Development of a new Gadolinium-Based Contrast Agent

The finding several years ago that small amounts of gadolinium (Gd) could be deposited in the brains of patients who had received several doses of certain gadolinium-based contrast agents (GBCAs), (albeit without any apparent clinical consequences) prompted the European regulatory authorities to withdraw some GBCAs (those of linear structure) from the market and issue recommendations that the lowest possible dose of GBCAs compatible with diagnostic objectives of MRI examination should always be administered.
In this context, one of the leading manufacturers of MRI contrast media, the French company Guerbet, has been developing a high-relaxivity macrocyclic GBCA, known as Gadopiclenol.
With Gadopiclenol now having successfully completed phase III trials, we wanted to find out more about the current status and future potential of this MRI contrast agent so we spoke to Dr. Philippe Bourrinet, SVP Development, Medical and Regulatory Affairs and Group Responsible Pharmacist at Guerbet.

Philippe Bourrinet is Senior Vice-President of Development, Med. & Reg. Affairs at Guerbet, France

Q *Before we get into the details of the development of Gadopiclenol itself, could you please give us an update on the current situation regarding the issue of the deposition of Gd in the brains of patients who have received multiple doses of certain GBCAs?*

Yes, of course. First of all, it should be remembered that GBCAs are frequently used in the MR examinations of patients who have brain lesions with associated damage to the blood-brain barrier, so in these particular cases, it is not that surprising or even unexpected that short-lived presence of Gd can be found temporarily in the brain.
However, what was reported a few years ago was that small amounts of Gd could be deposited in some very specific areas of the brain such as the dentate nucleus, where the deposits last for a long time. The subsequent studies on the subject that have been published over the last few years are consistent. They show that traces of Gd can indeed be found in the brain after the administration both of linear and macrocyclic GBCAs.
However, there is a difference between the situation with macrocyclic or linear GBCAs. Any traces of macrocyclic GBCAs are usually found in unchanged form (that is with the Gd complexed in the original chelate). These are rapidly washed out from the brain structures.
In contrast, Gd deposits found after the administration of linear GBCAs are usually found as free Gd or in complexes with other macromolecules. Such deposits are not cleared from the brain or, if so, only extremely slowly. The accumulation of Gd in the brain from linear GBCAs has been clearly shown to be dose-dependent.
It should however be pointed out that, so far, no clinical consequences or pathologies have been identified that could be associated with the presence of the small deposits of Gd in brain structures. We are also not aware of any difficulties in the interpretation of subsequent brain MR images in patients with T1 hypersignals caused by the presence of Gd deposits. The original finding of Gd deposits was made in the brain, but measurable Gd concentrations can also be found in other organs. The mechanisms of the formation of such non-brain deposits seem to be the same as those in the brain, e.g. in terms of differences between linear and macrocyclic GBCAs. The lower chemical stability and the higher propensity of linear GBCAs to

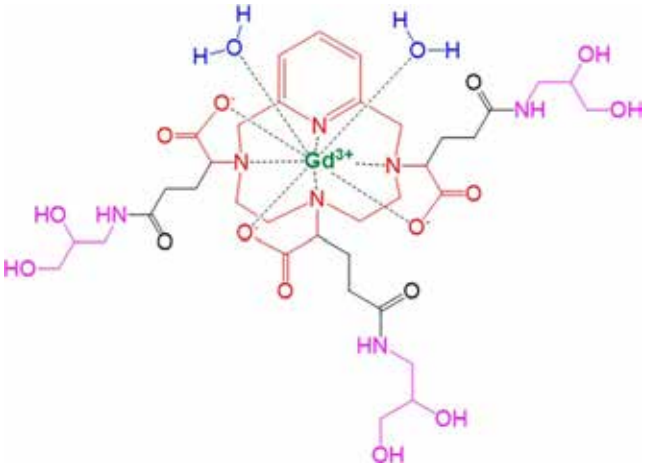
release free Gd into the body has been known since the 1980's when gadopentate dimeglumine and gadoterate meglumine were developed.
And, speaking of Dotarem, Guerbet's leading GBCA is the one with the highest chemical stability, which contributes to the good safety profile of the product.

Q *One concern at the early stages of the Gd deposition story was that radiologists could be so reluctant to administer GBCAs that in fact the chances of missing lesions in images would be increased, with negative consequences for the diagnosis and management of patients — consequences potentially more serious than the effect of Gd deposition itself. Is there any evidence that such situations occurred?*

So far as I am aware there is no evidence that such regrettable situations occurred, apart perhaps from some marginal cases. It is really important to remember that all the major Health Authorities in the world (e.g. FDA, EMA, PMDA, etc) have confirmed the very favorable risk/benefit ratio of macrocyclic agents. However, as a precautionary measure, the Summary of Product Characteristics and Product Information (SmPC/PI) sheets for GBCAs were amended in Europe, in the USA and in many other countries to specify that GBCAs should be used at the lowest effective dose and only when the diagnosis cannot be made without contrast. This advice is understandable and common sense. Since the authorities issued the advice, there has been a slight increase in the number of unenhanced scans being carried out but also, and perhaps more importantly, there has been a heightened awareness of the need to minimise the number of unnecessary repetitive examinations.
However, the use of GBCAs is still required in a large number of clinical indications. Radiologists recognise this and, by and large, we haven't seen any any reluctance on the part of radiologists to administer GBCAs. What we can say is that the whole Gd deposition story has accelerated the conversion of the market to macrocyclic GBCAs, except for certain liver scans where the use of some linear hepato-specific GBCAs is still indicated — and approved by the authorities.

Q *Talking of authorities, the regulatory situation regarding GBCAs is slightly different in the USA compared to Europe, where the linear GBCAs have been suspended (with the exception mentioned above of gadoxetate and gadobenate for liver imaging). In the USA, where linear GBCAs have not actually been withdrawn from the market, has there also been a move to macrocyclic forms?*

Yes. The US market has moved strongly to macrocyclics over the last 10 years, with some linear agents like gadopentate dimeglumine and gadoversetamide even having been voluntarily withdrawn by companies for commercial reasons. However, linear agents are still being used in the USA.



The structure of Gadopiclenol. It is a small non-specific non-ionic macrocyclic gadolinium complex which has been engineered to allow two water molecules simultaneous access to the chelated Gd3+ ion instead of only one for the current GBCAs. Without any protein binding and an extra cellular GBCA profile, this doubling water exchange affects the effectiveness of each GBCA molecule, which enables a halving of the dose while maintaining a similar contrast enhancement efficacy

Q *Now let's get onto your new GBCA itself. In what way is it different from the structure of your current leading GBCA product, Dotarem?*

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Q *As you said, your current GBCA product gadoterate meglumine is very stable chemically, so there is very little long-term deposition of free Gd in the brain. Given that, what were the principal design objectives of the Gadopiclenol development program ?*

Before we get into the details, it is important to always remember that, as of today, this GBCA is still an investigational product, not yet approved by any regulatory authority for human use.
Having said that, Gadopiclenol is a non-specific macrocyclic GBCA, developed by Guerbet, which has a relaxivity 2 to 3-fold higher than those of other GBCAs currently on the market. We started the development project around 2007-2008, that is shortly after the issue of Nephrogenic Systemic Fibrosis (NSF) arose (NSF occurs in some patients with severe renal impairment who had been administered GBCAs, with linear GBCAS

being involved in the vast majority of cases).

The overall design objective of the development project was to develop a new GBCA with a very high relaxivity in order to be able to reduce the Gd dose administered to patients, as compared to the doses needed with existing agents. The expectation was that the high relaxivity would enable high image quality to be attained, even at a significantly lower administered dose of contrast agent. Other initial design specifications were that the agent had to be macrocyclic and very stable. Osmolality was not an important specification in the design of the molecule, as in practice this is not an issue with GBCAs, due to the low injected volume compared for example to iodinated contrast agents.

Right from the beginning of the development project it was made clear that there could be absolutely no compromise on safety — an attitude that you can readily understand, occuring as it does in the company that developed gadoterate meglumine, with its excellent safety profile.

To get back to the relaxivity objective, it is interesting to note this was achieved thanks to an optimal design of the chemical structure and not by protein binding or other *in vivo* interactions as occurs with other high relaxivity agents [See Table]. Achieving high relaxivity while administering less Gd to patients in a contrast-enhanced MRI examination addresses the concern of Gd deposition, and is especially important in fragile and/or chronic patients who may require multiple injections over several years.

All the development efforts of this agent were carried out by Guerbet and our R&D teams are justifiably very proud of their achievement. The development of gadopiclenol is a good, practical example of the application of Guerbet's mission statement, namely "*we build lasting relationships so that we enable people to live better by caring for people, by focusing on patient outcomes, by continuously provide innovative solutions, by daring to make bold choices and by advancing through knowledge-sharing*".

"...Achieving high relaxivity while administering less Gd to patients .. is especially important in fragile and/or chronic patients who may require multiple injections over several years..."

Q *Now the all-important Phase III trials. Can you summarize the design and methodology of the trials, the endpoints used, the types of patients/cases and of course the results?*

We carried out two pivotal Phase III clinical trials which compared the diagnostic efficacy and safety of Gadopiclenol with Gadobutrol in several anatomical areas such as head and neck, thorax, abdomen, pelvis and musculoskeletal. The positive results of those studies were announced about a year ago.

A total of 560 patients were recruited for these two studies in over 60 hospital medical imaging departments in 13 countries.

The diagnostic benefit of injecting Gadopiclenol (0.05 mmol/kg) during MRI examinations was evaluated by assessing:

- the superiority of the examination with Gadopiclenol (0.05 mmol/kg) compared to the examination with no contrast agent;
- the non-inferiority of Gadopiclenol (0.05 mmol/kg) compared to Gadobutrol (0.1 mmol/kg) for the visualization and detection of lesions of the central nervous system and in the other anatomical areas studied [See images]

These pre-established endpoints were met in the studies.

In addition to these Phase III trials, a study was conducted on 80 children between 2 and 17 years of age in 19 centers in five European countries. This study showed that the pharmacokinetic profile of Gadopiclenol at 0.05 mmol/kg in children was similar to that in adults.

No major safety issues were reported during the development; adverse reactions reported during the two Phase III studies were similar for both of the products administered.

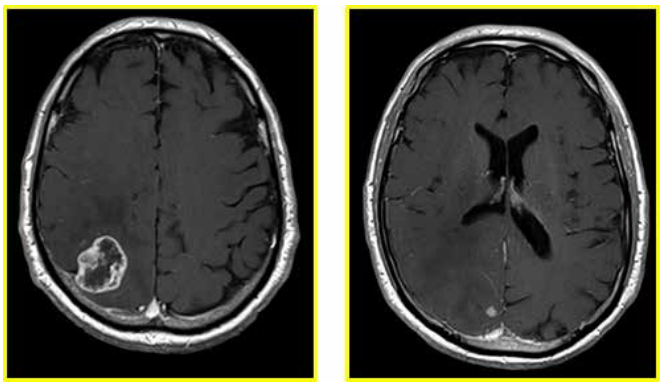
The details of the study designs can be found in the *clinicaltrials.gov* database. As I said earlier, those clinical data have not been yet assessed by any Health Authorities and Gadopiclenol has not yet been cleared for marketing.

Q *So what exactly is the current status of regulatory approval?*

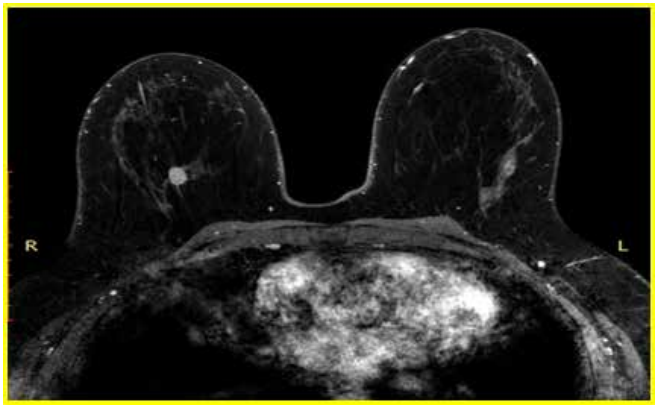
That question is very timely since Guerbet is very happy and proud to inform the radiological community that we have very recently filed (January 2022) Marketing Authorization dossiers for Gadopiclenol to both the US FDA and the EMA. The submitted

Contrast Agent	1.5 T		3.0 T	
	r1	r2	r1	r2
Gadobutrol	5.2 ± 0.3	6.1 ± 0.9	5.0 ± 0.3	7.1 ± 0.9
Gadobenate	6.3 ± 0.3	8.7 ± 0.9	5.5 ± 0.3	11.0 ± 1.0
Gadoterate	3.6 ± 0.2	4.3 ± 0.9	3.5 ± 0.2	4.9 ± 0.9
Gadopiclenol	12.8 ± 1.3	15.1 ± 1.5	11.6 ± 1.2	14.7 ± 1.5

In vitro relaxivities at 1,5 T and 3.0 T ffor Gadobutrol, Gadobenate, Gadoterate and Gadopiclenol.The data are expressed as mean relaxivities ($mM^{-1}.sec^{-1}$) ± standard deviations. Table adapted from reference



Example of contrast-enhanced brain MRI scans, of a 65-year-old male patient with brain metastases in the right occipital-parietal lobes. Gadopiclenol was administered at 0.05 mmol/kg. Images obtained from the phase III PICTURE study.



Example of contrast-enhanced breast MRI scan of a 55-year-old patient with a cancer (< 1 cm) in the right breast. Gadopiclenol was administered at 0.05 mmol/kg. Image obtained from the phase III PROMISE study.

dossiers contain 13 years of development data generated by the Guerbet teams including non-clinical & clinical studies, data on the manufacturing process for the active ingredient and the finished dosage form. The criteria for approval of a contrast agent which, after all, is administered intravenously are the same as those for any pharmaceutical drug. In particular, it is required to show a favorable risk/benefit ratio. We are very confident that the demonstration of clinical efficacy will satisfy the regulatory requirements and expectations of the Health Authorities. FDA granted a priority review to our Application so we expect FDA approval as early as September 2022. EMA approval is expected in 2023.

Q *Let's turn to future development and marketing. You have recently announced a collaboration with Bracco for future development of gadopiclenol. What is the rationale for this?*

Yes, we indeed announced in December 2021 that we had signed with Bracco Imaging a global collaboration agreement for Gadopiclenol, which will result in Guerbet and Bracco Imaging commercializing the product independently under different brand names. Both Guerbet and Bracco Imaging each own valuable intellectual property relating to Gadopiclenol.
We will collaborate with Bracco Imaging for development activities such as new indications or research studies. As for manufacturing, Guerbet will manufacture the Gadopiclenol active ingredient and supply vials to Bracco Imaging for up to seven years. Following a technology transfer, both companies will then have the right to manufacture the product.
There will be no collaboration at all for the commercialization, as we remain competitors.

Q *Now let's turn to the future. How do you see MRI in general, and CE-MRI in particular, developing in the near-/middle-term. How do you see Guerbet's role?*

MRI is still a fast-growing market as the modality is being used more often and is gradually becoming more widely accessible, even in emerging countries, where there is a very high growth potential.
Thus, CE-MRI is widely used, and will continue to be so, since from the radiological point of view the administration of contrast agents is quite simply indispensable for many clinical diagnoses. In terms of which contrast agents should be used, macrocyclic GBCAs will remain the agents of choice for CE-MRI as their safety profile and favorable risk/benefit ratio are very well established. The use of linear non-specific GBCAs will likely continue to decrease over the years and should ultimately disappear completely.
We have recently noticed a renewed interest in Mn-based contrast agents, where it appears that several companies are working on experimental Mn contrast agents, apparently on the grounds that alternatives to GBCAs are needed because of the Gd deposition issue that has arisen over the last few years. Time will tell if those agents can actually bring anything useful to the radiological community and, more importantly, to patients. The challenge to achieve a better safety profile with Mn-based contrast agents than that with macrocyclics GBCA is enormous, especially in the light of the not very successful previous experience with mangafodipir some years ago. The extent of the task in front of Mn-based agents can be seen from the fact it took nearly 20 years from the launch of the two first GBCAs to demonstrate the clinical relevance of the higher stability of macrocyclic GBCAs. These data ultimately resulted in the use of macrocyclics being favored.

As for how we at Guerbet see the future of MRI more broadly, we clearly anticipate a growing use of augmented intelligence (AI) systems in MRI exams, whether they involve the use of a contrast agent or not. Guerbet is working extensively in this area and has a dedicated team and business unit already active in the field.
So with our current offering of gadoterate meglumine, our AI projects & systems and in the near future Gadopiclenol (as always, if approved by the Health Authorities), we at Guerbet are confident of remaining a leader in MRI for a long time to come.