Safety, tolerability, efficacy and pharmacokinetic study of increasing doses of B26826 in adult patients with known or suspected intracranial lesions referred for contrast-enhanced MRI of the brain.

Published: 22-12-2020
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- To determine the safety, - To investigate the pharmacokinetics (PK), and- To obtain pilot efficacy data

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54381

Source
ToetsingOnline

Brief title
FIH study with a new contrast medium (B26826) for Magnetic Resonance.

Condition

- Other condition

Synonym
contrast medium, intracranial lesions

Health condition

Intracraniële laesies verwezen voor contrastverbeterde MRI van de hersenen

Research involving
Human

Sponsors and support

Primary sponsor: Bracco Imaging S.pA.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: B26826, Contrast medium, Intracranial lesions, magnetic resonance (MRI)

Outcome measures

Primary outcome

- To determine the safety,

- To investigate the pharmacokinetics (PK), and

- To obtain pilot efficacy data

Secondary outcome

N/A

Study description

Background summary

The process of MRI is based upon the ability to induce and detect the resonance of small magnetic fields, or moments, of some atomic nuclei which have the inherent properties of spin and charge. The most abundant of the naturally occurring spinning nuclei in the human body is the hydrogen nucleus, or proton, found in water and lipids. As is true for any charge in motion, protons generate a moment, which behaves with all the characteristics of a magnet. When placed into an external, strong magnetic field (in clinical practice, ranging from 1.5 T to 3.0 T), these small magnets align with the axes of the applied field. If a pulse of specific radiofrequency energy is then introduced, the protons will absorb this energy and re-orient themselves against the external magnetic field. When the radiofrequency pulse is then discontinued, the *excited* nuclei re-align themselves with the axes of the external magnetic field and, in doing so, release the absorbed energy as a detectable characteristic radiofrequency signal. This process of relaxation can be

measured as relaxation times, termed T1 (spin-lattice relaxation) and T2 (spin-spin relaxation), which characterize the rate of relaxation of the excited protons.
Gadolinium-based contrast agents (GBCAs) are most commonly used to shorten the T1 relaxation time of tissues for T1-weighted images in traditional MR imaging causing signal intensity (SI) enhancement in the areas where contrast agents distribute. Differential SI enhancement between abnormal and normal structures, or contrast enhancement, is used to detect and characterize disease in several regions of the body.
In the central nervous system (CNS), contrast enhancement produced by intravenous (IV) injection of GBCAs is a combination of two primary processes: intravascular (vascular) enhancement and interstitial (extravascular) enhancement. Intravascular enhancement may reflect abnormal vascularity, i.e., neovascularity, vasodilatation or hyperemia, and shortened transit time or shunting through the vasculature. The blood vessels that vascularize the CNS possess unique properties, termed the blood-brain barrier (BBB), which allow these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain.
The intact BBB prevents leakage of GBCAs into these tissues. Interstitial enhancement is related to enhancement resulting from alterations in the BBB permeability, whereas intravascular enhancement results from and is proportional to increases in blood flow or blood volume.
Therefore, the primary reasons for the use of GBCAs in MRI of the CNS are to increase the difference in SI between areas with BBB breakdown or with abnormal vascularity and normal areas, in order to detect/exclude presence of brain or spine lesions, determine lesion location and size, characterize lesions through assessment of internal morphologic features, to delineate lesion borders and distinguish them from surrounding edema or normal tissues, and/or to define their extent and relationship with adjacent structures in patients with suspected primary or secondary tumors, focal neurologic deficits, endocrinology disorders, or other conditions.
The degree of contrast enhancement produced by GBCAs depends on their concentration in the tissues or blood, and on their relaxivity. Relaxivity reflects the capability to shorten water proton relaxation rates T1 and T2/T2* and is a measure of the potency of GBCAs to increase the relaxation rates (R1 and R2) of surrounding water protons. Proton relaxation rate is the property that provides MRI signal: the higher the relaxation rate, the higher the SI on T1-weighted images and the higher the contrast enhancing efficacy of a GBCA.
Stability, the strength with which the GBCA chelate holds on to the gadolinium (Gd) ion, is another differentiator of the GBCAs: those with a macrocyclic chelate bind most tightly to the gadolinium and thus are characterized by a higher stability than linear GBCAs. The higher the stability of a GBCA, the lower the propensity of the chelate to undergo transmetallation, which is the replacement of Gd by other metal ions like zinc, iron, or copper in the chelate, and subsequent release of Gd, which immediately binds to a number of substrates in blood and tissues (endogenous anions like phosphates, carbonates and citrates, or macromolecules) and forms Gd-compounds that may be retained in

tissues. Lower-stability GBCAs are associated with a higher level of retention of Gd-compounds in brain and body tissues.
The first contrast agent approved for MRI of the CNS was the linear GBCA Magnevist® (gadopentetate dimeglumine). This was followed by: i) the macrocyclic GBCAs Dotarem® and Clariscan* (gadoterate meglumine), ProHance®(gadoteridol) and Gadovist® (gadobutrol); ii) and by the linear GBCAs Omniscan® (gadodiamide), MultiHance® (gadobenate dimeglumine), and OptiMARK® (gadoversetamide). All these GBCAs are characterized by similar relaxivity, with the only exception of the linear GBCA MultiHance, whose relaxivity is higher at all field strengths of MRI scanners. The higher relaxivity of MultiHance was repeatedly shown to provide a significantly better contrast enhancement, measured as contrast-to-noise ratio (CNR) and lesion-to-brain ratio (LBR), and significantly better conspicuity and delineation of CNS lesions, better definition of extent of brain and spine disease, and better depiction of the internal architecture/morphology of CNS lesions when compared with the same dose of lower-relaxivity GBCAs. Additionally, half dose of MultiHance was shown to produce comparable morphologic and morphometric assessment of intracranial lesions when compared with the full dose of the lower-relaxivity GBCA Dotarem®.
However, the stability of MultiHance is lower than that of the macrocyclic GBCAs. Currently there are no approved GBCAs that are characterized by both a high relaxivity and a high stability. Therefore, Bracco has designed and is developing B26826, a new macrocyclic GBCA characterized by both an elevated in vivo stability and a very high relaxivity in blood, markedly higher than that of all the currently GBCAs, MultiHance included.

Study objective

- To determine the safety,
- To investigate the pharmacokinetics (PK), and
- To obtain pilot efficacy data

Study design

Study B26826-101 is the FIH study of the new GBCA B26826, designed as a multicenter (5 investigational centers, but additional centers may be added based on the complexity of the study), open-label, dose-escalation study of four ascending single intravenous doses of this MR contrast agent, and as a blinded, within-patient comparison of the contrast enhancement efficacy obtained with B26826 and a validated comparator, Gadovist®, in MRI of the brain.

Patients providing informed consent to participate in this study, scheduled for contrast-enhanced MRI of the brain and meeting the inclusion and exclusion criteria set forth in this protocol will be sequentially allocated to one of four dose cohorts, starting from the lowest B26826 dose to be tested.

Intervention

All patients will have their scheduled contrast enhanced MRI with Gadovist®. Gadovist® will be injected at the dose of 0.1 mmol Gd/Kg corresponding to 0.1 mL/Kg as per prescribing information.

At least 48 hours later and no later than 4 days the patients will be asked to return to the hospital to undergo the contrast enhanced MRI with B26826 (followed by an hospitalization of 48 hours).
There are 4 dose cohorts with a different dose of B26826. Patients will receive their allocated dose of B26826 and immediately undergo the magnetic resonance procedure.

B26826 and Gadovist® will be administered by intravenous injection as a bolus using sterile syringes and aseptic techniques at a rate of 1 mL/sec manually or using a power injector. If a power injector is used, a commercially available injector in place at the investigational site will be used for product administrations. All injections will be followed by at least 20 mL saline flush.

The same administration procedure must be used for both products within the same patient. B26826 will be administered in an escalating manner; the study will start with the lowest dose group (i.e., 0.025 mmol Gd/kg). Between each consecutive dose group there will be an interval of time sufficient for reviewing the safety data. The volume of B26826 to be administered is calculated based on the weight of patient and on the belonging group of the patient.

Study burden and risks

The aim of this study is to evaluate the safety and diagnostic efficacy of a new contrast medium (B26826) for Magnetic Resonance.
This is a diagnostic trial not a therapeutic one, for this reason there are no expected benefits about the management of the disease.
However, the new compound has such properties to result in a better efficacy compared to other contrast media currently used in Magnetic Resonance in terms of signal enhancement of the affected areas of the brain, allowing a more accurate evaluation of the pathology.
The information obtain from this study will be useful in the future for people suffering from the brain lesions, when they will have to undergo Magnetic Resonance examinations.

Disadvantages of participation in the study may be:
- possible side effects
- possible side effects/discomforts of the evaluations in the study

Participation in the study also means:

- could cost you extra time.
-You need to be hospitalized. Or longer than usual.
-You have to comply with the study agreements.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Provides written Informed Consent and is willing to comply with protocol requirements;
• Male and female between 18 and 75 years of age inclusive;
• Is referred for and has been scheduled to undergo a contrast-enhanced MRI examination of the brain;
• Has a Karnofsky Performance Score >=70.

Exclusion criteria

• Is a pregnant or lactating female. Exclude the possibility of pregnancy: • by testing on site at the institution (serum βHCG) within 24 hours prior to the start of Gadovist(r) administration, • by surgical history (e.g., tubal ligation or hysterectomy), • post-menopausal with a minimum 1 year without menses; • Has any known allergy to GBCAs; • Have congestive heart failure (class IV according to the classification of the New York Heart Association;); • Have suffered a stroke within a year; • Have received or are scheduled to receive any other contrast medium in the 24 hours preceding Gadovist(r) injection through 7 days following B26826 administration; • Have received or are scheduled to receive an investigational compound and/or medical device within 30 days before admission into the present study, through the 7 days post-administration of B26826; • Suffers from mild-to-severe chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m2 calculating using the abbreviated MDRD formula); • Has, in the previous 7 days before the first MRI with Gadovist® (0.1 mmolGd/kg) through B26826 administration, received prescription or non-prescription systemic medications (e.g., anticancer drugs, barbiturates, or phenothiazines) which, in the opinion of the Investigator, may interfere with the study procedure or affect safety and efficacy assessments; • Has received or are scheduled for one of the following: • Surgical, radiation or chemotherapeutic treatment within one weeks prior to the first examination or between the two examinations; • initiation of steroid therapy between the two examinations; • Has any contraindications to MRI such as a pacemaker, magnetic material (i.e., surgical clips) or any other conditions that would preclude proximity to a strong magnetic field • Are suffering from severe claustrophobia; • Has participated in a clinical trial of an investigational drug and/or medical device within 3 months before admission into this study; • Has any medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data, achieving study objectives, or completing the study and/or post-dose follow-up examinations; • Cannot reliably communicate with the Investigator or is not likely to co-operate with the requirements of the study.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-12-2021
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	22-12-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2021
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2020-003386-20-NL
CCMO	NL75814.078.20