challenging. Near-infrared fluorescence imaging is a technique that has gained a lot of attention over the last decade because of its role in intra-operative tumor tissue imaging3. This real-time imaging modality could provide clear tumor identification and demarcation and could become a useful tool to reduce positive resection margins. Subsequently, this technique can reduce rates of re-interventions and therefore improve patient outcome.

**Study objective**

Part A: healthy volunteers
Primary objective

- To determine safety and tolerability of a single dose of VB5-845D-800CW in healthy volunteers.

Secondary objective
- To determine the pharmacokinetics of VB5-845D-800CW by measuring fluorescence in blood and urine samples and evaluating the relationship of fluorescence in superficial tissue (skin) and mucous membranes (lips).
- To determine the time of injection (and window) for part B

Part B: patients
Primary objective
- To assess safety of different doses of a single i.v. injection of VB5-845D-800CW.

Secondary objectives
- To define the optimal dose of VB5-845D-800CW for intraoperative imaging of upper GI and colorectal cancer using near-infrared fluorescence, defined as the dose with the largest difference in mean fluorescence intensity (MFI) between tumor and surrounding tissue.
- To assess the performance of VB5-845D-800CW in the intraoperative detection of upper GI or colorectal cancer by:
o Tumor-to-background ratio (TBR)
o Concordance between fluorescent signal, tumor status and EpCAM expression of resected tissue

**Study design**

Part A (healthy volunteers)
This will be a single-ascending dose, randomized, placebo-controlled study in 16 healthy volunteers. Three ascending dose levels of VB5-845D-800CW will be investigated in three non-overlapping cohorts. Within the first cohort a sentinel approach will be used: on the first day 2 subjects will be administered the study drug in a 1:1 ratio for active and placebo. The other subjects in this cohort will be randomized to active:placebo in a 3:1 ratio. In the following two cohorts 5 subjects will be randomized in a ratio of 4:1 active:placebo.

Part B (patients)
This will be an open-label exploratory study in 18 patients undergoing surgery (with curative intent) with the suspected clinical diagnosis esophageal/gastric- or colorectal cancer. Two dose levels of VB5-845D-800CW will be investigated in two cohorts. Each cohort will consist of at least 3 patients (maximum of 6 patients). An additional 6 patients will be included in the cohort with the most optimal dose level.

**Intervention**

In part A (healthy volunteers), three dose levels comprising 1.5 mg, 6.0 mg and 18.0 mg of VB5-845D-800CW will be investigated. The study drug will be administered intravenously via an infusion; 80 ml in 30 minutes.

In part B (patients), two dose levels comprising 6.0 mg and 18.0 mg of VB5-845D-800CW will be evaluated during surgery. The study drug will be administered intravenously via an infusion; 80 ml in 30 minutes.

**Study burden and risks**

There are no expected direct benefits to the healthy volunteers (part A) or patients (part B) who participate in the study. However, the participants may help others prospectively by contributing to the knowledge base for designing future studies with VB5-845D-800CW in patients with cancer. The risks to participants related to VB5-845D-800CW are not all known yet. Even though, previous studies have shown that both the non-de-immunized variant (VB6-845) and the fluorescent dye, IRDye800CW are well tolerated, it cannot be excluded that hypersensitivity reactions may occur. Other risks to subjects mainly relate to the i.v. injection and venous blood sampling. Intravenous injection and the use of cannulas are known to carry a small risk of infection and hematoma. Furthermore the presence of the near-infrared fluorescence camera system during surgery (part B) is not new and should create no problem with maintaining a sterile field. Interference with standard clinical care is not expected since the surgeons are to follow their normal standard of care during surgery.

# 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

Part A (healthy volunteers)
A maximum of sixteen (16) healthy volunteers will take part in this study.
Inclusion criteria
1) The subject is 18-65 years old at screening.
2) The subject is able and willing to comply with study procedures, and signed and dated informed consent is obtained before any study-related procedure is performed.
3) Female subjects need to be surgically sterile, post-menopausal or pre-menopausal with a negative urine pregnancy test at screening and just before administration of VB5-845D-800CW. Pre-menopausal female subjects have to agree to use an effective method of contraception for 90 days after administration. Male subjects have to agree to use an effective method of contraception for 90 days after administration.
4) The subject has a normal or clinically acceptable medical history, physical examination, and vital signs findings at screening.
5) The subject*s screening ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits they are considered to be clinically insignificant.
6) The subject has negative screening test results for hepatitis B, hepatitis C, and human immunodeficiency virus.
7) The subject has negative test results for drug and alcohol screening.
8) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

Part B (patients)
The study will be performed in maximum 18 patients. At each dose level 6 patients will be studied. An additional 6 patients will be included in the

cohort with the most optimum dose level.
Inclusion criteria
1) Patients > 18 years;
2) Patients capable and willing to give informed consent before study specific procedures;
3) Patients with suspected esophageal/gastric- or colorectal cancer, planned for an open or laparoscopic esophageal/gastric resection or colorectal resection respectively or transanal colorectal resection;
4) Normal and clinically acceptable medical history, medical physical examination and vital signs at screening;
5) The subject*s clinical laboratory tests are within normal limits, or if any are outside of normal limits they are considered to be clinically insignificant;
6) Absence of any physiological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

## Exclusion criteria

Part A (healthy volunteers)
A maximum of sixteen (16) healthy volunteers will take part in this study. ,
Exclusion criteria
1) Female subjects that are lactating or pregnant.
2) Unacceptable known diagnoses or diseases at baseline, e.g., known cardiovascular or pulmonary disease, renal or liver dysfunction, ECG or laboratory abnormalities, etc.
3) Use of prescription drugs, with the exception of contraceptive drugs.
4) Participation in a clinical trial within 90 days of screening or more than 4 times in the previous year.
5) History of significant allergies or anaphylactic reactions.

Part B (patients)
The study will be performed in maximum 18 patients. At each dose level 6 patients will be studied. An additional 6 patients will be included in the cohort with the most optimum dose level.
Exclusion criteria
Patients will be excluded if any of the criteria below apply:
1) History of a clinically significant allergy or anaphylactic reactions;
2) Patients pregnant or breastfeeding;
3) Any condition that the investigator considers to be potentially jeopardizing the patients well-being or the study objectives

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 14-09-2018 |
| Enrollment: | 34 |
| Type: | Actual |

## Medical products/devices used

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| Generic name: | Quest Artemis;Olympus;Stryker |
| Registration: | Yes - CE intended use |
| Product type: | Medicine |
| Brand name: | VB5-845D-800CW |
| Generic name: | NA |

# Ethics review

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| Approved WMO Date: | 09-08-2018 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 14-09-2018 |
| Application type: | First submission |

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| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-02-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-02-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-03-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-03-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-05-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-06-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-06-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 12-07-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 22-07-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# 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 | EUCTR2018-002859-15-NL |
| CCMO | NL66875.056.18 |