Prospective evaluation of potential effects of repeated gadoliniumbased contrast agent (GBCA) administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group*ODYSSEY

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To prospectively assess the potential effect of repeated exposure to either a linear or amacrocyclic gadolinium-based contrast agent (GBCA) on change from baseline to Year 5 inmotor and cognitive function among neurologically normal adults in…

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52180

Source
ToetsingOnline

Brief title
Longterm study of GBCAs on motor, cognitive function after repeated CE-MRI

Condition

- Other condition

Synonym
Long term Impact of exposure to GBCA

Health condition

motorische en cognitieve functie bij neurologisch normale volwassenen

Research involving
Human

Sponsors and support

Primary sponsor: IQvia
Source(s) of monetary or material Support: Bayer,Bayer HG;Bracco Imaging S.p.A.;GE Healthcare Pharma LLC;Guerbet,Bracco-Byk,GE Healthcare Pharma LLC,Guerbet

Intervention

Keyword: Effect, Exposure, GBCA, Neurological

Outcome measures

Primary outcome

o-Primary Endpoint to Assess Motor Function

One co-primary endpoint is the change from baseline to year 5 in motor function

as expressed

by composite z score, defined as the weighted sum of the z scores of the

individual tests.

Since each of these tests is considered equally important, each test will be

assigned an equal

weight.

The 4 tests to assess motor functions for the specific motor function domains

(described in

detail in Appendix 1) are the Nine Hole Peg Test (NHPT), the Finger Tapping

Test (FTT), the

Single Leg Stance Test (SLST), and the Timed Up and Go (TUG) test.

3.3.2 Co-Primary Endpoint to Assess Cognitive Function

The other co-primary endpoint is the change from baseline to year 5 in cognitive function as expressed by the composite z score, defined as the weighted sum of the z scores of the individual tests. Since each of the tests is considered equally important, each test will be assigned an equal weight.

The 3 tests to assess cognitive functions for the specific 5 cognitive function domains (described in detail in the separate Motor Function and Cognitive Testing Appendix) are the

Secondary outcome

Changes from baseline in the composite endpoints (Years 1 to 4) and in each individual test of motor and cognitive function (Years 1 to 5) will be assessed.

Additional secondary endpoints include:

• Evaluation of adverse events. The recording of AEs that occur after signing of the informed consent form (ICF) at Screening will be done at baseline and at each annual visit. Signs/symptoms, onset and end date, severity, causality, seriousness, treatment,

and outcome, will be recorded.

• Total gadolinium concentrations in blood plasma and urine samples collected at

baseline and at each annual visit will be determined. If the CE-MRI is obtained

at the

same visit, the blood and urine samples will be obtained prior to imaging.

Study description

Background summary

Gadolinium-based contrast agents have been used worldwide for about 30 years and have
been used in more than 450 million patients. For a broad spectrum of diseases, GBCAs are
indispensable adjuncts to MRI for detection and therapeutic guidance. Their accumulated
safety record is positive, with an extremely low rate of serious adverse reactions.1, 2,3,4,5,6,7
Until 2006, it was generally assumed that any GBCA administered to patients was excreted
shortly thereafter or that whatever amount might be retained by the body long term was so
small as to be clinically inconsequential.8 But in 2006, two European groups9,10 suggested that
the use of GBCAs could be the cause of nephrogenic systemic fibrosis (NSF), which is a rare
fibrosing disorder that occurs in patients with advanced kidney disease, including end-stage
renal disease requiring dialysis. The possibility that GBCA administration could trigger NSF
in patients with severe kidney disease rapidly led to permanent changes and restrictions in the
GBCA labeling and new standards of care that incorporated renal function testing before
administration, adherence to approved dosing regimens, and restrictions in the use of certain
agents in patients with severe renal dysfunction. This redefined the understanding of, and
approach to, the safety of GBCAs as a class.11 These studies also resulted in clear distinctions

in the relative safety of individual GBCAs within the clinically approved class. Although the pathogenesis of NSF has not been fully elucidated, its etiology is likely to be multifactorial.
Nevertheless, swift actions and risk minimization measures by the manufacturers, the radiologic community, and the regulators resulted in a dramatic decrease in the number of new NSF cases.
In 2013, researchers in Japan noted increased signal intensity in certain regions (globus pallidus [GP] and dentate nuclei [DN]) of the brain on the unenhanced scans of participants who had received multiple administrations of linear GBCAs.12 It was only after the publication of 3 investigations of autopsy specimens that gadolinium deposition in the areas of T1 signal intensity (SI) increase could be confirmed.3,4,5 The McDonald group evaluated 13 autopsy specimens from individuals (all of whom had had an estimated glomerular filtration rate [eGFR] >=49 mL/min/1.73 m2) who had undergone >=4 MR examinations with Omniscan and 10 autopsy specimens from individuals who had never received a GBCA.3 Compared with neuronal tissues of control patients, all of whom demonstrated undetectable levels of gadolinium, neuronal tissues of patients exposed to Omniscan contained 0.1-58.8 µg gadolinium per gram of tissue, in a significant dose-dependent relationship that correlated with signal intensity changes on precontrast T1-weighted MR images. Gadolinium deposition in the capillary endothelium and neural interstitium was observed only in the contrast group.3
The Kanda group evaluated autopsy specimens from 5 patients who had eGFRs >45 mL/min/1.73 m2 and who had received >=2 total doses of Magnevist (gadopentetate dimeglumine) and either Omniscan (gadodiamide) or ProHance (gadoteridol) and compared them to the findings from 5 autopsy specimens from patients who had not received GBCAs.

Using inductively coupled plasma mass spectrometry (ICP-MS), the Kanda group also found the presence of gadolinium, not only in the GP and DN but also in frontal lobe cortex, frontal

lobe white matter, and cerebellar white matter, at concentrations that far exceeded those seen
in the control group.5
Murata et al4 also performed a postmortem Gd deposition study of 9 decedents who had
single-agent exposures to 1 or more doses of a GBCA (including Gadavist [gadobutrol, 2
cases], ProHance [gadoteridol, 5 cases], MultiHance [gadobenate dimeglumine, 1 case] and
Eovist [gadoxetate disodium, 1 case]). They also found 9 control decedents who had had no
MRI or no CE-MRI during their lifetime. Tissue samples from GP, the head of the caudate
(CA), the white matter from the centrum semiovale (CSor WMCS), the putamen (PU), the
DN, and the pons (PO) were collected and analyzed with ICP-MS. None of the decedents had
severe renal failure. Importantly, none had primary brain tumors or cerebral metastases, and
none had received cerebral radiation therapy. Results of the study revealed that Gd is also
deposited in human brain tissues with the macrocyclic agents Gadavist and ProHance and
with the 2 linear protein-interacting agents MultiHance and Eovist. As in previous
postmortem studies of brain tissue,3,5 the levels of Gd in brain tissue were highest in GP and
DN but Gd was also present in all other brain tissues sampled, including CA, CSor WMCS,
PU, and PO, although at much lower concentrations.4 It was not possible to draw any firm
conclusions from these data about differences seen between different agents since for some
GBCAs measurements were available from only a single case and, as the authors
acknowledged, previous GBCA administrations could not be excluded. However, a number of
studies that used ICP-MS to measure Gd in brain tissue of rats exposed to GBCAs showed
clear differences in the content of Gd between macrocyclic and linear GBCAs,13,14,15,16 and
also within each class of linear and macrocyclic GBCAs.16,17
The detection of retained Gd in human brain parenchyma following repeated intravenous
administration was unexpected for several reasons, not the least of which is that the
administered GBCA molecules were considered unable to pass through an intact blood-brain

barrier (BBB). Thus, the question of how the retained Gd could be found on the other side of the BBB within the human brain parenchyma remained another aspect of the puzzle that had to be solved.

A recent publication by McDonald et al verified the presence of intraparenchymally retained Gd in the complete absence of known perturbations of the BBB.6 This observation contributes to the growing body of evidence that the cerebrospinal fluid (CSF) and the glymphatic system play a role in the normal biodistribution of intravenously administered GBCAs, even in the absence of significant renal disease. These findings tend to support those of an animal study by Jost et al18 and those of clinical studies by Öner et al,19 Iliff et al,20 Naganawa et al,21 and others 22, 23 who have documented the normal role that the CSF and the glymphatic system play in the biodistribution of intravenously administered GBCAs and the likely role in providing a pathway to the brain parenchyma that bypasses the otherwise intact BBB. This brings up the intriguing possibility that although the 1- to 2-hour biologic half-lives typically reported for GBCAs are well known, a smaller component of the administered dose may well experience a longer effective biologic half-life during its glymphatic transition stage.

No histological abnormalities were detected in the brain after multiple administrations of either linear or macrocyclic GBCAs in animals.14,16 Moreover, no study showed any morphological changes or obvious tissue reactions such as degeneration or inflammation.

These findings are consistent with the few available clinical data reporting the lack of apparent histological changes in sections of DN from patients, including children,7 who received Omniscan up to a total cumulative dose of 500 mL3,6 and other agents including linear and macrocyclic GBCAs.24

Finally, to date, no neurological symptoms or conditions have been associated with abnormal T1 signal intensity increase in deep brain areas. In addition, Welk et al conducted a

population-based study and found no statistical evidence for an association between exposure
to GBCAs and development of Parkinsonism in elderly patients.25 Studies aimed at detecting
and measuring elemental Gd in brain tissues following exposure to GBCAs showed that the
highest levels were in the DN and in the GP.3, 4, 5, 24 Given that GP lesions are typically
associated with motor deficits, including parkinsonism, tremor, and dystonia,26, 27, 28 the
results of the Welk study do not support the hypothesis that GBCA administration is
associated with parkinsonism at the dosing regimen reported.

Study objective

To prospectively assess the potential effect of repeated exposure to either a linear or a
macrocyclic gadolinium-based contrast agent (GBCA) on change from baseline to Year 5 in
motor and cognitive function among neurologically normal adults in comparison to a matched
non-GBCA-exposed control group.

Secondary Objectives
• To assess the change from baseline in the composite endpoints (motor and cognitive)
at each of the post-baseline time points (Years 1 to 4) in GBCA-exposed participants
as compared to controls.
• To assess the change from baseline for each of the individual tests (motor and cognitive) at each of the post-baseline time points (Years 1 to 5) in GBCA-exposed
participants as compared to controls.
• To evaluate safety through collection of adverse events.
• To assess total Gd concentrations (as measured in a central laboratory) in blood and
urine samples taken from exposed and control participants at the time of the annual
visit.

Study design

This study will be conducted as a prospective, multinational, multicenter, longitudinal cohort
study in 2 groups of participants exposed to GBCAs (either linear or

macrocyclic no generics
permitted in this study) and a matched control group of participants not exposed to any
GBCA. Assignment to GBCA will be non-randomized and will be based on medical need and
usual institutional practice.
All participants must be neurologically normal adults. Participants in the GBCA arms are
expected to undergo >=5 CE-MRIs in order to evaluate the association of repeated administration of GBCAs. Each GBCA participant will receive the same GBCA throughout
the study. Participants in the control group should have never been exposed to any GBCA in
the past and should not receive GBCAs during the study; however, they will continue to
receive any clinically indicated imaging required (including, but not limited to, UE-MRI,
and/or unenhanced/enhanced computed tomography [CT], ultrasound [US] and/or X-ray).
All participants will undergo neurologic function assessment using a comprehensive battery
of motor and cognitive tests administered annually over the course of >=5 years.

Intervention

N/A

Study burden and risks

N/A

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Participant must be an adult having reached legal majority age and less than 65 years
old.
2. Participant must be neurologically normal, defined as free of unstable neurologic and
psychiatric disease as confirmed by a normal neurologic examination at screening.
3. Participant agrees to be tested as per protocol for 5 consecutive years
4. Participant (GBCA-exposed or controls) agrees to undergo UE-MRI of the brain at
enrollment and at the end of the observation period (5 years).
5. Patient affiliated to national health insurance according to local regulatory requirements, where applicable.
6. Participants should have at least 1 of the following indications:
• Medium to high risk for breast cancer or with dense breasts undergoing breast cancer screening with MRI
• Elevated PSA under active diagnostic surveillance of prostate cancer
• Chronic liver disease (eg. liver cirrhosis limited to Child Class A, post-hepatitis
chronic hepatopathy, or primary sclerosing cholangitis) for surveillance of hepatocellular carcinoma development
• Low-grade colorectal cancer or neuroendocrine tumor undergoing surveillance for
liver metastases
• Branch-duct intraductal papillary mucinous neoplasm (IPMN) of the pancreas (maximum size <= 2 cm) undergoing imaging surveillance.

Exclusion criteria

1. As evidenced by history or determined in the neurologic exam at screening, concurrent
neurological and/or psychiatric disease (or treatments) that could influence the results
of the study*s motor and cognitive tests. Examples include but are not limited to:
• Cerebrovascular disease.
• Multiple sclerosis.
• Neurodegenerative disease.
• Malignant disease other than listed in indications.• Carcinoid tumors.
• Epilepsy.
• Prior neurosurgery.
• Psychotic disorders or any prior psychotic episode not otherwise specified (NOS)*any documented prior history of chronic schizophrenia.
• Remittent or current medically confirmed major depressive disorder or bipolar disorder. History of long-term major depression or bipolar affective disorder with
an active episode in the past 2 to 5 years.
• Neurodevelopmental disorders (eg, trisomy 21).
• Uncontrolled severe migraine.
• Uncontrolled or controlled anxiety or depression within 6 months before enrollment.
• Screening scores of <=24 on the MMSE and/or >=11 on the HADS.
2. Prior, planned, or ongoing chemotherapy or brain irradiation.
3. Use of concomitant medication(s) affecting neuro-cognitive or motor function (an
authorized exception is a single intake before the study MRI because of anxiety if
administered after the motor and cognitive test evaluation):
• Regular use of benzodiazepines or non-benzodiazepine hypnotics. Long-acting benzodiazepines (eg, diazepam) should not be administered within 24 hours prior to cognitive testing.
• Short/medium-acting benzodiazepines (eg, alprazolam, lorazepam, oxazepam, temazepam), except if used chronically for sleep and on a stable dose for 8 weeks
prior to Screening Visit 1 or 12 hours prior to cognitive testing.
• Regular use of anticholinergic drugs (anticholinergics for bladder control with
limited cognitive effects are permitted).
• Long-term use of corticosteroids or methotrexate, cladribine.
• Regular use of antidepressants (eg, anticholinergics, tricyclics, monoamine oxidase
inhibitors [MAOIs], norepinephrine-dopamine reuptake inhibitors [NDRIs], selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine

reuptake inhibitors [SNRIs], or lithium, anti-epileptics, and/or antipsychotic drugs:
Use of antidepressants is allowed if at stable doses for 8 weeks prior to Screening
Visit. Antipsychotics used on a regular basis, except for low doses of atypical antipsychotics (e.g., risperidone, aripiprazole, or quetiapine), anticonvulsants with
limited cognitive effects, such as lamotrigine, pregabalin, levetiracetam for treatment of pain, and other non-epilepsy indications, are allowed as-needed basis
or if used at a stable dose for 8 weeks prior to Screening Visit
• CNS stimulants (eg, for ADHD).
4. Substance or alcohol abuse as determined by the investigator.
5. Alcoholic cirrhosis.
6. Any history or presence of other relevant chronic disease that prevents participation in
the study or that may confound neurofunction testing.
7. Renal disease, defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2, calculated by using the Modification of Diet in Renal Disease
(MDRD) formula or the Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
8. History of environmental/occupational/other exposure to one or more chemicals that
may affect cognitive and/or motor function, including, but not limited to, heavy metals
(arsenic [As], cadmium [Cd], lead [Pb], manganese [Mn], and mercury [Hg]), pesticides, solvents, or carbon monoxide.
9. Anticipated, current, or past conditions (medical, psychological, social, or geographical) that, in the opinion of the investigator, would compromise the participant*s safety or her/his ability to participate in the study (eg, clinically
significant vitamin B12 deficiency, folic acid deficiency, uncontrolled thyroid dysfunction from medical history).
10. Clinical indications requiring >1 CE-MRI every 6 months.
11. Receipt of any investigational product or participation in any other clinical trial within
30 days prior to enrolling in this study or while enrolled in this trial.
12. Previous enrollment in this study.
13. Pregnant or nursing (lactating) women.
14. Presence of any metal-containing joint implants/prostheses.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-03-2022
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dotarem
Generic name:	gadoteric acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gadovist
Generic name:	gadobutrol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MultiHance
Generic name:	gadobenic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Primovist
Generic name:	disodium gadoxetate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ProHance

Generic name:	gadoteridol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-09-2021
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	24-10-2022
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2019-004730-42-NL
CCMO	NL78113.099.21