# A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen (PSMA) Half Life Extended (HLE) Bispecific T-cell Engager (BiTE) AMG 160 in Subjects With Metastatic Castration Resistant Prostate Cancer (mCRPC)

Published: 03-04-2019
Last updated: 10-01-2025

Main objective:Parts 1, 3, 4, 5 en 6: AMG 160 monotherapy• Evaluate the safety and tolerability of AMG 160 in adult subjects• Part 1 only: Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)Part 2: AMG 160 in combination...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Other condition |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON52552

**Source**
ToetsingOnline

**Brief title**
20180101

### Condition

- Other condition
- Prostatic disorders (excl infections and inflammations)

**Synonym**

Metastatic Castration-Resistant, Prostate Cancer

**Health condition**

prostaat kanker

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Amgen
**Source(s) of monetary or material Support:** Amgen

## Intervention

**Keyword:** Metastatic Prostate Cancer

## Outcome measures

**Primary outcome**

Primary Endpoint

• dose-limiting toxicities (DLTs)

• treatment-emergent adverse events

• treatment-related adverse events

• changes in vital signs, electrocardiogram (ECG), and clinical laboratory

tests

**Secondary outcome**

Secondary study parameters/outcome of the study (if applicable):

• PK parameters for AMG 160 following IV administration including but not

limited to maximum serum concentration (Cmax), minimum serum concentration

(Cmin), area under the concentration-time curve (AUC) over the dosing interval,

accumulation following multiple dosing, and, if feasible, half-life (t1/2)

• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with Prostate Cancer Working Group 3 (PCWG3) modifications

• prostate-specific antigen (PSA) response

• duration of response (DOR) (radiographic and PSA)

• 68Gallium (68Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography(PET)/computed tomography (CT) and 18F-fluorodeoxyglucose (FDG) PET/CT based response evaluation (Parts 4 and 5 are not included)

• time to progression (radiographic and PSA)

• progression-free survival (PFS) (radiographic and PSA)

• 1, 2, and 3-year overall survival (OS)

• circulating tumor cells (CTCs) - response (CTC0) and rate of CTC conversion

• other PCWG3-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)

• PK parameters of specific probes of CYP enzymes including, but not limited to, Cmax, area under the concentration-time curve over a 24 hour period (AUC24) and, if feasible, t1/2

Please see protocol section 4 for more information.

# Study description

**Background summary**

Part 1: AMG 160 monotherapy
AMG 160 is a novel half-life extended (HLE) bispecific T-cell engager (BiTE®)

molecule designed to direct T effector cells towards prostate specific membrane antigen (PSMA)-expressing cells. This is a first-in-human study in adult subjects with mCRPC to assess AMG 160 safety and tolerability, pharmacokinetics (PK), and anti-tumor activity, with additional exploratory objectives to assess pharmacodynamics (PD), correlative biomarker analysis, immunogenicity, and patient reported outcomes. Two separate dose expansion parts (1a and 1b) will be included into Part 1. Dose expansion 1a will enroll approximately 50 subjects, independent of PSMA status. Dose expansion 1b will enroll approximately 50 subjects after selecting for PSMA+ subjects only.

Part 2: AMG 160 Combination with Pembrolizumab
It has been shown that the BiTE molecule mode of action leads to an upregulation of immune checkpoints, such as PD-1 on immune cells and PD-L1 on tumor cells, and that the combination of the BiTE molecule blinatumomab with the PD-1 inhibitor nivolumab is safe and tolerable in subjects with acute lymphoblastic leukemia (ALL) with evidence of antitumor activity (Kobold, et al 2018; Webster, et al, 2018). Part 2 of the study will
evaluate the safety and tolerability of AMG 160 given in combination with the PD-1 inhibitor pembrolizumab, with additional objectives to explore pharmacokinetics (PK), pharmacodynamics, immunogenicity, and anti-tumor activity of AMG 160 when given in combination with pembrolizumab.

Part 3 will be conducted in US and Canada only.
Part 4 will be conducted in Australia and US only.

Part 5: AMG 160 Outpatient Cohort With 8 hour Monitoring
Based on review of Part 4 safety data including the analysis of CRS severity and onset/resolution of CRS-related symptoms requiring intervention (ie, hypotension, hypoxia, confusion), Part 5 may be opened to evaluate AMG 160 administration in outpatient settings that can manage hypotension and are able to transfer subjects to a hospital within 2 hours if required. Part 5 will be opened only if safety data from Part 4 demonstrates that 24-hour monitoring is sufficient for AMG 160 administration and that further reduction of in-clinic monitoring may be appropriate. In Part 5, up to 20 subjects will be enrolled to evaluate the safety and tolerability of AMG 160 when administered in outpatient infusion centers with 6 to 8-hour monitoring for cycle 1 doses. Home Health services may be used to monitor subjects after discharge.
Part 5 will be conducted in Australia and US only.

Part 6 will be conducted in US only.

Key benefits in humans will be investigated and will be described when the data become available. Potential benefits include reduction or regression of prostate cancer disease burden.
Based on biological mechanism, nonclinical toxicity studies of AMG 160, and clinical safety experience with other BiTE® antibody constructs and PSMA targeting agents, the key safety risks for AMG 160 include CRS,

gastrointestinal toxicities, neurologic toxicities, and TLS.

Please see protocol synopsis for more information.

**Study objective**

Main objective:

Parts 1, 3, 4, 5 en 6: AMG 160 monotherapy
• Evaluate the safety and tolerability of AMG 160 in adult subjects
• Part 1 only: Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)

Part 2: AMG 160 in combination with pembrolizumab
• Evaluate the safety and tolerability of AMG 160 in combination with pembrolizumab in adult subjects
• Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of AMG 160 in combination with pembrolizumab

Secondary objectives:

Parts 1, 3, 4, 5 en 6: AMG 160 monotherapy
• Characterize the pharmacokinetics (PK) of AMG 160
• Evaluate preliminary anti-tumor activity of AMG 160
• Part 6 only: Evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma exposures of specific probes of CYP enzymes

Part 2: AMG 160 in combination with pembrolizumab
• Characterize the pharmacokinetics (PK) of AMG 160 in combination with pembrolizumab
• Evaluate preliminary anti-tumor activity of AMG 160 in combination with pembrolizumab

**Study design**

Study design:

Part 1: AMG 160 Monotherapy
• Part 1 is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 160 administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC (up to 90 subjects; Figure 2-1). To reduce the incidence of cytokine release syndrome (CRS), the cycle 1 dosing schedule may be adapted to include an alternate dosing schedule involving a planned 3-day extended IV infusion within the first week of cycle 1 followed by target doses (short-term IV infusions).

Extended IV Infusion Dosing:
You will receive a dose via IV infusion beginning on day 1 for 3 consecutive days (can last 2-7 days). All following doses will be short-term IV doses (that is, 60 minutes each). The next doses will be given on days 8 and 22 in cycle 1 followed by a 1-week free infusion period. After this cycle, you will resume study visits as cycle 2 day 1 and receive AMG 160 by short-term IV doses every 2 weeks thereafter (days 1 and 15).

The study will consist of:
• dose-exploration phase
• dose-expansion phase (1a and 1b)

The dose-exploration phase of the study will estimate the MTD of AMG 160 using a Bayesian logistic regression model (BLRM). A recommended phase 2 dose (RP2D) may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.
Dose expansion 1a will enroll approximately 50 subjects, independent of PSMA status. Dose expansion 1b will enroll approximately 50 subjects after selecting for PSMA+ subjects with <= 3 prior lines of therapy.

Part 2: AMG 160 Combination with Pembrolizumab
This combination dose exploration study will explore the safety, pharmacokinetics, and efficacy of AMG 160 in combination with the PD-1 inhibitor pembrolizumab in approximately 30 subjects with mCRPC.
AMG 160 will be administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC. The starting dose of AMG 160 will be 1 dose level below the dose level that has been recommended as safe and tolerable by DLRT. To reduce the incidence of CRS, the cycle 1 dosing schedule includes a multi-step and/or eIV infusion dosing schedule (See section 7.1.1.1). Pembrolizumab will be dosed 200 mg IV every 4 weeks (30 minute IV infusion) on AMG 160 dosing days and pembrolizumab infusion will take place after AMG 160 infusion and post-infusion flush. The DLRT may modify the AMG 160 and pembrolizumab dosing schedule based on emerging safety data.

Part 3: Etanercept Prophylaxis for AMG 160-related CRS
Part 3 will evaluate the effect of etanercept premedication on the safety, tolerability, and efficacy of AMG 160. Specifically, Part 3 will assess whether prophylaxis with the TNF-α inhibitor etanercept might decrease the frequency and severity of CRS without compromising the efficacy of AMG 160.

Part 4: AMG 160 Administration of AMG 160 With 24-hour Monitoring
Part 4 will evaluate administration of AMG 160 in oncology outpatient centers that can manage hypotension and are able to transfer patients to an inpatient hospital (within 2 hours) if necessary. The outpatient cohort will be initiated after MTD/RP2D is declared (Figure 2-1).

Part 5: AMG 160 Outpatient Cohort With 8 hour Monitoring
Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

The Netherlands will not take part in part 3, 4, 5 and 6.

A number of mitigations were implemented on study to improve the safety profile, including step dosing (lower dose prior to target dose), 3-day eIV infusion for the first dose in cycle 1, corticosteroid premedication (IV, oral [PO], and ophthalmic administrations), and prophylactic IV hydration. These measures improved the safety profile, reducing the incidence and severity of CRS events. The MTD/RP2D of the study was declared as 0.09 mg 3-day eIV infusion in week 1 followed by 0.3 mg target dose in week 2 (and every 2 weeks thereafter) along with prophylactic mitigations, including dexamethasone premedication in cycle 1, prophylactic steroid eye drops in cycles 1 to 2, and optional prophylactic IV hydration in cycle 1.

For more information, please refer to protocol section 5.

**Study burden and risks**

See section E9 en E9a

# Contacts

**Public**
Amgen

Minervum 7061
Breda 4817 ZK
NL
**Scientific**
Amgen

Minervum 7061
Breda 4817 ZK
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

All parts
- Age >= 18 years at the time of signing the informed consent
- Subjects with histologically or cytologically confirmed mCRPC who are refractory to a novel antiandrogen therapy (abiraterone, enzalutamide, and/or apalutamide) and have failed at least 1 (but not more than 2) taxane regimens (or who are deemed medically unsuitable to be treated with a taxane regimen or have actively refused treatment with a taxane regimen). Progression on novel antiandrogen therapy may have occurred in the non-metastatic CRPC setting.
- Expansion cohort 1b only: maximum of 3 systemic therapies administered in any prostate cancer disease setting (including chemotherapy, systemic radiotherapy, novel hormonal, or investigational therapies, but not including ADT or bone targeted therapies)
- Expansion cohort 1b only: subjects with baseline PSMA-positive disease assessed by PSMA PET scan (central assessment)
- Subjects must have undergone bilateral orchiectomy or must be on continuous ADT with a gonadotropin releasing hormone (GnRH) agonist or antagonist
- Total serum testosterone <= 50 ng/dL or 1.7 nmol/L
- Evidence of progressive disease, defined as 1 or more PCWG3 criteria:
• PSA level >= 1 ng/mL that has increased on at least 2 successive occasions at least 1 week apart
• nodal or visceral progression as defined by RECIST 1.1 with PCGW3 modifications
• appearance of 2 or more new lesions in bone scan
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1

Please see section 6.1 of the protocol.

## Exclusion criteria

All parts
- Pathological finding consistent with pure small cell, neuroendocrine carcinoma of the prostate or any other histology different from adenocarcinoma
- Radiation therapy within 4 weeks of first dose (or local or focal radiotherapy within 2 weeks of first dose)
- Central nervous system (CNS) metastases, leptomeningeal disease, or spinal

cord compression
- Prior major surgery within 4 weeks of first dose
- Active autoimmune disease or any other diseases requiring immunosuppressive therapy while on study
- Presence of fungal, bacterial, viral, or other infection requiring IV antimicrobials for management within 7 days of dosing
NOTE: Simple urinary tract infections and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with sponsor. Screening for chronic infectious conditions is not required.
- History of arterial or venous thrombosis (eg, stroke, transient ischemic attack, pulmonary embolism or deep vein trombosis) within 12 months of first dose of AMG 160
- Symptomatic peripheral sensory or motor neuropathy of grade >= 3
- History or presence of clinically relevant CNS pathology as uncontrolled epilepsy or seizure disorder, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, and psychosis
- Myocardial infarction, unstable angina, cardia arrhythmia requiring medication, and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of AMG 160
- Unresolved toxicities from prior anti-tumor therapy not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 1, with the exception of alopecia or toxicities that are stable and well-controlled AND there is agreement to allow by both the investigator and sponsor
- History of other malignancy within the past 2 years, with the following exception(s):
• malignancy treated with curative intent and with no known active disease present for >= 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
• adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
• adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- History or evidence of gastrointestinal inflammatory bowel disease (ulcerative colitis or Crohn disease) or any other gastrointestinal disorder causing chronic nausea, vomiting, or diarrhea (defined as >= 2 CTCAE grade 2)
- Prior PSMA-targeted therapy (subjects on prior PSMA radionuclide therapy may be eligible if discussed with Amgen medical monitor prior to enrollment)
NOTE: subject cannot have received PSMA radionuclide therapy < 35 days prior to enrollment if subject received < 2 cycles therapy; for each additional cycle of therapy, an additional 30 days are required for wash out)
- Any anticancer therapy or immunotherapy within 4 weeks of start of first dose, not including LHRH/GnRH analogue (agonist/antagonist). Subjects on a stable bisphosphonate or denosumab regimen for >= 30 days prior to enrollment are eligible
- Needing chronic systemic corticosteroid therapy (prednisone dose > 10 mg per

day or equivalent) or any other immunosuppressive therapies (including anti-TNFα therapies) unless stopped 7 days prior to dosing
- Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.
- History or evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection unless agreed upon with medical monitor and meeting the following criteria:
• negative test for SARS-CoV-2 RNA by real time polymerase chain reaction (RT-PCR) within 72 hours of first dose of AMG 160 OR
• no acute symptoms of COVID 19 disease within 10 days prior to first dose of AMG 160 (counted from day of positive test for asymptomatic subjects).

Part 2 only
- History or evidence of interstitial lung disease or active, non-infectious pneumonitis
- Subjects on a prior PD-1 or PD-L1 inhibitor who experienced a Grade 3 or higher immune-related adverse event

Part 3 only
- Evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product (subjects receiving etanercept prohylaxis only).

Part 6 only
- Subjects with latent or active tuberculosis at screening
- Use of any known inhibitors or inducers of drug-metabolizing enzymes within 30 days prior to study start and through start of cycle 3.
- Use of the following components of the CYP phenotyping cocktail (midazolam HCl, warfarin sodium, vitamin K, omeprazole, and dextromethorphan HBr) within 14 days prior to cycle 1 day 1.

Please refer to protocol section 6.2 for more information.

# Study design

## Design

**Study type:** Observational invasive

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

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| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 09-12-2019 |
| Enrollment: | 17 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Acapatamab |
| Generic name: | Acapatamab |
| Product type: | Medicine |
| Brand name: | Keytruda |
| Generic name: | Pembrolizumab |
| Registration: | Yes - NL intended use |

## Ethics review

Approved WMO

| | |
|---|---|
| Date: | 03-04-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 13-05-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 02-08-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 15-10-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 27-01-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-01-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 15-05-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 19-05-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-08-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 19-08-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-10-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek |

| | |
|---|---|
| | (Assen) |
| Approved WMO Date: | 23-02-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-05-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 16-10-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-02-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-03-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-11-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 12-11-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-12-2022 |

| | |
|---|---|
| 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 | EUCTR2018-003301-26-NL |
| ClinicalTrials.gov | NCT03792841 |
| CCMO | NL68429.056.19 |

# Study results

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|---|---|
| Date completed: | 03-07-2023 |
| Results posted: | 04-06-2024 |

**First publication**
19-04-2024