Phase 1/1b Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 as Monotherapy and in Combination with AMG 404 in Subjects with Glioblastoma or Malignant Glioma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Published: 06-09-2017
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Primary Objective:*Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion in monotherapy (Arm 1) and in combination with AMG 404 (anti-programmed cell death-1 (PD-1) antibody(Arm 2) in subjects with…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON48548

Source
ToetsingOnline

Brief title
20160132

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
malignent brain tumor, spongioblastoom

Research involving
Human

Sponsors and support

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

Intervention

Keyword: EGFRvIII, Glioblastoma, Phase 1/1b

Outcome measures

Primary outcome

Primary Endpoint:

* Dose limiting toxicities (DLT), treatment-emergent adverse events, treatment-related adverse events and clinically significant changes in vital signs, physical examinations, and clinical laboratory tests

Secondary outcome

Secondary Endpoint(s):

* Serum PK parameters for AMG 596 including, but not limited to, average steady-state concentration (Css), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life (t1/2) for serum AMG 596
* PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (Cmax), time to achieve Cmax (tmax) and AUC.
** PK parameters for AMG 596 dosed in combination with AMG 404 including, but not limited to, average steady-state concentration (Css), area under the concentration-time curve (AUC), clearance, volume of

distribution and half-life (t1/2) for serum AMG 596

* Objective response (OR) as per modified RANO, time to response, response

duration and time to progression (TTP); progression met AMG 596 monotherapie of

AMG 596 in combinatie met AMG 404

Study description

Background summary

Glioblastomas or malignant gliomas are still known to represent a therapeutic challenge characterized by inevitable disease recurrence. The high medical need in this indication has driven the development of new immunotherapeutic approaches over the last several years. T-cell redirection to EGFRvIII-expressing tumor cells deserves attention as EGFRvIII is a unique surface receptor not expressed in normal brain tissue or outside the brain and is the most common EGFR mutation subtype in the brain. Preclinical studies have demonstrated that AMG 596, an EGFRvIII targeting BiTE®, facilitates interaction between T-cells and EGFRvIII-positive GBM cells independent of peptide-MHC expression or a functional T-cell receptor. Furthermore,inflammatory responses are able to occur in the brain, indicating leucocyte infiltration into the brain; additionally, penetration of the blood brain barrier by activated T-cells has been demonstrated. These observations together with the most recently published case report on response of glioblastoma to CAR T-cell therapy support the opportunity for antitumor immune responses to AMG 596. Upon recurrence after primary surgery, management of glioblastoma depends on age, performance status, histology, initial therapy response, time from original diagnosis and whether the occurrence is local or diffuse. In the case of diffuse or multiple tumor recurrences, palliative care is the preferred choice. In patients with localized disease, combination of surgery, nitrosourea-based therapies and radiation (standard re-irradiation or highly conformal) is used with poor results. A response to chemotherapy is unlikely after 2 consecutive agents have failed to produce a response Moreover, no survival benefit has since been demonstrated for any new agent in a randomized trial. With the current study, a new immunotherapeutic option will be explored. After establishing the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) in the recurrent setting, the safety and tolerability of AMG 596 will be further explored as a maintenance therapy following adjuvant radiochemotherapy after initial surgery assuming that subjects with lower disease burden may better tolerate treatment.

Study objective

Primary Objective:
*
Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion in monotherapy (Arm 1) and in combination with AMG 404 (anti-programmed cell death-1 (PD-1) antibody(Arm 2) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and in the maintenance treatment phase of newly diagnosed glioblastoma (maintenance setting Group 2)

Secondary Objective(s):
*
* Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion either in monotherapy or in combination with AMG 404
* Evaluate the pharmacokinetics (PK) of AMG 404 in serum when administered by short term infusion in combination with AMG 596
* Evaluate the clinical benefit of AMG 596 and AMG 596 in combination with AMG 404 as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent and in the maintenance setting
* Evaluate progression free survival (PFS) at 6 and 12 months after initiation of treatment for any Part, Arm and Group of the study

Exploratory Objective(s):
*
* Evaluate the pharmacokinetics (PK) of AMG 596 and AMG 404 in cerebrospinal fluid (CSF)
* Evaluate pharmacodynamic evidence and biological impact of AMG 596 in monotherapy and in combination with AMG 404 by characterization of eg, changes in cytokine levels and other soluble factors as a result of T-cell activation in peripheral blood and CSF, cellular changes in tumor tissue, changes in expression of EGFRvIII and related markers
* Evaluate the formation and incidence of anti-AMG 596 and anti-AMG 404 antibodies

Study design

This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma, exploring of AMG 596 monotherapy (Arm 1) and the combination of AMG 595 with AMG 404 (Arm 2). Both Arm 1 and Arm 2 consist of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). Both Arm 1 and Arm 2 will enroll 2 groups of subjects according to disease stage, recurrent disease (Group 1) and maintenance treatment after SoC in newly diagnosed disease (Group 2).
Part 1, Dose Escalation: The purpose of dose escalation is to make a preliminary estimate of the Recommended Phase 2 Dose (RP2D)/ Maximum Tolerated Dose (MTD) of AMG 596 monotherapy and in combination with AMG 404. Treatment is divided into 2 periods: (1) DLT period 1 for day 1 to day 7 of AMG 596

infusion and (2) DLT period 2 for day 8 to day 28 of infusion (applies for both Arms). This distinction between DLT period 1 and DLT period 2 is maintained throughout dose escalation until the end of the dose escalation phase. Observations from other bispecific T-cell engager (BiTE®) studies have shown that the occurrence of initial non-cumulative toxicities associated with cytokine release within the first 48 hours after start of infusion may limit dose escalation resulting in the utilization of below doses assumed to be associated with anti-tumor activity. However, should the initial dose (DLT period 1) be limited by severe adverse events related to first dose effects (e.g., cytokine release associated adverse events), an MTD for the first dose step may be defined. Further dose escalation in DLT period 2 is possible resulting in a step-dosing and a second (and higher) MTD. This approach supports the ongoing evaluation of initial toxicity, as well as after an MTD for the start dose has been defined. The start dose based on preclinical evaluations for the estimation of the Minimum Anticipated Biological Effective Level (MABEL) is 4.5 µg/day. Further pre-specified nominal AMG 596 doses for potential use in any dose escalation Arms are 15, 45, 150, 500, 1000, 1500, 3000, 6000, 12000 *g/day. The dose level review team (DLRT) may consider treating at intermediate doses if required. If the MTD or a biological active dose considered the RP2D is not reached within the pre-planned nominal dose range, the DLRT may decide to expand the nominal dose range to dose levels > 12000 *g/day after careful consideration of all available safety, laboratory, and PK information. The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and separately in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2) and separately for AMG 596 monotherapy and in combination with AMG 404.

Group 1, Recurrent Disease
AMG596 monotherapy (Arm 1)
* Dose Escalation in single subject cohorts:
o In first cohorts AMG 596 will be administered as a cIV infusion for 7-day on/7-day off at escalating doses with N=1 per cohort. In the single subject cohorts, only a limited number of subjects will be enrolled at dose levels anticipated to be lower than those at which visible pharmacodynamics activity including adverse events related to AMG 596 therapy will be expected. In addition, the investigator together with the subject will decide on subsequent treatment duration carefully. Subjects are allowed to stay on study in 7-day on/7-day off cycles until discontinuation criteria apply.
o Combination of AMG 596 and AMG 404: The starting dose of AMG 596 is 15 ug/day administered in 28 days on, 14 days off cycles
and the defined AMG 404 dose is 480 mg every 4 weeks.
o The cohort size will be increased to N=2-4 subjects (ie, Start of multiple subject cohorts) after observation of
* Treatment-related adverse events of common terminology criteria for adverse events (CTCAE 4.0) grade 2 or higher and/or
* Quantifiable cytokine levels in blood or CSF above baseline

* Dose Escalation in multiple subject cohorts:
o Subjects in the first multiple subject cohort receive the same dose as the last single subject cohort
o All subjects receive AMG 596 in 28 days on, 14 days offinfusion cycles until treatment discontinuation criteria apply.
It is anticipated that dose-escalation will proceed according to the pre-planned nominal doses though intermediate dose levels may be used if required after reviewing all available safety data. When a first DLT is observed, the Bayesian logistic regression model (BLRM) will be used to guide dose level selection (Neuenschwander et al., 2008). The cohort size will be N=2-4 subjects. On a limited basis, after agreement between the investigator and medical monitor, one additional subject may be allowed to be enrolled if the subject has been determined to be eligible and the cohort has been filled. In this case, all five subjects will be reviewed and assessed in the Dose Level Review Meeting (DLRM).
After each cohort, the model*s recommended MTD dose level for evaluation is the dose level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.25 probability of an excessive or unacceptable TPI. The target TPI is (0.20, 0.33], and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The actual dose selected at each dose decision may be at or below the model*s recommended dose as determined by the DLRT after considering all information. Dose escalation will be completed when any of the following occurs:
* * -The maximum total sample size of N=45 DLT evaluable subjects (including single subject cohorts) is reached for AMG 596 monotherapy and N=30 DLT evaluable subjects for AMG 596 in combination with AMG 404
* -The BLRM model recommends the same dose level at least 2 times and that at least 6 subjects have been treated at the recommended RP2D/MTD dose level. If step -dosing is required, this stopping criterion applies separately to each period.
* -The highest planned dose level is reached without any DLTs being observed

AMG 596 and AMG 404 Combination Therapy (Arm 2)
The starting dose of AMG 596 is 15 ug/day administered in 28 days on, 14 days off cycles and the defined AMG 404 dose is 480 mg every 4 weeks. Combination therapy will start with multiple subject cohorts N=2-4. BLRM will be used to guide dose selection with the same model described previously in the section for Arm 1.
Dose escalation to Arm 2 will be completed when any of the following occurs:
* -The maximum total sample size of N=40 DLT evaluable subjects is reached
* -The BLRM model recommends the same dose level at least 2 times and that at least 6 subjects have been treated at the recommended RP2D/MTD dose level. If step -dosing is required, this stopping criterion applies separately to each period.

* -The highest planned dose level is reached without any DLTs being observed

Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease
* A first cohort will start after observation of a first objective anti-tumor response in Group 1 subjects with recurrent EGFRvIII-positive glioblastoma or malignant glioma. The starting dose of AMG 596 monotherapy in Group 2 will be decided by DLRT and will be the current highest dose deemed safe of Group 1. Treatment may consist either of 28-day flat dose AMG 596 cIV infusion or step-dosing as established for recurrent disease. Further treatment cycles with 14-day breaks between cIV infusions will be provided until any of the treatment discontinuation criteria applies.
* The starting dose of AMG 596 in combination with AMG 404 for Group 2 will be one dose level below the selected start dose for AMG 596 monotherapy and an AMG 404 dose of 480 mg.
* The BLRM will be used to guide dose level selection. The cohort size will be N=2-4 subjects. The actual dose selected at each dose decision may be at or below the model*s recommended dose as determined by the DLRT after considering all information.
* Dose escalation in Group 2 will be completed when any of the following occurs..
* The maximum sample size of N=15 DLT evaluable subjects is reached for AMG 596 monotherapy or N=20 DLT evaluable subjects for the AMG 596 in combination with AMG 404.
* At least 6 subjects have been treated at the recommended RP2D/MTD dose level
* The highest pre-specified nominal dose level is reached without any DLTs being observed

Part 2: Dose Expansion
The purpose of dose expansion will be to further explore safety and to evaluate preliminary antitumor activity in subjects with recurrent disease (Group 1) and in subjects in the maintenance setting (Group 2). It is anticipated that 15 subjects will be enrolled to Group 1 and up to 25 subjects will be enrolled to Group 2.
In Group 2 (maintenance setting), the objective response rate (ORR) of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. The ORR in Group 2 will be evaluated after 10 subjects are treated and have been evaluated at the first on study imaging scan or have discontinued the study before that. If ORR is lower than 5%, enrollment may be terminated due to futility. Otherwise, the ORR will be evaluated for additional new subjects and the futility stopping rules are calculated using a Bayesian predictive probability design (see Section 10.2. for details).

During dose expansion and separately for the monotherapy arm (combining data from Groups 1 and 2) and for the combination arm (combining data from Groups 1 and 2), Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible

early trial termination has been reached. The threshold for holding enrollment is as follows: *4 grade 4 or higher treatment-related adverse events for 10 enrolled subjects, *6 grade 4 or higher treatment-related adverse events for 20 enrolled subjects, *9 grade 4 or higher treatment-related adverse events for 30 enrolled subjects and study is complete at 35 enrolled subjects. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions: 1) Terminate the trial 2) Amend the protocol to potentially improve the benefit/risk for subjects (e.g. increase safety monitoring, modify dose/schedule, mandate premedication) 3) Continue dose expansion without any changes. See Section 10.2 for further details regarding the derivation of these thresholds.

A BLRM design may be used to update the estimate of the RP2D/MTD using data from subjects enrolled to dose escalation and dose expansion. Based on this revised RP2D/MTD estimate and reviewing all available safety data, the dose level for dose expansion may be revised.
The subjects enrolled in Part 2 dose expansion will be followed for imaging evaluation until the earliest of: clinically significant disease progression, death, consent withdrawal, start of new anti-tumor therapies or 12 months after treatment initiation. Subjects who stopped treatment will be contacted for long term follow up for up to 12 months after treatment initiation.

Please refer to protocol section 3.1.

Intervention

All subjects will be hospitalized for the following periods:
Cycle 1:
* For the first 7 days of AMG 596 monotherapy (Arm 1)
* For the first 8 days of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on day 8
* For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2
* For additional 72 hours after AMG 596 step dose if necessary

Cycle 2 and all subsequent cycles:
* For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2
* For additional 72 hours after AMG 596 step dose if necessary.

Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator.
AMG 404 can be administered in an outpatient setting starting from cycle 1 day 36 onwards. Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 day 36 onwards.

Restart of the infusion should be performed in the clinic/hospital under the supervision of
the investigator or designee and the subject should be hospitalized for a minimum of
24 hours when the infusion interruption meets the following criteria:
* associated to an AE, or
* interruption > 24 hours due to a pump related issue.
Dosing with AMG 596 or AMG 596 in combination with AMG 404 can continue unless the subject becomes intolerant to investigational product, the signs and symptoms of clinical progression are evident as determined by the investigator, or the subject withdraws consent. Tumor evaluations by MRI will occur every 10 to 12 weeks from start of treatment. Earlier assessments can be made if clinically indicated at the discretion of the managing physician. Modified RANO criteria (Appendix D) will be used allowing subjects to stay on study until clinically significant disease progression if no other treatment discontinuation criteria apply. Upon discussion with the Sponsor, subjects may continue to receive treatment after radiographic confirmation of progressive disease as long as they continue to derive clinical benefit in the opinion of the investigator and until further increase in tumor burden. For analysis purposes, date of PD is the date of initial observed PD.

Study burden and risks

All subjects will be hospitalized for the following periods:
Cycle 1:
* For the first 7 days of AMG 596 monotherapy (Arm 1)
* For the first 8 days of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on day 8
* For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2
* For additional 72 hours after AMG 596 step dose if necessary

Cycle 2 and all subsequent cycles:
* For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2
* For additional 72 hours after AMG 596 step dose if necessary.
Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator.

AMG 404 can be administered in an outpatient setting starting from cycle 1 day 36 onwards. Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 day 36 onwards.

For risks, see E9

Contacts

Public
Amgen

Minervum 7061 7061
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NL
Scientific
Amgen

Minervum 7061 7061
Breda 4817ZK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Written informed consent, subject is at least 18 years of age
* Eastern Cooperative Oncology Group (ECOG, Appendix F) Performance Status of * 1
* Life expectancy of at least 3 months, in the opinion of the investigator.
* Must have pathologically documented, and definitively diagnosed World Health Organization (WHO) grade 4, glioblastoma or lower grade malignant gliomas with EGFRvIII positive tumor
* Must have recurrent disease confirmed by MRI (Group 1) or completed SoC therapy such as surgery with adjuvant radiochemotherapy with or without maintenance temozolomide according to local standards for newly diagnosed disease (Group 2)
* Group 1 subjects must have * 1 index lesion by modified RANO criteria,

exemption: non-measurable disease is allowed for subjects with re-surgery (surgery for recurrent disease) before start of screening
* Group 2 subjects must have radiographically measurable disease, or non-measurable disease or both at the time of enrollment are allowedConfirmed EGFRvIII positivity at time of study enrollment
* Hematological, hepatic and renal function as described in protocol page 35

Exclusion criteria

History or evidence of central nervous system bleeding within 6 months before enrollment
-Evidence of acute intracranial / intratumoral hemorrhage, except for subjects with
stable grade 1 hemorrhage or fresh biopsy
-Known hypersensitivity to immunoglobulins or to any other component of the IP formulation
-Prior malignancy (other than in situ cancer) unless treated with curative intent
and without evidence of disease for > 2 years before screening
-Infection requiring intravenous antibiotics that was completed < 1 week of study
enrollment (day 1) with the exemption of prophylactic antibiotics for long line insertion or biopsy
-Known positive test for human immunodeficiency virus (HIV)
-Active hepatitis B and C based on the following results:
-Unresolved toxicities from prior antitumor therapy, defined as not having resolved
to CTCAE, version 4.0 grade 1
-Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, or investigational agent) within 14 days (Group 2 subjects) or 5 half-lives (whichever is longer: for Group 1 subjects) of day 1. Avastin, Pembrolizumab must be stopped 14 days prior to day 1.
-Treatment with nontopical systemic corticosteroids within 14 days before enrollment (day 1)
-Major surgery within 7 days of study day 1 with the exception of biopsy and long
line insertion
-Male and female of reproductive potential who are unwilling to practice an highly effective method(s) of effective birth control
-Female who is pregnant or lactating/breastfeeding or who plans to be pregnant or breastfeed
-Male who is unwilling to abstain from sperm donation while on study through 30 days after receiving the last dose of AMG 596 and through 4 months (120 days) after
receiving the last dose of AMG 404.

The following Exclusion Criteria apply in addition for enrollment in combination cohorts
with AMG 404:
History of solid organ transplantation.
Prior treatment with anti-PD-1, anti-PD-L1, CTLA-4 or other checkpoint inhibitor drugs
Prior treatment with AMG 596 monotherapy arm is not eligible to enroll in the combination therapy arm.
Live vaccine therapies within 4 weeks prior to study drug administration
Evidence of interstitial lung disease or active, non-infectious pneumonitis
History of any immune-related colitis.
Active or history of any autoimmune disease or immunodeficiencies.
Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or cardiac
arrhythmia requiring medication.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-08-2018
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG 404
Generic name:	AMG 404
Product type:	Medicine

Brand name:	AMG 596
Generic name:	AMG 596

Ethics review

Approved WMO Date:	06-09-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2021
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	20160132
EudraCT	EUCTR2017-001658-32-NL
CCMO	NL62180.029.17

Study results