A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer*s Disease

Published: 21-12-2016
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Primary Objective:To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 814907 to patients with mild ADSecondary Objective:To characterize the cerebrospinal fluid (CSF)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON55789

Source
ToetsingOnline

Brief title
ISIS 814907-CS1

Condition

- Mental impairment disorders

Synonym
Dementia; Alzheimer Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Alzheimer Disease, Cerebral Spinal Fluid, ISIS 814907, Lumbar Puncture

Outcome measures

Primary outcome

Patient safety will be monitored closely during the study by the Investigator

and the FSMG. Further oversight of compliance with study safety procedures will

be provided by the Ionis Medical Monitor.

Safety and tolerability evaluations include:

• Physical examination and standard neurological assessment (including fundi)

• Vital signs (Heart Rate, Blood Pressure, orthostatic changes, weight)

• ECG

• AEs and concomitant medications

• Columbia Suicide Severity Rating Scale (C-SSRS)

• CSF safety labs (cell counts, protein, glucose)

• Plasma laboratory tests (clinical chemistry, hematology)

• Urinalysis

• Neuroimaging assessments will be conducted using a 3T MRI scanner, and safety

scans must be reviewed locally by a trained neuroradiologist:

- Safety MRI sequences (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DWI) at Screening

and Study Day 169/Week 25 Clinical and volumetric neuroimaging measures will be

used to monitor for unexpected deterioration.

Secondary outcome

(1) Pharmacokinetic Evaluations

(2) Exploratory Evaluations:

- Biochemical: Potential CSF and blood/plasma biomarkers include, but are not

limited to neuronal and synaptic injury markers, innate immune activation

markers, complement components and lipid-related biomarkers

- Neuroimaging:

o Structural MRI (hippocampal, whole brain and ventricular volumes)

o Arterial Spin Labelling (ASL)

o FDG-PET (Cohorts C and D only)

- Functioning/ability to perform activities of daily living: Functional

Activities Questionnaire (FAQ)

- Cognitive: Repeatable Battery for the Assessment of Neuropsychological Status

(RBANS) and Mini-mental state examination (MMSE)

- Neuropsychiatric: Neuropsychiatric Inventory - Questionnaire (NPI-Q)

Study description

Background summary

This is the first study of ISIS 814907 in humans, and it will be conducted in patients with mild AD. It is necessary to conduct this study in patients, rather than in healthy volunteers, because ISIS 814907 is a Central Nervouws System (CNS) acting agent to be administered via IT (via spinal canal)

administration. The assessment of safety is the primary objective of this study. However, the participating patients may not be too advanced in their disease process to enable detection of clinical and/or biomarker changes suggesting potential for clinical benefit to be demonstrated.

In this study, patients are aged >= 50 years and <= 74 years to avoid undesirable comorbid illness that is more common in older individuals. Moreover, in older, late-onset AD patients, Alzheimer*s pathology is usually confounded by multiple, non-AD, age-related

Study objective

Primary Objective:
To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 814907 to patients with mild AD

Secondary Objective:
To characterize the cerebrospinal fluid (CSF) pharmacokinetics of ascending dose-levels of multiple IT bolus administrations of ISIS 814907

Study design

ISIS 814907-CS1 is a randomized, double-blinded, placebo-controlled study of multiple IT bolus administrations of ISIS 814907 in patients with mild AD aged 50-74 years.

Intervention

Part 1:
A sentinel dosing strategy will be implemented. The first 2 patients at a given dose level will be assigned 1:1 active:placebo, and at least 1 week must elapse between initiation of treatment in these 2 patients and initiation of treatment in additional patients at this dose level. The remaining patients will be assigned to active or placebo at a 5:1 ratio (cohorts with N = 8), 8:2 ratio (cohorts with N = 12), or 11:3 ratio (cohorts with N = 16) to ensure a 3:1 active:placebo balance in each cohort. During the study, PK and PD data will be compared to the ISIS 814907 levels and PD effects that are expected according to the preclinical PK/PD model. Based on these reviews, the dose level(s) for future cohort(s) may be adjusted.
Each patient will receive 4 doses of Study Drug with a 28-day interval between doses. In the event of a dosing interval change for Cohort D, each patient will receive 2 doses of Study Drug with an 84-day interval between doses. Patients not completing the intended course of all study drug administrations may be replaced up to a limit of 25% of the cohort sample and only if their treatment assignments remain blinded and if the reason for premature discontinuation from the Treatment Period does not involve a dose-limiting toxicity (DLT).

Part 2:
The open-label LTE part of the study will start with Cohort C completers and allow all patients completing Cohorts C and D to seamlessly transition from Part 1 to Part 2. This means that for Cohorts C and D patients Day 253 in Part 1 will correspond to Day -1 in Part 2. In Part 2, the Treatment Evaluation Period of 48 weeks will be followed by a Post-Treatment Period of 16 weeks. For Cohorts A and B patients there will be a variable gap of time between the end of Part 1 and entry into Part 2. Cohort A and B patients, who complete the Part 1 Treatment Evaluation and the Post-Treatment Periods, will be invited back to participate in Part 2. Patients who prematurely discontinue the Treatment Evaluation Period, or the Post-Treatment Period, in Part 1, and patients whose treatment assignment has been unblinded during Part 1 due to a safety issue, will not be allowed to participate in Part 2. There is no prescribed minimum or maximum interval of time required before Cohort A and B patients completing Part 1 can enter Part 2 of the study, however all Cohort A and B patients participating in the LTE, Part 2 should be enrolled in Part 2 prior to the last patient in Cohort D entering Part 2 of the study. Patients who participated in Cohorts A and B will be able to start Part 2 of the study once the FSMG has reviewed the Part 1 Cohort C data during the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1) and will start the Part 2 Treatment Evaluation Period at the Cohort C dose given on a quarterly (84-day interval) basis. Dose levels and dosing regimen in the LTE, Part 2 could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor. All patients in Part 2 will receive ISIS 814907.

Study burden and risks

Patients are asked to undergo procedures described in the tables on pages 94-108 of the study protocol. These procedures include physical and neurological examination, vital signs, urine pregnancy tests (female; childbearing patients), ECG, MRI, PET scan, lumbar puncture for CSF, blood draw, answer questions of investigator and study team and administration of study drug. Additionally, fertile patients who are sexually active must consent to use an effective form of contraception with their sexual partners throughout participation in the study. Patients are also asked to inform their study doctor on their medication use and change in health status. Partners of study subjects will also be requested to consent for study participation and answer questions about the study participant*s daily living activities and the presence or absence of certain behaviors related to AD.

The study drug may cause side effects.
There have been 42 subjects treated with ISIS 814907 in Part 1 and Part 2 in this ongoing study.
Side effects seen in patients treated with ISIS 814907 during Part 1 include:
• Confusion (8.8%; 3 out of 34 patients)
• Restlessness (5.9%; 2 out of 34 patients)

• Anxiety (2.9%; 1 out of 34 patients)

In animal testing of ISIS 814907, the only side effect observed was a temporary deficit in lower spinal reflexes (in the lower legs, knee and ankle reflexes in particular) 2 to 4 hours following ISIS 814907 dosing in some animals. The side effect typically resolved within 48 hours following ISIS 814907 dosing. The reduced reflexes occurred at all doses tested, including in animals receiving placebo. However, these reduced reflexes were common only at doses much higher than will be used in this study. Patient may also experience discomfort while performing blood draw (i.e. pain, swelling, bruising, risk of infection, etc.), lumbar puncture (i.e. pain in lower back, temporary pain or numbness to the legs, etc.), ECG (i.e. adhesive used for the electrodes from the ECG may irritate patient*s skin), MRI and PET scan

Contacts

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Scientific
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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 1:
1. Patient is able to read, understand, and provide written informed consent (signed and dated)
2. Male or female, aged 50-74 years, inclusive, at Screening
3. AD of mild severity (CDR Global score of 1 or CDR Global Score of 0.5 with a Memory score of 1;; MMSE 20-27, inclusive) at Screening
4. Reduced CSF Aβ42 at Screening, consistent with a diagnosis of mild AD
5. Elevated CSF total tau and p-tau at Screening, consistent with a diagnosis of mild AD
6. Diagnosis of probable AD dementia based on National Institute of Aging-Alzheimer Association (NIA-AA) criteria (may be either amnestic or nonamnestic [Global CDR score of 1.0] presentation) at Screening
7. Body Mass Index (BMI) >= 18 and <= 35 kg/m2
8. Total body weight > 50 kg (110 lbs)
9. Able and willing to meet all study requirements, including travel to Study Center, procedures, measurements and visits, including:
a. Reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center), unless neurological examination or admission, if needed, can be arranged promptly at a suitably equipped and staffed alternative facility and these arrangements have been discussed and agreed to by the Ionis Medical Monitor
b. Adequately supportive psychosocial circumstances, in the opinion of the Investigator
c. Caregiver/trial partner committed to facilitate patient*s involvement in the study who is reliable, competent, at least 18 years of age, willing to accompany the participant to select study visits and to be available to the Study Center by phone if needed and who, in the opinion of the Investigator, is and will remain sufficiently knowledgeable of the patient*s ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to study outcome measures requiring caregiver input
d. Adequate visual and auditory acuity for neuropsychological testing
10. Able to read at a level necessary to complete study assessments
11. No evidence or prior diagnosis of general learning disability
12. Females must be non-pregnant, non-lactating and either surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved)
13. Males must be surgically sterile, abstinent or, if engaged in sexual relations with a female of child-bearing potential, must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 814907 or placebo) or end of the study, whichever is

longer, Part 2:
1. Able to read, understand, and provide written informed consent (signed and dated)
2. Able and willing to meet all study requirements in the opinion of the Investigator, including:
a. Adequately supportive psychosocial circumstances
b. Caregiver/trial partner committed to facilitate patient's involvement in the study who is reliable, competent, at least 18 years of age, willing to accompany the participant to select study visits, and to be available to the Study Center by phone if needed, and who, in the opinion of the Investigator, is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to study outcome
measures requiring caregiver input
c. Adequate visual and auditory acuity for neuropsychological testing
d. Able to tolerate blood draws and lumbar punctures
3. Must have completed the Treatment Evaluation and Post-Treatment Periods in MAD, Part 1 of the study
4. Females must be non-pregnant, non-lactating and either surgically sterile (e.g. bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved)
5. Males must be surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, must agree to use and acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ISIS 814907 or end of study, whichever is longer.

Exclusion criteria

Part 1:
1. First or second degree family member among the investigational or Sponsor staff directly involved in the trial
2. Any contraindication or unwillingness to undergo MRI scanning (e.g., metal implants including MRI incompatible IUDs, claustrophobia, agitation or tremor of a severity that precludes MRI scans)
3. Any contraindication or unwillingness to undergo LP
4. Patient receives daily nursing care due to cognitive condition
5. Evidence of clinically-relevant neurological disease other than the disease being studied, including
a. Cerebrovascular disease (history of TIA, stroke, significant vascular disease [large vessel stroke, diffuse white matter hyperintensities {WMHs}, multiple lacunes, bilateral thalamic lesions, and/or > 5 microhemorrhages on brain MRI] or modified 8-item Hachinski Ischemia Scale score >= 4)

i. In addition to microhemorrhages, the degree of WMH severity will be centrally rated on T2 FLAIR and GRE T2 star images using the Age Related White Matter Changes (ARWMC) scale (e.g., WMHs > 5 mm, rated on a 4-point scale ranging from 0 (no lesions) to 3 (diffuse involvement of the entire region), within 5 regions in each hemisphere; a score of 3 in a region constitutes the presence of diffuse WMH)
ii. Multiple lacunes are rated as the presence of at least 2 lacunes in the basal ganglia and at least 2 lacunes in the frontal white matter. To meet the criterion for the presence of bilateral thalamic lesions, at least 1 lesion must to be present in each thalamus.
b. Current infectious/metabolic/systemic diseases affecting CNS
c. History of a serious infectious disease affecting the brain in the 5 years prior to Screening
d. History of clinically-significant head trauma (i.e., any loss of consciousness for > 5 minutes), including motor vehicle accident and/or concussion in the 3 years prior to Screening
e. MRI scan at Screening shows evidence for a potential alternative etiology for dementia (i.e., non-AD etiology)
f. History of generalized seizures in the 3 years prior to Screening
6. Psychiatric diagnosis/symptoms interfering with assessment of cognition
a. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 6 months prior to Screening. For patients with (i) a suicide ideation score >= 4 on the Columbia Suicide Severity Rating Scale (C SSRS) within the last 6 months, or (ii) suicidal behaviors within the last 6 months (as measured by the answer *Yes* on any of the C-SSRS Suicidal Behavior Items, a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. Patients deemed by the Investigator to be at significant risk of suicide should be excluded
b. Major depressive episode within 6 months prior to Screening (with the exception of patients in remission on allowed concomitant antidepressant medication) or at risk for psychosis, confusional state or violent behavior in the opinion of the Investigator
c. Geriatric Depression Scale Short Form > 6
d. History of alcohol or drug dependency/abuse within 3 years prior to Screening
7. Clinically-significant cardiac conditions including cardiac failure, angina or previous acute coronary syndrome within 6 months of Screening
8. Ongoing or recent (within 12 weeks of Screening) uncontrolled, clinically-significant medical condition including:
a. Hematological, hepatic, diabetes, hypertension, thyroid or endocrine disease, gastrointestinal disease, dialysis, or abnormal renal function
b. Retinal impairment or disease that would interfere with the ability to comply with study procedures
c. Peripheral vascular disease that would interfere with the ability to comply with study procedures
d. Known history of or positive test for human immunodeficiency virus (HIV),

hepatitis C, chronic hepatitis B consistent with CDC interpretation of serology panel or syphilis
9. History of bleeding diathesis or coagulopathy and/or platelet count < LLN at Screening
10. A medical history of brain or spinal abnormalities by MRI/CT or history that might interfere with the LP process, CSF circulation or safety assessment, including subarachnoid hemorrhage, suggestions of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, spina bifida occulta, chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome, frontotemporal brain sagging syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome
11. Any medical condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment
12. History of malignancy within 5 years prior to Screening, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, localized prostate carcinoma. Patients with other malignancies that have been treated with potentially curative therapy with no evidence of recurrence for >= 5 years post-therapy may also be eligible if approved by the Sponsor Medical Monitor
13. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed 3 days prior to Study Day -1
14. At Screening, have any condition such as medical, psychiatric or neurological other than the tauopathy under study which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study
15. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Use of a disallowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to the start of Screening
17. Change in dose regimen of an allowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to the start of Screening
18. Change in dose regimen of a cholinesterase inhibitor or memantine within 8 weeks prior to the start of Screening
19. Change in dose regimen of estrogen replacement therapy within 4 weeks prior to the start of Screening
20. Change in dose regimen of nutraceuticals or supplements within 4 weeks prior to the start of Screening
21. Use of warfarin
22. Use of Neudexta (dextromethorphan and quinidine)
23. Prior treatment with an active immunotherapy agent targeting the CNS
24. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
25. Any medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
26. Any history of gene therapy or cell transplantation or any experimental

brain surgery
27. Clinically-significant laboratory, vital sign or ECG abnormalities at Screening (including HR < 45 bpm, SBP < 90 mmHg and confirmed BP readings > 170/105 mmHg)
28. Any hepatic, glucose, renal, hematology or thyroid laboratory tests above or below the limits of normal that are considered to be clinically-significant must be discussed with the Sponsor Medical Monitor
29. Clinically-significant B12 or folate deficiencies at Screening or previous deficiencies that have not been corrected for at least 12 weeks prior to Screening, Part 2:
1.Treatment with another IP within 1 month of Reg, or 5 half-lives of investigation agent, whichever is longer
2.Use of a disallowed CNS-active or antipsychotic medication within 4 wks or 5 half-lives(whichever is greater) prior to Reg
3.Change in dosing regimen of an allowed CNS-active or antipsychotic medication within 4 wks or 5 half-lives(whichever is greater) prior to Reg
4.Change in dose regimen of a cholinesterase inhibitor or memantine within 8 wks prior to Reg
5.Change in dose regimen of estrogen replacement therapy within 4 w

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-01-2018
Enrollment:	9
Type:	Actual

Ethics review

Approved WMO Date:	21-12-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-06-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-10-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	07-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2019
Application type:	Amendment
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Approved WMO Date:	07-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	23-09-2019
Application type:	Amendment
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Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2016-002713-22-NL
CCMO	NL60032.000.16

Study results

Results posted: 14-08-2023

First publication
11-08-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File