An open-label study to investigate the safety, tolerability, and Pharmacokinetics/Pharmacodynamics of risdiplam (RO7034067) in adult and pediatric patients with spinal muscular atrophy

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This study has been transitioned to CTIS with ID 2023-506739-14-00 check the CTIS register for the current data. Primary ObjectivesThe primary objectives of this study are as follows:• To evaluate the safety and tolerability of risdiplam.• To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49730

Source
ToetsingOnline

Brief title
JEWELFISH

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Spinal muscular athrophy; genetic progressive neuromuscular disease characterized by profound weakness and muscle atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd

Intervention

Keyword: pediatric, pharmacokinetic/pharmacodynamic, risdiplam, spinal muscular atrophy

Outcome measures

Primary outcome

SAFETY OUTCOME MEASURES

• Incidence and severity of adverse events, with severity determined according

to National Cancer Institute Common Terminology Criteria for Adverse Events

(NCI CTCAE) scale, Version 4.0.

• Incidence of treatment discontinuations due to adverse events.

• Incidence of abnormal laboratory values.

• Incidence of abnormal ECG values.

• Incidence of abnormal vital signs (body temperature, systolic and diastolic

blood pressure, heart rate, respiratory rate).

• Physical examination including examination of the skin, mouth, pharynx and

larynx. For patients aged 9*17 years old at screening, physical examination

will include formal Tanner staging for pubertal status.

• Neurological examination.

• Height, weight, and head and chest circumference.

• Incidence of emergence or worsening of symptoms as measured by the

Columbia-Suicide Severity Rating Scale (C-SSRS) (adult version for adults and

adolescents, pediatric version for patients aged 6 11 years)

• Ophthalmological examination

Secondary outcome

PHARMACOKINETIC OUTCOME MEASURES

• Concentration per timepoint listed

• Cmax

• AUC

• Concentration at the end of a dosing interval (Ctrough) to assess steady-state

• Other PK parameters as appropriate.

PHARMACODYNAMIC OUTCOME MEASURES

• SMN mRNA in blood: Blood samples will be collected at the times specified in the Schedules of Assessments and detailed tables, to isolate mRNA and measure the relative amount of SMN mRNA and its splice forms. Housekeeping genes for the quantitative analysis of RNA will also be measured.

• SMN protein levels in blood.

EXPLORATORY OUTCOME MEASURES

• Disease-related adverse events

• Motor function measure (MFM) (32 item version)

• Hammersmith Functional Motor Scale Expanded (HFMSE)

• Revised Upper Limb Module (RULM)

• Gross Motor Scale of the Bayley Scales of Infant and Toddler development*Third \Edition (BSID III)

• Hammersmith Infant Neurological Examination Module 2 (HINE 2).

• Six-minute walk test (6MWT) (for ambulant patients only)

• Sniff nasal inspiratory pressure (SNIP)

• Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and peak cough flow (PCF)

• SMA Independence Scale (SMAIS) (Sensor data collected using smartphone-based monitoring as part of the digital biomarker approach)

• Ventilation-free survival (i.e., without need for permanent ventilation, defined as >= 16 hours of non invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following, the resolution of an acute reversible event or tracheostomy)

• Ability to swallow

Study description

Background summary

SMA (spinal muscular atrophy) is the leading genetic cause of death in infants and young children. In milder forms, it results in profound motor and respiratory disabilities and major orthopedic deformities. One drug was recently approved in the USA, the European Union, Canada and other jurisdictions for the treatment of SMA in pediatric and adult patients (the antisense oligonucleotide nusinersen) but the medical need in SMA for alternative treatment options is still very high. There is currently no oral treatment for SMA that provides stabilization or improvement of motor function, which would be of immense value for patients and parents/caregivers.
Small molecule SMN2 splicing modifiers such as risdiplam represent a potential treatment option for patients with SMA, as they increase the amount of SMN protein within the CNS and throughout the body. Deficiency of SMN protein is the fundamental pathophysiological mechanism of SMA. There is increasing preclinical evidence to suggest that SMN restoration in the CNS can result in significant improvements in survival, motor function and disease pathology but is insufficient to fully ameliorate the SMA phenotype. By restoring SMN protein

levels in the CNS and in peripheral tissue, orally administered SMN2 splicing modifiers have the potential to provide improved efficacy over compounds administered to the CNS only.
Risdiplam has demonstrated effective correction of splicing of the human SMN2 gene. The compound shifts the balance of alternative splicing completely toward inclusion of SMN2 exon 7 and production of functional SMN protein in human cultured cells and in SMA mouse models (for details, see the risdiplam Investigator*s Brochure). Proof of mechanism for the change in SMN2 splicing in terms of SMN2 mRNA was established with risdiplam in a single ascending dose study in healthy subjects. Proof of mechanism in terms of an increase in SMN protein was previously demonstrated with another compound having a similar mechanism of action, RO6885247, with an up to 2 fold increase in SMN protein observed upon treatment with RO6885247.
This exploratory, open-label study is designed to assess the safety, tolerability, PK and PD of risdiplam in patients with SMA (aged 6 months to 60 years) previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101 or olesoxime. Considering the different therapeutic agents currently approved or in development for SMA and the possibility that patients with a poor response to and/or lack of tolerability towards another agent may need alternative treatment options, it is important to evaluate the safety and PK/PD response to risdiplam in these patients compared to treatment naïve patients. The results of this study will allow an assessment of the safety and tolerability of risdiplam and to characterize the PK/PD relationship of risdiplam in these non-naïve patients in order to inform clinical development of risdiplam. The PK of risdiplam will be assessed throughout the study. The PD characteristics of risdiplam will be measured in terms of SMN protein and SMN mRNA splice forms.

Study objective

This study has been transitioned to CTIS with ID 2023-506739-14-00 check the CTIS register for the current data.

Primary Objectives
The primary objectives of this study are as follows:
• To evaluate the safety and tolerability of risdiplam.
• To investigate the pharmacokinetics (PK) of risdiplam and metabolites as appropriate.

Secondary Objective
The secondary objective for this study is as follows:
• To investigate the PK-pharmacodynamics (PD) relationship of risdiplam. The PD investigations will include analyses of SMN mRNA splice forms and SMN protein.
Exploratory Objectives
The exploratory objectives for this study are defined below:
• To evaluate the safety of treatment with risdiplam in terms of the proportion of patients who experience a pre-specified disease-related adverse event.

• To evaluate the efficacy of treatment with risdiplam in terms of motor function as assessed through the following measures:
- Motor function measure (MFM) (patients aged 2*60 years)
- Hammersmith Functional Motor Scale Expanded (HFMSE) (patients aged 2-60 years)
- Revised Upper Limb Module (RULM) (patients aged 2-60 years)
- Six-minute walk test (6MWT) of walking capacity in ambulant patients (patients aged 6-60 years)
- Bayley Scales of Infant and Toddler development - Third Edition (BSID-III) (patients aged 6 months to < 2 years)
• To evaluate the efficacy of treatment with risdiplam in terms of achievement of motor milestones as assessed through the Hammersmith Infant Neurological Examination (HINE) Module 2 (patients aged 6 months to < 2 years)
• To evaluate the efficacy of treatment with risdiplam on respiratory function as assessed through the following measures:
- Sniff nasal inspiratory pressure (SNIP) (patients aged 2-60 years)
- Forced vital capacity (FVC) (patients aged 6*60 years)
- Forced expiratory volume in 1 second (FEV1) (patients aged 6-60 years)
- Peak cough flow (PCF) (patients aged 6*60 years)
• To evaluate time-matched QT profiles in patients treated with risdiplam (patients aged 12-60 years
• To evaluate the efficacy of treatment with risdiplam in terms of patient-reported independence (patients aged 12-60 years and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS) (patients aged 2-60 years)
• To evaluate patients* adherence to smartphone-based monitoring (patients aged 6-60 years)
• To evaluate the collected sensor data from smartphone-based monitoring and its potential correlations with patients* MFM score (patients aged 6-60 years)
• To assess time to death (patients aged 6 months to < 2 years)
• To assess time to loss of swallowing (patients aged 6 months to < 2 years)
• To assess time to permanent ventilation (patients aged 6 months to < 2 years)

Study design

This is a multi-center, exploratory, non-comparative and open-label study to investigate the safety, tolerability, PK and PK/PD relationship of risdiplam in adults and children and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101 or olesoxime.
Treatment with risdiplam will initially be evaluated over a 24-month period. After completion of the 24-month treatment period, the patient will be given the opportunity to enter the extension phase of the study, which will include regular monitoring of safety, tolerability and efficacy. The patient's treatment in the extension will continue for up to 4 years after the last patient is enrolled in the study or until risdiplam is commercially available in the patient*s country, the study is terminated per local regulation, or the

Sponsor decides to terminate the study, whichever occurs first.

Intervention

Two-bottle formulation - Powder and solvent for oral solution, 20 mg and 120 mg
Risdiplam *two-bottle* clinical formulation is a powder and solvent for constitution to an oral solution. Risdiplam drug product is composed of two bottles; one containing 20 mg or 120 mg of risdiplam substance (no excipients) and another with excipients blend (powder for solvent for reconstitution). The excipient blend bottle is constituted with water for injection and entirely transferred to the drug substance bottle to yield an oral solution containing 0.25 mg/mL or 1.5 mg/mL of risdiplam.

One-bottle formulation - Powder for oral solution, 60 mg
Risdiplam *one-bottle* clinical formulation is a powder for constitution to an oral solution. Each bottle contains 60 mg of risdiplam substance with excipients. The powder is constituted with purified water to yield an oral solution containing 0.75 mg/mL of risdiplam.
Throughout the study, the study medication (risdiplam) should be taken once daily in the morning with the patient*s regular morning meal, except when site visits are planned and study medication will be administered at the clinical site.

All IMPs will be supplied and packaged by the Sponsor.

Study burden and risks

Patients are asked to undergo procedures described on pages 124 - 143 of the study protocol. These procedures include physical examination, neurological examination, blood and urine sample collection, vital signs, ECG, eye and vision exams, pulmonary testing and completion of questionnaires, answer questions of investigator and study team and administration of study drug. Additionally, fertile subjects are asked to use contraceptives, and female subjects of childbearing potential will have pregnancy tests.
The study medication is a nonregistered medication. Possible known side effects are described in the Investigators Brochure and patient information and can also occur during this study. Adverse events that were reported with use of study drug in clinical trials were: fever, sore throat, headache, rash, cough, infection of throat, infection of upperairways, infections including upper respiratory tract infections and air infections, gastrointestinal problems including diarrhea, constipation and vomiting and respiratory illnesses including lung collapse and lung congestion.
Study procedures may also cause discomforts:
Blood draw: Drawing blood can cause pain, bruising, or infection where the needle is inserted. Some people experience dizziness, fainting, or upset stomach when their blood is drawn.

Electrocardiogram (ECG): Skin pads may cause redness, irritation, or itching.
Muscle tests: Tests may be difficult to perform and may cause fatigue.
Eye and vision tests: Eye drops used in test may cause sensitivity to light

Risdiplam has demonstrated effective correction of splicing of the human SMN2 gene. The compound shifts the balance of alternative splicing completely toward inclusion of SMN2 exon 7 and production of functional SMN protein in human cultured cells and in SMA mouse models (for details, see the risdiplam Investigator*s Brochure). Proof of mechanism for the change in SMN2 splicing in terms of SMN2 mRNA was established with risdiplam in a single ascending dose study in healthy subjects. Proof of mechanism in terms of an increase in SMN protein was previously demonstrated with another compound having a similar mechanism of action, RO6885247, with an up to 2 fold increase in SMN protein observed upon treatment with RO6885247.
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Contacts

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Hoffmann-La Roche

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Scientific
Hoffmann-La Roche

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Males and females 6 months to 60 years of age inclusive (at screening)
2. Confirmed diagnosis of 5q-autosomal recessive SMA, including:
- Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the SMN1 gene.
- Clinical history, signs, or symptoms attributable to SMA.
3. Previous enrollment in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previous treatment with any of the following:
- Nusinersen (defined as having received >=4 doses of nusinersen, provided that the last dose was received >= 90 days prior to screening)
- Olesoxime (provided that the last dose was received <= 18 months and >= 90 days prior to screening)
- AVXS-101 (provided that the time of treatment was >= 12 months prior to screening)
4. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonization (ICH) and local regulations. Alternatively, a legally authorized representative must be able to give consent for the patient according to ICH and local regulations and assent must be given whenever possible.
5. Adequately recovered from any acute illness at the time of screening and considered well enough to participate in the opinion of the Investigator.
6. For women of childbearing potential: negative blood pregnancy test at screening, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:
- Women must remain abstinent (refrain from heterosexual intercourse) or use

two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 28 days after the final dose of study drug. Women must refrain from donating eggs during this same period.
- A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (>= 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established and proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- A vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of child bearing potential trial participant, and provided the vasectomized partner has received medical assessment of the surgical success.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
7. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
- With a female partner of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 4 months after the final dose of study drug. Men must refrain from donating sperm during this same period. This period is required for small molecules with potential for genotoxic effect and includes the spermatogenic cycle duration and drug elimination process.
- With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the final dose of study drug.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
8. For patients aged 2 years or younger at screening:
- Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator.
- Medical care meets local accepted standard of care, in the opinion of the

Investigator.
- Would be able to complete all study procedures, measurements and visits, and the parent or caregiver of the patient has adequately supportive psychosocial circumstances, in the opinion of the Investigator.
- Parent or caregiver of patient is willing to consider nasogastric, naso-jejunal or gastrostomy tube placement, as recommended by the Investigator, during the study (if not already in place at the time of screening) to maintain safe hydration, nutrition and treatment delivery.
- Parent or caregiver of patient is willing to consider the use of non invasive ventilation, as recommended by the Investigator during the study (if not already in place at the time of screening).

Exclusion criteria

1. Inability to meet study requirements.
2. Concomitant participation in any investigational drug or device study.
3. With the exception of studies of olesoxime, AVXS-101, or nusinersen: Previous participation in any investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer.
4. Any history of gene or cell therapy, with the exception of AVXS-101.
5. Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator.
6. Inadequate venous or capillary blood access for the study procedures, in the opinion of the Investigator.
7. For patients aged < 2 years, hospitalization for a pulmonary event within 2 months prior to screening and pulmonary function not fully recovered at the time of screening.
8. Lactating women.
9. Suspicion of regular consumption of drugs of abuse.
10. For adults and adolescents only, i.e., aged > 12 years, positive urine test for drugs of abuse or alcohol at screening or Day -1 visit.
11. Cardiovascular, blood pressure, and heart rate:
- Adults: Sustained resting systolic blood pressure (SBP) > 140 mmHg or < 80 mmHg, and/or diastolic blood pressure (DBP) > 90 mmHg or <40 mmHg; a resting heart rate < 45 bpm or > 100 bpm if considered to be clinically significant by the Investigator.
- Adolescents (12*17 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 50 bpm or > 100 bpm if considered to be clinically significant by the Investigator.
- Children (6*11 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 60 bpm or > 120 bpm, if considered to be clinically significant by the Investigator.
- Children (2*5 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 70 bpm or > 140 bpm if considered to be clinically significant by the Investigator.

- Children (6 months to < 2 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <70 bpm or > 170 bpm, if considered to be clinically significant by the Investigator.
12. Presence of clinically significant ECG abnormalities before study drug administration (e.g., second or third degree AV block, confirmed QTcF >460 msec for patients aged >= 10 years, or QTcB > 460 ms for children up to age 10 years (Bazett*s correction is more appropriate in young children) from the average of triplicate measurements, or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death) indicating a safety risk for the patient as determined by the Investigator.
13. History of malignancy if not considered cured.
14. For patients aged > 6 years, significant risk for suicidal behavior in the opinion of the Investigator, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).
15. Any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to first dose administration
16. Use of any OCT-2 and MATE substrates within 2-weeks before dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine) including the mother, if breastfeeding the patient.
17. Use of the following medications within 90 days prior to enrollment: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase (HDAC) inhibitory effect, and medications with known phototoxicity liabilities (e.g., oral retinoids including over-the-counter formulations, amiodarone, phenothiazines and chronic use of minocycline). (Patients who are on inhaled corticosteroids, administered either through a nebulizer or an inhaler, will be allowed in the study).
18. Recently initiated treatment for SMA (within 6 weeks prior to enrollment) with oral salbutamol or another B2-adrenergic agonist taken orally is not allowed. Patients who have been on oral salbutamol (or another B2-adrenergic agonist) for >= 6 weeks before enrollment and have shown good tolerance are allowed. The dose of B2-adrenergic agonist should remain stable as much as possible for the duration of the study. Use of inhaled B2 adrenergic agonists (e.g., for the treatment of asthma) is allowed.
19. Any prior use of chloroquine, hydroxychloroquine, retigabin, vigabatrin or thioridazine, is not allowed. Use of other medications known to or suspected of causing retinal toxicity within one year prior to enrollment is not allowed.
20. Clinically significant abnormalities in laboratory test results, e.g., ALT values exceeding 1.5 fold the upper limit of normal, unless the elevated ALT level is considered of muscular origin (i.e., in the absence of other evidence of liver disease) which is supported by elevated creatine kinase and LDH. Out

of range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels per se do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before enrollment to confirm eligibility.
21. Donation or loss of blood >= 10% of blood volume within 3 months prior to screening.
22. Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation.
23. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the patient in this study.
24. Recent history (less than 1 year) of ophthalmological diseases (e.g., glaucoma not controlled by treatment, central serous retinopathy, inflammatory/infectious retinitis unless clearly inactive, retinal detachment, retinal surgery, intraocular trauma, retinal dystrophy or degeneration, optic neuropathy, or optic neuritis) that would interfere with the conduct of the study as assessed by an opthalmologist. Any other abnormalities detected at screening (e.g., retinal layer abnormalities, edema, cystic or atrophic changes) should be discussed with the Investigator, the Ophthalmologist, and with the Sponsor, who will jointly make the decision if the patient may be enrolled in the study. Patients in whom SD-OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled.
25. Any prior use of an inhibitor or inducer of FMO1 or FMO3 taken within 2 weeks (or within 5 elimination half-lives, whichever is longer) prior to dosing.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	12-06-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	risdiplam (RO7034067)
Generic name:	risdiplam (RO7034067)

Ethics review

Approved WMO Date:	20-11-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-05-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-506739-14-00
EudraCT	EUCTR2016-004184-39-NL
CCMO	NL67869.041.18