SYNOPSIS

NAME OF COMPANY: GUERBET

NAME OF FINISHED PRODUCT: Dotarem®

NAME OF ACTIVE SUBSTANCE:
Meglumine gadoterate (Gd-DOTA)

Title of the study:
Safety and efficacy evaluation of Dotarem® in magnetic resonance imaging (MRI) in patients with central nervous system (CNS) lesions (SENTIO Study)
Protocol No.: DGD-44-050 **IND No.:** 65 041
EudDRACT No.: 2010-020319-34

Investigators: A total of 52 investigators participated, 46 of whom included patients. No coordinating investigator was designated.

Study centers: 52 centers were opened, 46 of which included patients, 15 in the United States, 6 each in France and Germany, 3 each in Argentina, Austria, Chile and Spain, 2 each in Brazil, Italy and Korea, and 1 in the United Kingdom.

Publication (references): None

Study period:	**Clinical phase:**
Date of first inclusion: 16 September 2010 (FPFV) Date of study end for last patient: 16 November 2011 (LPLV)	III (US and Korea) / IV (other countries)

Objectives:

Primary objective

To demonstrate the superiority of Dotarem®-enhanced MRI as compared to unenhanced MRI in terms of lesion visualization (border delineation, visualization of internal morphology and degree of contrast enhancement) in CNS lesions with a disruption of the BBB and/or with abnormal vascularity (including tumoral, vascular, inflammatory or infectious diseases) (off-site assessment).

Secondary objectives:

- Evaluation of lesion visualization (border delineation, visualization of internal morphology and degree of contrast enhancement) by on-site readers.
- Evaluation of efficacy of enhanced MRI compared to unenhanced MRI by lesion counting, signal intensity, image quality and diagnostic confidence.
- Comparison of Dotarem®-enhanced MRI with Magnevist®-enhanced MRI in terms of lesion evaluation (border delineation, visualization of internal morphology and degree of contrast enhancement), lesions number and location, signal intensity, image quality, diagnostic confidence (on-site and off-site readers).
- Assessment of inter- and intra-reader agreement of MRI images for off-site readings
- Comparison of the clinical and biological safety of Dotarem®-enhanced MRI with Magnevist®-enhanced MRI.
- Evaluation of the safety and efficacy of Dotarem® in a pediatric population.

Methodology:

Multicenter, randomized, double-blind, fixed sequence (unenhanced MRI followed by either Dotarem®- or Magnevist®-enhanced MRI), active comparator study. Patients served as their own control for Dotarem® evaluations and Magnevist® served as an internal validation.
Adult patients were randomly assigned to receive Dotarem® or Magnevist® in a 2 to 1 ratio.
Pediatric patients were assigned to the Dotarem® group only.

NAME OF COMPANY: GUERBET		
NAME OF FINISHED PRODUCT: Dotarem®		
NAME OF ACTIVE SUBSTANCE: Meglumine gadoterate (Gd-DOTA)		

An unenhanced MRI (within 28 days of screening) was followed immediately by the contrast-enhanced MRI.
Patients were assessed for safety at 24 ± 4 hours after the contrast agent administration.
MR images of all patients were read by each of the 3 off-site blinded independent readers. All patients enrolled at a given site were evaluated by 1 on-site radiologist.

Number of subjects (planned and analyzed):
Planned: Approximately 396 enrolled patients (360 adults, 36 pediatric); 300 evaluable adults (200 Dotarem®, 100 Magnevist®) and 30 Dotarem® pediatric patients.
Actual: 416 patients enrolled (377 adults, 39 pediatric patients); 364 randomized AIP adults (245 Dotarem®, 119 Magnevist®) and 38 AIP pediatric patients; evaluable populations determined according to reader and MRI modality.

Diagnosis and criteria for inclusion:
Adult patients (legal majority age) and pediatric patients aged ≥2 years (in Latin America and the US only) scheduled to undergo a routine contrast-enhanced MRI of the CNS with at least 1 highly suspected or known CNS lesion (intracranial and spine) with a disruption of the blood brain barrier and/or with abnormal vascularity (including tumoral, vascular, inflammatory or infectious diseases) based on the results of previous imaging procedures.
Female patients had to use effective contraception or be surgically sterile or post-menopausal (for at least 12 months). Patients or the patient's parent or legal guardian had to be able to understand and sign the informed consent form. Main non-inclusion criteria were acute or chronic grade IV/V renal insufficiency with GFR <30 mL/min/1.73 m², receipt of any contrast agent within 3 days prior to study contrast administration, or scheduled to receive any contrast agent within 24 hours after the study contrast administration, contra-indication to MRI (e.g., pacemaker, aneurysm clip or severe claustrophobia) or known allergy to gadolinium chelates.

Test product, dose, mode of administration, batch No.:
Dotarem® (Gd-DOTA) 0.1 mmol/kg (0.2 mL/kg), intravenous bolus, ~2 mL/sec (adult population) or ~1 mL/sec (pediatric population).
Batch number: 10DCC002

Reference product, dose, mode of administration, batch No.:
Magnevist®, 0.1 mmoL/kg (0.2 mL/kg), intravenous bolus, ~2 mL/sec (adult population only)
A commercial preparation was used.

Duration of treatment:
A single Dotarem® or Magnevist® administration was performed lasting ~4-15 seconds in adult patients and ~2-10 seconds in pediatric patients.
Total duration of participation (screening to 24 hours post contrast-enhanced MRI follow up) was between 2 and 29 days.

Primary criteria for evaluation:
The primary efficacy measure was lesion visualization under Dotarem® at the patient level determined using 3 co-primary endpoints evaluated with a 3-point scale: 1) lesion border delineation, 2) internal morphology and 3) degree of contrast enhancement, by 3 independent blinded off-site readers. The primary analysis compared Pre (uncontrasted) vs. Paired (uncontrasted and contrasted) images in the 5 largest representative lesions.

NAME OF COMPANY: GUERBET		
NAME OF FINISHED PRODUCT: Dotarem®		
NAME OF ACTIVE SUBSTANCE: Meglumine gadoterate (Gd-DOTA)		

The study was considered successful if 2 of the 3 readers simultaneously met the alternative hypothesis for the primary objective ($\mu_1 > \mu_0$; $1-\beta = 0.80$) in the Dotarem® group with a statistically significant ($p \leq 0.025$) positive mean score per patient all 3 co-primary endpoints. Post (contrasted) images were reviewed in a secondary analysis.

Secondary criteria for evaluation:

- Lesion visualization, 3-point scale, patient level, on-site

The following were performed for off-site and on-site readings unless otherwise specified:

- Lesion visualization, 3-point scale, lesion level
- Lesion number and location
- Image quality, 3-point scale
- Level of diagnostic confidence, 5-point scale
- Signal intensity
- Inter- and intra-reader agreement (off-site only)
- Comparison of Dotarem®-enhanced MRI to Magnevist®-enhanced MRI in terms of lesion visualization, lesion number and location, image quality, level of diagnostic confidence and signal intensity
- Comparison of Dotarem® to Magnevist® in terms of adverse events (AEs), injection-site tolerance, changes in vital signs, ECG recordings (patient subset) and laboratory findings
- Safety and efficacy of Dotarem® in a pediatric population

Statistical methods:

Populations

AIP: all patients who were eligible and had signed the informed consent form

FAS: all patients with valid primary co-endpoint assessments

PP: all FAS patients without significant protocol deviations or violations

Safety: all patients receiving at least 1 injection of either contrast agent

Analyses: Descriptive statistics were used to summarize demographic, efficacy and safety data. Logistic regression models were used to evaluate the primary endpoint in the FAS and PP with center adjustment and subject repeated measures. A student t-test for a single group with 0.025 type-one error was used to demonstrate the superiority of Dotarem® according to the co-primary endpoints on a per patient basis for the primary endpoint. Secondary endpoints were analyzed by regression models in the FAS.

SUMMARY - CONCLUSIONS:

A total of 402 AIP patients were included, 364 randomized adults (245 Dotarem®, 119 Magnevist®) / 38 Dotarem® pediatric patients.

Nine adults withdrew prematurely including 7 who were not treated (5 Dotarem®, 2 Magnevist®) and 2 patients (Dotarem®) who did not complete the 24-hour follow-up; 2 treated pediatric patients withdrew prior to completing the 24-hour follow-up.

Major protocol deviations were reported in 7.8% of Dotarem® adult patients, 7.6% of Magnevist® adult patients, and 18.4% of Dotarem® pediatric patients.

NAME OF COMPANY: GUERBET		
NAME OF FINISHED PRODUCT: Dotarem®		
NAME OF ACTIVE SUBSTANCE: Meglumine gadoterate (Gd-DOTA)		

Demography

Adults

The AIP population had a mean age of 55 years (range 18-94), 53.8% were female and mean BMI was 27.0 ± 5.2 kg/m², 83.0% were Caucasian and 11.5% were Asian. Concomitant conditions included disorders of the nervous system (47.0%), vascular (35.4%), metabolic (28.6%), gastrointestinal (25.8%) and psychiatric (25.0%). Allergic tendencies were reported in 26.7% of patients (2 patients in each arm had previous medication allergic reactions). In addition, 11 patients (3.0%; 9 Dotarem®, 2 Magnevist®) had skin rash/tightness/blistering, and 5 (1.4%; all Dotarem®) had edema of the extremities.

Demographic and disease characteristics were well balanced between arms.

Pediatric

The AIP population had a mean age of 7 years (range 2-17), 57.9% were female and mean BMI was 18.6 ± 4.2 kg/m², 68.4% were Caucasian and 23.7% were black. Concomitant conditions were mainly nervous system disorders (50.0%). Allergic tendencies were reported in 18.7% of patients (1 patient had a previous medication allergic reaction), 2 patients (5.3%) had skin rash/tightness/blistering and 3 (7.9%) had respiratory conditions.

Efficacy

Populations were defined for each reader at the patient and lesion levels according to each MRI modality (Pre, Post and Paired).

Adults

Primary endpoint

Lesion visualization was significantly superior (p<0.001) in the FAS for all the 3 co-primary endpoints and for all off-site readers when comparing Paired to Pre, as shown below. Results were similar in the PP populations (p<0.001).

Readers	**R1 (Vossoug)**		**R2 (Tsiouri)**		**R3 (Maldjia)**	
Modality	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
N patients (FAS)	**224**	**230**	**224**	**230**	**222**	**235**
Border delineation score						
Mean (SD)	1.06 (1.23)	3.30 (2.64)	1.62 (1.43)	4.49 (2.94)	1.43 (1.29)	2.54 (2.30)
Estimate	1.09	3.35	1.65	4.57	1.43	2.58
Variation Paired-Pre	2.26		2.92		1.15	
Prob>T	<0.001		<0.001		<0.001	
Internal morphology score						
Mean (SD)	0.97 (1.05)	3.70 (2.63)	1.76 (1.24)	4.49 (2.93)	1.45 (1.13)	2.93 (2.30)
Estimate	0.97	3.72	1.80	4.57	1.42	2.96
Variation Paired-Pre	2.75		2.77		1.54	
Prob>T	<0.001		<0.001		<0.001	
Contrast enhancement score						
Mean (SD)	0.01 (0.20)	3.11 (2.52)	0.01 (0.15)	3.73 (2.67)	0.01 (0.13)	2.95 (2.44)
Estimate	0.05	3.18	0.05	3.81	0.02	3.01
Variation Paired-Pre	3.13		3.76		2.99	
Prob>T	<0.001		<0.001		<0.001	

NAME OF COMPANY: GUERBET		
NAME OF FINISHED PRODUCT: Dotarem®		
NAME OF ACTIVE SUBSTANCE: Meglumine gadoterate (Gd-DOTA)		

Secondary endpoints

Results are presented in the FAS and apply to all 3 off-site readers and on-site readings (Post evaluations were not performed for on-site images).

- Lesion visualization for all 3 co-primary endpoints:
  - Mean scores and variations for Magnevist® Paired and Pre images were of a similar order of magnitude to those of Dotarem® and Magnevist® superiority over unenhanced images was also demonstrated ($p<0.001$).
  - Mean variations for Post Dotarem® vs. Pre images showed statistical superiority ($p<0.001$ for all except internal morphology for 1 off-site reader, $p=0.037$).
  - Mean incidence of "seen perfectly" scores on Paired Dotarem®/Magnevist® images showed statistical superiority over Pre images ($p<0.001$ for border delineation and internal morphology).
  - Incidence of "better" Paired image scores compared to Pre was ≥75% for all endpoints other than for border delineation for 1 off-site reader.
  - Mean differences between Paired/Post and Pre scores, incidences of "seen perfectly and "better" scores were not significantly different between Dotarem® and Magnevist®
- Mean number of lesions identified with Paired or Post imaging was slightly higher than with Pre imaging for both Dotarem® and Magnevist® and were not significantly different between Dotarem® and Magnevist®.
- Mean image quality scores were significantly higher with Paired/Post images compared to Pre ($p<0.001$, other for 1 off-site reader with $p=0.016$ with Magnevist® and $p=0.988$ for Dotarem®) and were not significantly different between Dotarem® and Magnevist®.
- Mean diagnostic confidence scores were significantly higher with Paired/Post images compared to Pre images ($p<0.001$) and were not significantly different between Dotarem® and Magnevist®.
- CNR was significantly higher in Post images compared to Pre for all readers ($p<0.001$). Mean percentage lesion enhancement and CNR were not significantly different between Dotarem® and Magnevist®.
- Intra-reader agreement for Pre images was fair for border delineation and moderate for internal morphology and contrast enhancement. For Paired and Post images, agreement was generally moderate for border delineation and contrast enhancement, and poor for internal morphology for all readers. Inter-reader agreement was largely poor for all modalities and all reader combinations with the exception of contrast enhancement for Paired (moderate) and Post (fair) for all reader combinations, and for all 3 modalities for border delineation for 1 reader combination.

Pediatric

For all 3 off-site readers and the on-site readings (Post evaluations were not performed for on-site):

- Mean scores for each lesion visualization endpoint were higher for Paired/Post images vs. Pre.
- Incidence of lesions with a "seen perfectly" score was higher for Paired/Post images vs. Pre.
- A similar number of lesions were identified with all 3 MRI modalities.

- Mean image quality and diagnostic confidence scores were higher with Paired/Post images compared to Pre.
- CNR was notably higher in Post images compared to Pre for all 3 off-readers and in Paired compared to Pre for the off-site reading.

Safety

A total of 395 patients were evaluated for safety (240 adult Dotarem®, 38 pediatric patients Dotarem® 117 adult Magnevist®).

Mean adult dose was 0.2 ± 0.01 mL/kg (both arms), mean volumes were 15.1 ± 3.6 mL (Dotarem®) and 15.2 ± 3.4 mL (Magnevist®), mean injection rate was 2.0 mL/sec. Mean pediatric dose was 0.2 ± 0.01 mL/kg, mean volume was 7.3 ± 4.0 mL, mean injection rate was 1.1 mL/sec.

Five adults (3 Dotarem®, 2 Magnevist®) were dose non-compliant (<80%).

TEAEs were reported in 9.6% of adult Dotarem® patients and 13.7% of Magnevist® patients, and 21.1% of pediatric patients. Related AEs were reported in 3.8% adult Dotarem® and 7.7% Magnevist® patients, and in 15.8% of pediatric patients.

Administration site conditions/systemic inflammatory response/chest pain were reported in 2.5% of Dotarem® adults versus 6.8% of Magnevist® patients and 2.6% of pediatric patients. Injection site pain in adults was reported in 1 Dotarem® and 3 Magnevist® patients, burning in 2 patients (one in each arm), inflammation in 3 patients (1 Dotarem®, 2 Magnevist®), and skin eruption in 1 Dotarem® patient. One pediatric patient had an injection site event. No hypersensitivity allergic reactions were reported. Related nausea and/or vomiting was reported in 2 adult (0.8%) and 2 pediatric (5.3%) Dotarem® patients but no Magnevist® patients, and related diarrhea occurred in 1 Dotarem® adult (0.4%). Two pediatric patients (5.3%) had related headache.

No deaths occurred, 2 patients (1 Magnevist® adult and 1 Dotarem® pediatric patient) had non-related SAEs on study, 1 Dotarem® adult had severe related nausea and no patients had related AEs leading to treatment interruption.

When comparing baseline (pre-dose) to 24 hours later (post injection), no clinically relevant trends in mean hematology/biochemistry laboratory parameters and urinalysis or vital signs (blood pressure and heart rate) were apparent in either Dotarem® or Magnevist® adult patients and no pediatric patients had clinically significant changes. A small and equivalent increase in mean QTc was seen in both Dotarem® and Magnevist® adult patients and pediatric patients when comparing baseline to 30 minutes post-injection. Three Dotarem® adults (4.8%) and 2 pediatric patients (16.7%) evaluated for ECG shifted from a normal ECG pre-treatment to an abnormal ECG ~30 min post-treatment. This included 1 patient with flat T waves, 1 patient with inverted T waves, 1 patient with abnormal rhythm sinus bradycardia and a conduction finding of intraventricular conduction defect, 2 patients with a slight increase in QTcB (pre-defined max. value 450 ms). No patients had a QTcB >460 ms or an increase in QTcB from baseline of >15 ms or an abnormal QTcF (pre-defined max. value 450 ms).

Conclusion

Dotarem® (0.1 mmol/kg intravenous bolus, administered at 2 mL/sec in adults, 1 mL/sec in pediatric patients) significantly improved diagnostic capabilities over unenhanced MRI alone for visualization of CNS lesions in adults. Combined use of unenhanced and Dotarem®

NAME OF COMPANY: GUERBET		
NAME OF FINISHED PRODUCT: Dotarem®		
NAME OF ACTIVE SUBSTANCE: Meglumine gadoterate (Gd-DOTA)		
contrast-enhanced MRIs gave significantly better lesion visualization (patient and lesion level), lesion identification, diagnostic confidence, image quality and signal intensity compared to the unenhanced procedure alone. The validity of Dotarem® efficacy as a contrast agent was validated against the approved contrast agent Magnevist® and had a better safety profile, notably with fewer injection site conditions. The use of Dotarem® in a pediatric population appears effective and safe.		