A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered Alone or in Combination with Atezolizumab to Subjects with Locally Advanced or Metastatic Solid Tumors

Published: 14-12-2017
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Dose-Escalation Stage (Combination Therapy Cohorts):The primary objective is as follows:• To determine the maximum tolerated dose (MTD) and/or recommended dose and schedule for the subsequent Expansion Stage of daily oral administration of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50370

Source
ToetsingOnline

Brief title
ELE18421-184021 (XL184-021)

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer and kidney cancer

Research involving
Human

Sponsors and support

Primary sponsor: Exelixis, Inc
Source(s) of monetary or material Support: Exelixis;Inc.

Intervention

Keyword: Locally Advanced, Metastatic Solid Tumors

Outcome measures

Primary outcome

SAFETY ASSESSMENTS

Safety evaluations will include assessments of AEs (including irAEs and AESIs), vital signs, ECGs, laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, relationship to study treatment, and relationship to immune effects (ie, irAEs) will be assessed by the investigator. Severity grade will be defined by the NCI CTCAE version 4.

TUMOR ASSESSMENTS

Tumor response will be assessed using RECIST 1.1 (Appendix G). Additional exploratory efficacy evaluation will include the application of irRECIST for immune response (Appendix H). Subjects will be assessed using a magnetic resonance imaging (MRI) or a CT scan from the date of the first dose of study treatment until the later of radiographic disease progression per RECIST 1.1 as determined by the investigator or the date of the decision to permanently discontinue study treatment. Radiographic tumor assessments will continue on the protocol-defined schedule, regardless of whether study treatment is reduced, interrupted, delayed, or discontinued.

Chest / Abdomen / Pelvis/ Neck: Unless otherwise described, CT of

Chest/Abdomen/Pelvis (CAP) or CT chest and MRI abdomen/pelvis will be performed in all subjects at screening and every 6 weeks (± 5 days) after initiation of study treatment throughout the first 12 months on study. Upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). For subjects with DTC and head & neck cancer, CT/MRI of the neck will be performed in addition to the CAP assessments. Subjects with head & neck cancer will be using the same imaging schedule after screening. For subjects with DTC the imaging frequency after screening will be every 9 weeks after initiation of study treatment throughout the first 12 months on study; upon completion of 12 months on study, these assessments will be performed every 12 weeks (± 7 days). Low dose non-contrast CT images from combined positron emission tomography/computed tomography (PET/CT) imaging cannot be used for tumor evaluations in this study.

Brain: MRI (or CT) of the brain will be performed at screening in all subjects with RCC, head and neck cancer, and NSCLC and for subjects with the other tumor indications who have a history or clinical symptoms of brain metastasis. After study treatment initiation MRI (or CT) scans of the brain are only required in subjects with documented, treated brain metastasis or if clinically indicated by signs and symptoms suggestive of new central nervous system (CNS) metastases. Assessments after the first dose of study treatment will be performed every 12 weeks (± 7 days). MRI is the preferred imaging method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless contraindicated. Subjects without documented brain metastasis during the screening assessment are not required to undergo brain

imaging after initiating study treatment unless clinically indicated. In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before first dose of study treatment.

Bone scans: Technetium bone scans (TBS) will be performed at screening in all subjects with CRPC and for subjects with the other tumor indications who have a history or clinical symptoms (ie, bone pain) of bone metastases. After study treatment initiation bone scans are only required in subjects with documented bone lesions or if clinically indicated by signs and symptoms suggestive of new bone metastases. Assessments after the first dose will follow routine clinical practice (approximately every 12 weeks throughout the first 12 months and every 24 weeks thereafter). Lesions identified on bone scan are not to be recorded as target, non-target, or new lesions. Bone scan findings alone cannot be used for the determination of progression or response in this study and need to be corroborated by CT/MRI. Bone lesions corroborated by CT/MRI must be reported as non-target or new lesions. PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.

Subjects enrolled in the SAC or SAA cohorts who experience Investigator-assessed radiographic progression per RECIST 1.1 may be eligible to receive the combination therapy in the Second Agent Add-On Stage (see Section 3.5.2.4 for more details). A new baseline tumor status will be established for these subjects based upon their most recent set of scans performed prior to receiving the first dose of the second agent in the Second

Agent Add-On Stage; if these scans were taken > 4 weeks prior to first dose of the second agent, new scans will be required to establish the baseline.

For the purpose of determining radiographic study endpoints for selected cohorts, central review of radiographic images may be conducted by a BIRC. All protocol-required radiographic tumor assessments for these selected cohorts will be sent to the BIRC, which also will review prior radiation history data and prior local therapy information for the purpose of selection of target lesions. Details are provided in the Imaging Manual.

TUMOR MARKER ASSESSMENTS

For subjects with CRPC, HCC, OC, CRC, and DTC, tumor marker samples (ie, PSA, alpha-feta protein [AFP], CA125, carcinoembryonic antigen [CEA], and thyroglobulin, respectively) will be collected at screening, Day 1 of every third cycle (or every 9 weeks, whichever is earlier) for the first 12 months on study, and then Day 1 of every fifth cycle (or every 15 weeks, whichever is earlier) until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission). For subjects with CRPC who receive combination treatment in the Second Agent Add-On Stage, PSA samples will be collected at screening for that stage, Day 1 of every third cycle on that stage (or every 9 weeks, whichever is earlier) for the first 12 months, and then Day 1 of every fifth cycle of that stage (or every 15 weeks, whichever is earlier) until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission). The tumor marker assessments will not

be used to determine progressive disease or to make study treatment decisions in this study.

OVERALL SURVIVAL FOLLOW-UP ASSESSMENTS

Subjects will be contacted (eg, in person or by telephone) approximately every 12 weeks (± 14 days) after the Post Treatment Follow-Up Visit to assess survival status and to document receipt of subsequent anticancer therapy unless consent to participate in survival follow-up is withdrawn or the Sponsor deems sufficient efficacy data have been collected for the study.

PHARMACOKINETIC ASSESSMENTS

Dose-Escalation Stage:

Blood samples for PK analysis will be obtained on the date of first dose of study treatment (C1D1; prior to study treatment administration [cabozantinib and atezolizumab], approximately 5 min after completion of the atezolizumab infusion, and at 2 h, 4 h, and 6-8 h after cabozantinib dosing), and prior to study treatment dosing on C1D10, C2D1, and C3D1.

Expansion Stage:

Combination Therapy Expansion Cohorts:

Blood samples for PK analysis will be obtained for plasma cabozantinib and serum atezolizumab concentration measurement on the date of first dose of study treatment (C1D1; prior to study treatment administration [cabozantinib and atezolizumab], approximately 5 min after completion of the atezolizumab infusion, and 2 h after the first dose of cabozantinib) and prior to study treatment dosing (atezolizumab infusion) on C2D1 and C3D1.

Exploratory SAC Cohorts:

Blood samples for PK analysis will be obtained for plasma cabozantinib on the date of first dose of cabozantinib treatment (C1D1; prior to cabozantinib treatment administration) and on C2D1 and C3D1.

Exploratory SAA Cohort:

Blood samples for PK analysis will be obtained for serum atezolizumab concentration measurement on the date of first dose of study treatment (C1D1; prior to study treatment administration, approximately 5 min after completion of the atezolizumab infusion) and prior to study treatment dosing on C2D1 and C3D1.

In the Dose-Escalation Stage and for the Combination-Therapy Cohorts in the Expansion Stage, samples will be analyzed for the plasma concentration of cabozantinib and the serum concentrations of atezolizumab. Only the PK of cabozantinib will be assessed for subjects in the SAC Cohorts, and only the PK of atezolizumab will be assessed for subjects in the SAA Cohort. PK will not be assessed in subjects who receive combination therapy after progression on single agent therapy (Second Agent Add-On Stage).

IMMUNOGENICITY ASSESSMENTS

Blood samples will be obtained from all subjects in the combination treatment cohorts and subjects in the Exploratory SAA Cohort in the Expansion Stage for immunogenicity assessment predose on C1D1, C3D1, C7D1, and at the Post-Treatment Follow-up Visit. For subjects who radiographically progress per RECIST 1.1 on single-agent therapy in the SAC Cohorts and transition to combination therapy, blood samples for immunogenicity assessments will be collected predose on Add on Cycle 1 Day 1 (aoC1D1), aoC3D1, and aoC7D1 in the

Second Agent Add-On Stage and at the Post Treatment Follow-up Visit. For subjects who radiographically progress per RECIST 1.1 on single-agent therapy in the SAA Cohort and transition to combination therapy, a blood sample for immunogenicity assessment will be collected at the Post Treatment Follow-up Visit.

BIOMARKER ASSESSMENTS

Peripheral blood and tumor tissue will be collected and may be assessed for exploratory biomarker analyses. Peripheral blood samples will be obtained as specified in the Schedule of Assessments. Tumor tissue (archival) will be obtained prior to first dose of study treatment, and optional fresh tumor tissue biopsies may also be performed. Exploratory analyses may include the following:

• MET, AXL, and PD-L1 in tumor specimens for association with clinical outcomes

• Immune cell infiltration and tumor characteristics (ie, mutational load assessment) in tumor specimens and blood for association with clinical outcome

• Circulating immune cells in peripheral blood (ie, lymphocyte subset analyses by flow cytometry)

• Blood biomarkers (ie, cytokines/chemokines, VEGF)

• Evaluation of MMR and MSI status

Collection of biomarker samples may be halted early or sampling frequency may be modified at the discretion of the Sponsor.

For NSCLC subjects, available tumor mutation analysis reports (indicating EGFR status) should be provided at screening. For eligibility review for Expansion Cohort 8, prior PD-L1 reports from tests using the FDA approved pharmDx PD L1

22C3 kits should be provided early in screening.

Secondary outcome

For parameters/outcome, please see above.

Study description

Background summary

Multi-targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) represent two systemic modalities that have been instrumental in the recent advancements of anticancer treatment over the past several years. Both classes of therapies have demonstrated broad clinical effects leading to new approved treatment options across multiple tumor types. The success of these therapy types as single agents with distinct mechanisms of action has naturally led to interest in evaluating combinations of TKIs with ICIs in search of further, possibly synergistic, anticancer clinical effects. Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets programmed death receptor 1 ligand (PD L1) and inhibits the interaction between PD-L1 and its receptors, programmed death receptor 1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Atezolizumab injection for intravenous (IV) use (1200 mg once every 3 weeks [q3w]) has been approved in the US and EU for the treatment of adult patients with advanced urothelial carcinoma (UC) after prior platinum containing chemotherapy or in a subset of patients who are considered cisplatin-ineligible (different patient populations are indicated depending on region; Rosenberg et al 2016, Balar et al 2017). Atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin has been approved in the US for the first line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. Atezolizumab is also approved for adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (Fehrenbacher et al 2016; Tecentriq* US prescribing information [US PI] and European Medicines Agency Summary of Product Characteristics [EMA SmPC]). Recently, atezolizumab was also granted accelerated approval in the US for treatment in combination with paclitaxel protein bound (nab-paclitaxel) for adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (Schmid et al 2018) and was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al 2018, Tecentriq US PI). Treatment with atezolizumab is generally well-tolerated but can be associated with immune-related adverse events (irAEs).

Further, atezolizumab has demonstrated encouraging clinical activity in other tumor treatment settings: monotherapy in treatment-naïve advanced-stage NSCLC (Peters et al 2017), combination with chemotherapy and bevacizumab in treatment-naive advanced-stage NSCLC (Sociniski et al 2018), monotherapy in advanced renal cell carcinoma (RCC) (McDermott et al 2016), monotherapy in metastatic castration-resistant prostate cancer (mCRPC; Kim et al 2018), combination with bevacizumab in treatment-naïve advanced RCC (Motzer et al 2018), monotherapy in advanced triple-negative breast cancer (TNBC; Schmid et al 2017), monotherapy in advanced ovarian cancer (OC; Infante et al 2016), monotherapy in advanced endometrial cancer (EC; Fleming et al 2017), monotherapy and combination with bevacizumab in treatment-naïve hepatocellular carcinoma (HCC; Stein et al 2018; Roche data on file), monotherapy in advanced gastric cancer (GC; Taieb et al 2018), combination with bevacizumab (± chemotherapy) in advanced colorectal cancer (CRC; Hochster et al 2017), and monotherapy in advanced head and neck (H & N) cancer (Bahleda et al 2017). In addition, atezolizumab is currently being evaluated in combination with bevacizumab or molecular targeted therapies in anaplastic and differentiated thyroid cancer (NCT03181100).

Cabozantinib (XL184) is a potent inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, vascular endothelial growth factor receptor (VEGFR), AXL, and RET. Increased expression of MET and AXL has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of several cancers (Shojaei et al 2010, Zhou et al 2016, Sennino et al 2012, Ciamporcero et al 2015). In addition, targets of cabozantinib are implicated in promoting tumor immune suppression including TYRO3, MER, and AXL (tumor-assisted macrophage [TAM] family kinases).

Cabozantinib capsules (140 mg) are approved in the US for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the EU for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq® US PI and EMA SmPC). Cabozantinib tablets (60 mg) are approved in the US, Europe, and other regions for advanced RCC (different patient populations depending on region; Cabometyx® US PI and EMA SmPC). Based on the results from a randomized placebo-controlled Phase 3 study (CELESTIAL) in subjects who had received prior sorafenib, cabozantinib tablets (60 mg) as a single agent have also been approved in the US, EU, and other regions for an HCC indication (Cabometyx US PI and EMA SmPC).

Cabozantinib has also demonstrated encouraging clinical activity in other tumor indications: monotherapy in advanced urothelial carcinoma (Apolo et al [J Clin Oncol] 2016), in combination with ICIs in advanced urothelial carcinoma (Nadal et al 2018, Nadal et al 2017, Apolo et al [Ann Oncol] 2016), monotherapy in CRPC (Smith et al 2013, Smith et al 2014, Basch et al 2015), monotherapy or in combination with erlotinib in advanced NSCLC (Schöffski et al 2017, Neal et al 2016), monotherapy in RET-rearranged NSCLC (Drilon et al 2016), monotherapy in advanced TNBC (Tolaney et al 2017), monotherapy in advanced OC (Matulonis et al 2016, Vergote et al 2017), monotherapy in advanced EC (Dhani et al 2017; Mandilaras et al 2017), monotherapy in advanced GC (Schöffski et al 2017), in

combination with panitumumab in CRC (Strickler et al 2016), and monotherapy in radioactive-iodine refractory DTC (Brose et al 2018, Cabanillas et al 2014, Cabanillas et al 2017).
Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment through inhibition of immune-modulatory targets on immune cells. This might present an opportunity for synergistic effects from combination treatment with ICIs. The combination of cabozantinib with ICIs may also provide a strategy to overcome resistance to ICI therapy. This is based on recent observations in clinical trials where re-treatment with an ICI in combination with cabozantinib or a VEGFR-TKI that has a target profile similar to cabozantinib resulted in reversal of prior ICI resistance in advanced UC and NSCLC patients (Nadal et al 2018, Leal et al 2017). These results suggest that combining ICIs with cabozantinib may result in a tumor microenvironment that is conducive to re-sensitization to ICI therapy after prior progression on an ICI.
In this Phase 1b study, a total of 12 subjects with advanced RCC were enrolled in the Dose-Escalation Stage using a 3 + 3 design. Six (6) subjects were evaluated at both the 40-mg and 60-mg cabozantinib dose levels in combination with the standard dose of atezolizumab. Both dose levels of cabozantinib were generally well tolerated, and no dose limiting toxicities (DLTs) were observed. After reviewing all available safety and efficacy data of the Dose Escalation Stage, the Cohort Review Committee determined that cabozantinib 40 mg qd orally in combination with 1200 mg atezolizumab q3w IV is the recommended dose for the Expansion-Stage combination-therapy cohorts. The Cohort Review Committee decision was based on the favorable safety profile of the 40-mg cabozantinib dose level over a prolonged time on study treatment with less frequent dose reductions and encouraging preliminary efficacy, which was deemed to optimize the benefit/risk of the combination for the Expansion Cohorts.
The Expansion Stage is evaluating the efficacy and safety of cabozantinib 40 mg qd in combination with atezolizumab 1200 mg q3w across 20 tumor-specific cohorts of the following tumor types: RCC, UC, CRPC, NSCLC, triple negative breast cancer (TNBC), ovarian cancer (OC), endometrial cancer (EC), hepatocellular cancer (HCC), gastric cancer/gastroesophageal junction cancer/lower esophageal cancer (GC/GEJC/LEC), colorectal cancer (CRC), H&N cancer, and differentiated thyroid cancer (DTC). In order to establish the individual contributions of the components of the combination therapy, the Expansion Stage also includes three exploratory single-agent cabozantinib cohorts (UC, CRPC, and NSCLC) and one single-agent atezolizumab cohort (CRPC). The Study Oversight Committee (SOC) will review the efficacy and safety of the initially enrolled subjects (approximately 30 subjects in each cohort) and may recommend enrollment extension for up to 10 cohorts in which encouraging clinical activity has been demonstrated. The SOC can also recommend additional enrollment at a higher dose of cabozantinib (60 mg qd orally) in combination with 1200 mg atezolizumab q3w IV for tumor cohorts with modest clinical activity at cabozantinib 40 mg in combination with atezolizumab. The single-agent atezolizumab cohort will initially enroll 10 subjects. Enrollment

with approximately 30 subjects will depend on the observed efficacy among the first 10 enrolled subjects. The Expansion Stage was initiated on 26 March 2018. At the time of this protocol amendment the SOC has recommended extended enrollment for Cohort 1 (clear cell RCC), Cohort 6 (CRPC), and Cohort 7 (NSCLC, prior ICI therapy) following review of efficacy and safety data of the initially enrolled subjects.
This amendment provides for subjects enrolling in the cohorts receiving single-agent treatment with either cabozantinib or atezolizumab the opportunity to receive combination treatment with cabozantinib and atezolizumab after Investigator-assessed radiographic disease progression per Response Evaluation Criteria in Solid Tumors (version 1.1) (RECIST 1.1) given these subjects meet the eligibility criteria for receiving combination treatment (Second Agent Add-On Stage).

Study objective

Dose-Escalation Stage (Combination Therapy Cohorts):
The primary objective is as follows:
• To determine the maximum tolerated dose (MTD) and/or recommended dose and schedule for the subsequent Expansion Stage of daily oral administration of cabozantinib in subjects with solid tumors when taken in combination with atezolizumab.
The secondary objective is as follows:
• To evaluate the plasma pharmacokinetics (PK) of daily oral administration of cabozantinib in subjects with solid tumors when given in combination with atezolizumab.
• To assess safety of the combination therapy through the evaluation of incidence and severity of nonserious adverse events (AEs) and serious adverse events (SAEs), including immune-related adverse events (irAEs) and adverse events of special interest (AESIs).
The exploratory objective is as follows:
• Correlation of immune cell, tumor cell, and blood biomarker analyses with clinical outcome
• ORR as assessed by the Investigator per RECIST 1.1
Expansion Stage (Combination-Therapy Cohorts):
The primary objective and endpoint is as follows:
• To evaluate preliminary efficacy of the combination therapy by estimating the ORR as assessed by the Investigator per RECIST 1.1
The secondary objective is as follows:
• To assess safety for the combination therapy through the evaluation of incidence and severity of nonserious AEs and SAEs, including irAEs and AESIs.
The exploratory objectives and endpoints are as follows:
• ORR as assessed by the Investigator per immune-related RECIST (irRECIST) for immune response
• Duration of response (DOR) as assessed by the Investigator per RECIST 1.1
• Progression-free survival (PFS) as assessed by the Investigator per RECIST 1.1
• ORR, DOR, and PFS as assessed by a Blinded Independent Radiology Committee

(BIRC) per RECIST 1.1 for selected cohorts
• Overall survival (OS)
• Correlation of immune cell, tumor cell, and blood biomarker analyses with clinical outcome
• Changes in tumor infiltration and/or histology or other molecular changes as determined from optional tumor biopsy
• To further evaluate the plasma pharmacokinetics (PK) of daily oral administration of cabozantinib in subjects with solid tumors when given in combination with atezolizumab.
• Tumor marker changes from baseline in select tumor indications
• Evaluation of mismatch repair (MMR) and microsatellite instability (MSI) status in relevant tumor indications
• Changes in prostate-specific antigen (PSA response rate) from baseline for CRPC cohorts
Exploratory Single-Agent Cabozantinib (SAC) Cohorts:
• Descriptive efficacy, safety, PK, and biomarker analyses of single-agent cabozantinib (SAC) in UC, CRPC, and NSCLC subjects
• Descriptive efficacy and safety analyses of combination therapy after progression on single-agent cabozantinib therapy
Exploratory Single-Agent Atezolizumab (SAA) Cohort:
• Descriptive efficacy, safety, PK, and biomarker analyses of single-agent atezolizumab (SAA) in CRPC subjects
• Descriptive efficacy and safety analyses combination therapy after progression on single-agent atezolizumab therapy

Study design

see enclosed protocol synopsis (study design)

Intervention

Please see ICF (Standard), Appendix 4: Study Procedures and Tests.

Study burden and risks

Please see protocol section 1.4: Overall Risk Benefit Assessment.

Contacts

Public
Exelixis, Inc

Harbor Bay Parkway 1851
Alameda CA 94502

US
Scientific
Exelixis, Inc

Harbor Bay Parkway 1851
Alameda CA 94502
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

see protocol (enclosed to submission)

Exclusion criteria

see protocol (enclosed to submission)

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):	12-09-2018
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Atezolizumab
Generic name:	Atezolizumab
Product type:	Medicine
Brand name:	Cabozantinib
Generic name:	Cabozantinib

Ethics review

Approved WMO Date:	14-12-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2018

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-06-2020

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-05-2022

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-001792-24-NL
CCMO	NL62108.091.17