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A PHASE II STUDY OF FERUMOXYTOL AND GADOLINIUM MAGNETIC RESONANCE IMAGING AT 3T AND 7T IN SUBJECTS WITH PRIMARY OR METASTATIC BRAIN TUMORS EITHER BEFORE OR AFTER THERAPY.

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1 OBJECTIVES

1.1 Primary

The goal of this descriptive (not definitive) study is to study an adequate number of subjects to evaluate the impact of MRI magnet field strength (3T versus 7T), contrast agent (ferumoxytol and gadolinium), tumor size, and tumor permeability on a series of imaging measures to monitor and evaluate tumor characteristics.

Following are the specific objectives for this study:

1.1.1 Primary Aim 1: To compare quantitative blood brain barrier permeability measurements (K^{trans}) of a standard gadolinium (Gd) MRI contrast agent at 3 T and 7 T using dynamic contrast enhancement (DCE) MRI.

We hypothesize that contrast agent detection sensitivity is improved at 7 T compared to 3 T, allowing the construction of K^{trans} parametric maps with higher precision. The primary outcome measure for these analyses will be T_1-weighted image contrast to noise ratio (CNR), calculated as the signal increase caused by the Gd agent divided by background noise.

1.1.2 Primary Aim 2: To compare dynamic susceptibility contrast (DSC) based perfusion measures at 3 T and 7 T.

We hypothesize that due to increased T2* susceptibility effects the 7 T images will provide a higher CNR compared to 3 T images. The primary outcome measure for these analyses will be the CNR, calculated as the signal intensity decrease caused by the Ferumoxytol bolus, divided by the background noise.

1.2 Secondary

1.2.1 To describe the blood brain barrier permeability to Ferumoxytol and to a standard gadolinium-based MRI contrast agent using signal intensity changes as described above.

1.2.2 To describe cerebral blood volume (CBV) measurements obtained using a standard gadolinium MRI contrast agent and ferumoxytol. CBV will be quantified using dynamic susceptibility contrast (DSC) techniques with Gd or Ferumoxytol contrast agents. The use of DSC techniques with standard Gd MRI contrast agents in tumors with leaky blood vessels can lead to inaccurate CBV estimates because of Gd extravasation. We expect to obtain lower blood volume estimates with ferumoxytol than with gadolinium in leaky tumors. We do not expect significant differences in less leaky tumors.

1.2.3 To evaluate tumor microvascularity on susceptibility-weighted images (SWI). The susceptibility weighted images will be acquired before and after ferumoxytol administration to investigate blood vessel visibility within the tumor bed. Morphological and caliber differences of intratumoral vessels in comparison to normal cortical penetrating vessels will be analyzed.

1.2.4 To describe the microscopic distribution of ferumoxytol particles in tissue

2 BACKGROUND

2.1 The blood-brain barrier in CNS tumors

The BBB is an anatomical feature of CNS capillaries that consists of a continuous layer of endothelial cells bound together with tight junctions that allow very little transcellular or pericellular leakage of blood-borne molecules (5, 36). In normal brain, the BBB limits permeability based on electric charge and lipid solubility, and normally excludes molecules of greater than M_r 180. The neurovascular unit is a new, integrated approach

to thinking about and working with the BBB. It is comprised not only the BBB endothelial cells but also the basement membrane, pericytes, microglia and astrocytic foot processes in the capillary microenvironment. Local environmental and cellular factors and the varying integrity of the neurovascular unit impact barrier permeability in tumors of the CNS, both before and after treatment. Brain tumors often have a leaky blood-tumor barrier (BTB) because the neovasculature in the tumor lacks some BBB characteristics (5). The barrier in the brain around malignant tumors can have variable permeability due to neovascularization, inflammation, and gliosis. The well-vascularized, actively proliferating edge of the tumor is particularly variable and complex in terms of barrier integrity (18, 29, 36).

Cancer treatments such as steroids, chemotherapy, radiotherapy, or anti-angiogenesis therapy induce changes in tumor vasculature, tumor permeability, and tumor cell viability. Many of these effects will occur hours to days after treatment, but changes in gross tumor volume can only be measured at later times (several days to weeks). Methods to measure early anti-tumor effects would be useful in predicting outcomes and modifying therapies to maximize response.

Cancer therapies can also induce BBB damage and inflammation at the neurovascular unit. Systemic chemotherapy can cause subtle cognitive dysfunction in up to 25% of cancer patients (1, 49), while radiotherapy of the brain can cause significant neuropsychological sequelae (3, 11). Potential mechanisms for radio/chemo toxicity include direct neurotoxic effects in the parenchyma, free radical-induced injury of the BBB or microvasculature, or secondary immunologic responses causing inflammatory reactions. Combination therapies have the potential for even more toxicity. For example, the two most commonly employed regimens for primary CNS lymphoma, whole brain radiation therapy (WBRT) and high dose methotrexate (MTX), have a synergistic toxic effect when WBRT precedes MTX (10, 38). One goal of this proposal is to evaluate new methods of imaging these phenomena in intracerebral tumor and in normal brain.

2.2 Ferumoxytol

MR imaging of the CNS is usually done with Gadolinium-based contrast agents with a short half-life (~30 min in blood), that give rapid and transient imaging of brain vascular permeability. The iron oxide nanoparticle MR contrast agents have also shown excellent potential for imaging in the CNS (14, 24). These agents consist of an iron oxide core with a variable coating that determines cellular uptake and biological half life. Ferumoxides (Feridex IV ®), a clinically approved SPIO, is 60-185 nm in size, partially coated with dextran, and is rapidly opsonized and endocytosed (22, 47). The USPIOs, with particle diameters of 20-50 nm, are completely coated either with native dextran (ferumoxtran-10 (Combidex ®)) (2, 6, 37), or with a semi-synthetic carbohydrate, as in the new agent ferumoxytol (16, 43). The coating bestows long plasma half lives of 14-30 hours (25, 50). On MR scans the iron oxide agents demonstrate hypointense signal drop out at all concentrations on T2-weighted images, but may show hyperintense (bright) signal on T1-weighted images in areas of low concentration. After MR of CNS delivery, the iron oxide particles may be localized within tissues with light microscopy and EM (19, 32, 33, 34, 35).

The USPIO MR agent, ferumoxytol may be useful for imaging brain tumors and the inflammatory processes associated with therapy of CNS lesions, as well as improved measurement of MR measurement of BBB permeability. In both animal brain tumor models and in brain tumor patients, IV ferumoxides alone does not show tumor enhancement, while ferumoxtran-10 clearly enhances most malignant tumor types tested (33, 34). Our clinical trial of ferumoxtran-10 has accrued 108 subjects to date (34, 52).

Although some studies have shown that iron oxide particles can be detected in malignant glial tumors after IV administration (15, 31), we find that relatively little iron staining is found within tumor cells. Instead, iron is concentrated in necrotic areas within the tumor and in cells around the tumor margin. Progressive accumulation of ferumoxtran-10 in reactive astrocytes and macrophages results in prolonged enhancement of brain tumors (up to 7 days) both in animal models (33) and in patients (34, 52). The cellular localization of iron oxide nanoparticles may improve imaging of inflammatory responses within the neurovascular unit (54).

In this proposal we will investigate the new USPIO MR contrast agent, ferumoxytol, in subjects with CNS tumors, in whom improved imaging of CNS lesions may be critical in improving patient management and therapy. Ferumoxytol can be given as a bolus for MRA analysis of the vasculature and perfusion imaging of the brain as has been done in the heart (43), without early vascular leak unlike Gd. Ferumoxytol has shown few significant adverse reactions even using extremely high doses in vitro and in preclinical trials (Investigator's Drug Brochure, 2005). A total of 516 subjects have received one or more doses of ferumoxytol, with 396 including safety data, with very low toxicity (Investigator's Drug Brochure 2005, 25, 50). Our pilot data indicate ferumoxytol is safe for brain tumor imaging.

2.3 Dynamic Contrast Enhanced (DCE) MR Imaging

MRI with dynamic contrast enhancement allows non-invasive in vivo quantification of CBV, MTT, and the permeability of the BBB. The original description of the technique by Tofts and Kermode (21, 51) extracted approximations of the influx rate constant (Ki) for Gd from time course plots of T2*-weighted signal changes after contrast infusion. The underlying tracer-kinetic model is referred to as the Kety-Schmidt model. Unlike indicator diffusion techniques that rely on direct detection of tracer, MR only indirectly detects the presence of contrast due to its shortening of the T2* and/or T1 spin relaxation rate constants of 1H in water. Potential limitations of the dynamic imaging techniques include susceptibility artifacts, relative rather than absolute quantification of cerebral blood volume, and inaccurate estimation of CBV in patients with permeable BBB (7). Many adjustments have been made to the standard model to attempt to bring results from dynamic MRI studies into closer agreement with more traditional methods of measuring permeability (45). Dynamic MRI permeability measurements have been validated against measurements made with 14C-sucrose autoradiography and scintillation counting (17). **Table 1** summarizes the measurement parameters that can be extracted from the dynamic imaging studies, with both Gd, and USPIO (28). The observed signal intensity variations in tissue and the blood pool are converted through a log-transformation to R2* changes (= 1/T2*). The curves of R2* changes versus time for selected tissue regions of interest (ROI) can be fit with a gamma-variate function, to approximate the shape of the first pass peak. The arterial input is used to determine the cut-off point for the fit, i.e. before appearance of the recirculation component. With this fitting procedure, one can determine the mean transit time (MTT). The outcome variable for assessing effects of therapy on tumors will be the cerebral blood volume (CBV) parameter, estimated from T2*-weighted DSC MRI with USPIO contrast. We expect USPIO leakage to be minimal during the first pass. CBV is calculated from the area under the curve (AUC) for serial DCE-MRI R2* curves, normalized by the R2* AUC for an arterial ROI. Cerebral blood flow (CBF) is estimated by model-independent numerical deconvolution of the tissue curves with the arterial input (39, 40). We can also extract the BBB permeability surface area product (PS) from the influx rate constant Ki, obtained with the Kety-Schmidt model (27, 28). The influx rate constant is related to both CBF and PS, and estimation of PS, therefore requires an independent quantification of CBF (**Table 1**). In addition, one can

use pre- and post-contrast T1 measurements with high spatial resolution (Look-Locker imaging) to determine R1 (= 1/T1) from before to approx. 10 min. after contrast injection, when the contrast agent has reached a semi-equilibrium. The R1 changes (ΔR1) in tissue, normalized by ΔR1 in the blood pool, give the blood-brain partition coefficient, which will be measured for Gd contrast, which traverses the BBB relatively rapidly in many tumor types. The partition coefficient for Gd provides a measure of the relative distribution volume for Gd in different tumor types, and can be compared to the CBV (measured with USPIO) to assess the degree of Gd contrast leakage.

Table 1. Summary of measurement parameters from dynamic contrast enhancement MRI

Parameter [Measurement]	Gamma-variate fit [42, 46]	Kety-Schmidt model [21]	Note
MTT [T2*-w DSC]	Calculated from gamma-variate fit to first pass tissue curve; subtract MTT of arterial input for normalization.	n.a.	For intravascular agent, MTT = CBV/flow (central volume principle [30])
CBV [T2*-w DSC]	Tissue first pass AUC, normalized by arterial input curve area [4, 42, 46]	n.a.	In tumors, leakage of Gd may allow CBV quantification only with USPIO
CBF [T2*-w DSC]	Only indirect estimate from CBF = CBV/MTT	Can only determine product of CBF and PS = K_i [21]	Calculated by numerical deconvolution of tissue curves [21, 39, 40]
PS [T2*-w DSC]	PS cannot be estimated with semi-empirical gamma-variate approach	Can only determine product of CBF and PS = K_i [21]	With independent CBF quantification, one can estimate PS from K_i and CBF.
Blood-brain partition coefficient - λ [Look-Locker T1 quant.]	Calculated by R_1 change in tissue (post-contrast R_1 – pre-contrast R_1, normalized by R_1 change in blood). Quantification of V_d is not based on any specific model. λ can also be obtained from Kety-Schmidt model.		Leakage of Gd contrast is assessed by comparison of λ for Gd with CBV

Abbreviations: MTT, mean transit time; DSC, dynamic susceptibility contrast; CBV, cerebral blood volume; AUC, area under curve; USPIO, ultrasmall superparamagnetic iron oxide particles; CBF, cerebral blood flow; PS, permeability-surface area product; K_i, influx rate constant; R_1, $R_1=1/T_1$

The dynamic MR techniques have been shown to be sensitive to changes in the BBB in animal models (7, 44). Of particular interest, Cha et al. assessed dynamic contrast imaging in a mouse glioma model using a 7T MR scanner (7). MR measurements of relative CBV agreed with histological measurement of microvascular density from the same tumors. This animal study correlated with the observation in our pilot ferumoxytol study that low molecular weight contrast agents such as gadolinium leak rapidly out of the vasculature. Leakage of contrast agent interferes with an accurate determination of CBV and MTT. Our preliminary dynamic MR measurements with ferumoxytol in patients (see section 2.4) show markedly reduced early leakage of the nanoparticles compared to Gd.

In human studies, dynamic MRI has been used to examine hemodynamics in solid tumors, providing in vivo data on the vascular pathophysiology and response to treatment

for breast, lung and prostate cancer and is increasingly used in clinical practice (20, 23, 26, 27, 41). Relative CBV (rCBV) maps derived from perfusion MR imaging data provide quantifiable estimates of regional blood volume that can be used to grade gliomas, differentiate different brain tumor types, and distinguish tumors from non-neoplastic lesions, and to assess brain tumor physiology (21). CBV maps and the rCBV values can be calculated in different areas using the ratio between the CBV in the pathological area and in the contralateral white matter. Large, solitary, necrotic metastases can be indistinguishable from high-grade astrocytomas using conventional MRI, but can be distinguished by dynamic contrast MRI (23). Inclusion of dynamic contrast MR imaging as part of a routine evaluation of brain tumors can lead to improved diagnostic accuracy, understanding of tumor pathophysiology, and detection and quantification of tumor angiogenesis. With further work, dynamic MR imaging could be used to assess existing and novel cancer therapies that target blood vessels.

To date, few studies have used USPIO MR contrast agents in dynamic imaging. In one animal study, de Lussanet evaluated a different USPIO (Clariscan NC200150) for dynamic MRI in a mouse subcutaneous colon carcinoma model using a 1.5T scanner (12, 13). They found that USPIO was equivalent to Gd for evaluating the endothelial transfer coefficient surface area product, while USPIO was significantly better than Gd for determining the fractional plasma volume (12, 13). However, it is difficult to draw conclusions from the low resolution images in this 1.5T study. The higher performance gradient systems with increased MR field strength will allow us to improve spatial resolution, while maintaining temporal resolution, and improve image quality because of the higher signal-to-noise ratio with increased field strength.(8, 9) Dynamic MR with USPIO has been reported in human breast cancer (48) and liver metastases (53).

2.4 Ferumoxytol Pilot Data

To date, 12 subjects have been assessed for ferumoxytol MR imaging in brain tumors. Neoplastic lesions were well seen on both 1.5T and 3T images. The signal-to-noise is higher on 3T scan compared to 1.5T, which translates into shorter scans in many instances. The T1 relaxation times are longer at 3T compared to 1.5T, and T1 contrast enhancement with Gd and ferumoxytol is improved. The ferumoxytol studies were comparable to Gd scans, although the enhancement was delayed and was predominantly in the peripheral aspects of the tumor. The signal intensity of enhancement was maximum at around the 24 hours time point post ferumoxytol injection then decreased over time, while the volume of enhancement slowly increased. Informative images were also obtained on intraoperative low field magnets (0.1 T) 48 hours after ferumoxytol injection. Ferumoxytol proved to be safe for bolus administration in subjects with primary high-grade brain tumors and/or cerebral metastases, and no adverse events occurred. The tumors usually showed increased CBV compared to healthy white matter. Because of initially intravascular localization of ferumoxytol the overestimation of CBV could be avoided in leaky tumors which is usually a problem when using Gd (Figure 1). Figure 1 shows the T1-weighted scans after Gd in comparison ferumoxytol, and the ROI analysis for evaluation of blood volume.

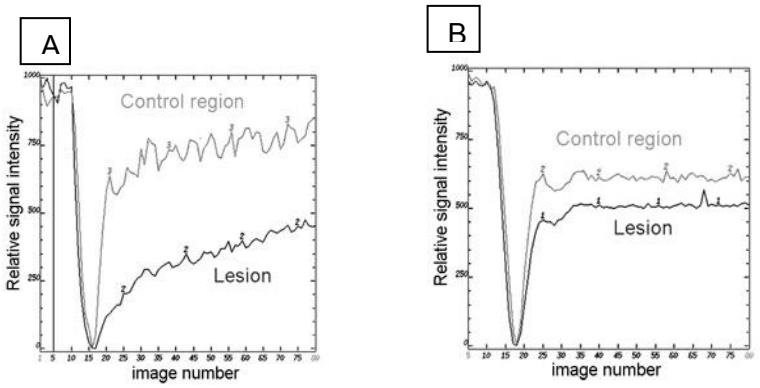


Figure 1.

Illustration of MTT measurement using Gd (A), and ferumoxytol (B).

In dynamic MRA using "Keyhole" imaging sequences the temporal resolution can be increased, which allows us to visualize the arterial, arterial/venous and venous phase of the vessels surrounding and within the tumor. Our initial experience suggests that a lower concentration of ferumoxytol (1:8 dilution) may decrease susceptibility artifacts. To visualize the small vessels, contrast enhanced time of flight (TOF) angiography provides high resolution equilibrium phase images, approaching that of catheter angiography. Because of the long plasma half-life and initially intravascular localization of ferumoxytol, the enhanced high-resolution TOF MRA resulted in good visualization of the vasculature without having artifacts due to contrast agent leakage out of blood vessels (**Figure 2**).

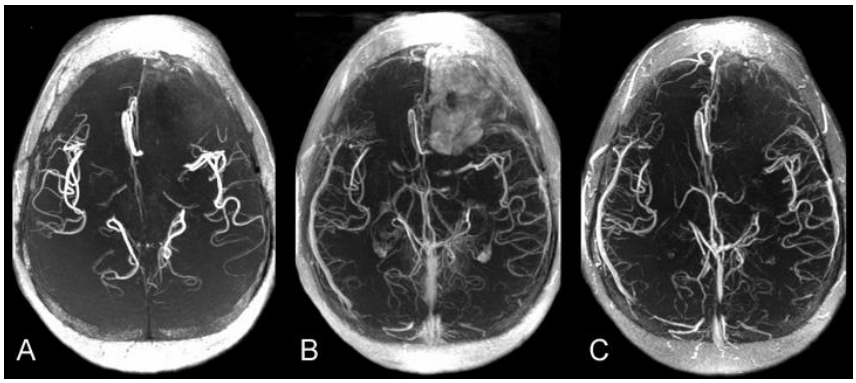


Figure 2.

TOF MRA without contrast (A), with Gd (B), and with ferumoxytol (C).

2.5 Study Rationale

Based on our preliminary study using ferumoxytol for dynamic MR imaging of brain tumors, we plan to extend this work to the highest available MR field strength for improved measurement of dynamic MR parameters. This study will show the feasibility of ferumoxytol administration and MR imaging using 3T and 7T MRI. Dynamic MR imaging to determine tumor permeability will be performed in two groups of subjects, those who have or have not had prior therapy for their brain tumor, in order to compare changes in BBB permeability before and after therapy. The utilization of ferumoxytol will allow more accurate measurements. In addition, tumor microvascularity changes will be studied pre- and post-treatment using susceptibility weighted imaging (SWI).

Subjects may be imaged at up to 4 time points to evaluate permeability and microvascularity changes of the tumor.

2.6 Safety and Preliminary Studies with Ferumoxytol

Ferumoxytol has provided improved imaging with minimal safety concerns in pre-clinical studies and IND sponsored studies. Ferumoxytol has few systemic reactions and can be given as a bolus for MRA analysis of vasculature. This agent did not show significant preclinical toxicity even using extremely high doses in preclinical trials with animals and in vitro using human blood cells.

2.6.1 Preclinical studies

Three animal studies evaluated the potential cardiovascular effects of ferumoxytol. Ferumoxytol and the vehicle control material, mannitol, were administered in escalating doses of 4, 40, and 200 mg Fe/kg intravenously to male and female beagle dogs. Each animal received all three doses. No effect on cardiovascular and respiratory parameters and no cardiac electrocardiographic abnormalities were detected. (Ferumoxytol Investigator's Drug Brochure, 2005). Additionally, there was no effect on arterial blood pressure, heart rate, femoral artery blood flow, left ventricular function, or respiratory function. No treatment related electrocardiographic abnormalities were found. There was an increase in urinary flow rate with both the vehicle control and ferumoxytol, this increase in diuresis was considered attributable to the mannitol. (Ferumoxytol Investigator's Drug Brochure, 2005). In a hemodynamic study in anesthetized rats, ferumoxytol caused no change in blood pressure parameters (mean arterial, systolic, diastolic, and pulse pressures) in three animals following intravenous administration of 120 mg Fe/kg. In a third hemodynamic study, guinea pigs received i.v. ferumoxytol at a dose level of 120 mg Fe/kg or a saline control (n = 9). One animal had a reduction in mean arterial blood pressure graded as mild. One animal appeared to be unstable post injection with fluctuating blood pressure over a period of 60 minutes. There were no hemodynamic changes in the other seven animals administered ferumoxytol or in two animals administered saline. A full panel of toxicity studies has been performed, which include: evaluation of acute and repeat dose administration, mutagenicity, reproduction, and immunotoxicity. Additional information can be found in the investigator's brochure. (Ferumoxytol Investigator's Drug Brochure, 2005).

Non-clinical toxicology-pathology studies are described in the investigator's brochure and include the following:

- Single dose studies in small and large animals
- Repeat dose studies in small and large animals
- Special studies: acute intravenous irritation study in rabbits, compatibility with human erythrocytes, compatibility with human plasma or serum, effect on in vitro clotting times, effect on coagulation in rat plasma, effect on rat paw edema, evaluation of the formation of immune complexes with Dextran Reactive Antibodies
- Genotoxicity studies: mutagenic activity, ability to induce chromosomal aberrations, in vivo clastogenic activity and/or disruption of the miotic apparatus
- Maternal and developmental toxicity in small animals

2.6.2 Clinical studies of Ferumoxytol

On June 20, 2009, the FDA approved ferumoxytol (FerahemeTM) to treat Iron Deficiency Anemia and Adult Chronic Kidney Disease Patients. The recommended dose is an initial

510 mg IV injection followed by a second 510 mg IV injection three to eight days later. Ferumoxytol is now commercially available in the U.S.A.

2.6.2.1 From the Investigational brochure 2009:

The ferumoxytol clinical development program has been comprised of eleven studies. These included three Phase 1 studies (two dose-escalation studies and a study of the electrocardiographic/QTC effects of ferumoxytol), two Phase 2 studies that evaluated the safety and efficacy of ferumoxytol for iron replacement in patients with Chronic Kidney Disease (CKD), and two Phase 2 imaging studies that assessed the feasibility of ferumoxytol as an MRI contrast agent. There were three open-label Phase 3 studies that examined the efficacy and safety of ferumoxytol relative to oral iron in patients with CKD Stages 1-5 either on or not on dialysis. A fourth Phase 3 study in patients with any stage of CKD evaluated the safety of ferumoxytol relative to placebo in a cross-over, double-blind manner. Ferumoxytol has been evaluated at exposures up to 2 x 510 mg, including two courses of 2 x 510 mg in three of the four Phase 3 studies. Specifically, the following regimens of ferumoxytol were given during the clinical program:

- ≤4 mg Fe/kg
- 1 x 125 mg
- 1 x 250 mg
- 1 x 510 mg
- 8 x 128 mg
- 4 x 255 mg
- 2 x 510 mg

Approximately 1,740 patients have been exposed to ferumoxytol in the entire clinical program, and approximately 1,509 patients have been exposed to ferumoxytol in the Phase 3 studies. To date, only one patient (0.06% of all patients exposed to ferumoxytol) has experienced an anaphylacoid reaction following treatment with ferumoxytol; this patient had a history of multiple drug allergies and experienced an anaphylactoid reaction (hot flashes and itching, with no respiratory compromise) and severe hypotension a few minutes after receiving ferumoxytol. There have been no deaths that were considered to be related to ferumoxytol treatment. There were 28 deaths in the clinical program, all of which have occurred in Phase 3 studies, with 16 deaths among the 1,740 patients exposed to ferumoxytol (0.9%) and 8 deaths among the 296 patients exposed to oral iron (2.7%). Four deaths occurred in patients who had signed an informed consent for enrollment but did not receive any test article. All deaths in the clinical program have been in patients with CKD, who have a high risk of death due to cardiovascular disease and other causes. In completed studies that used oral iron as a comparator, there was a lower rate of SAEs among patients exposed to ferumoxytol than among patients exposed to oral iron: 4.4% of ferumoxytol treated patients (64 of 1,451 patients) vs. 10.7% of oral iron-treated patients (17 of 159 patients). Patients exposed to placebo had the lowest rate of SAEs (1.7%; 13 of 780 patients). One patient each following ferumoxytol (0.1%), oral iron (0.6%), and placebo (0.1%) experienced an SAE that was considered by the investigator to be related to treatment. In Phase 3 Study 62,745-5, which enrolled CKD patients undergoing hemodialysis, 31 of 199 (15.6%) patients experienced an SAE following ferumoxytol administration and 8 of 70 (11.4%) patients experienced an SAE following oral iron administration. These data were taken from an unlocked database and

therefore are preliminary and patient to final verification. In the Phase 3 studies in patients with CKD (62,745-5, 62,745-6, 62,745-7, and 62,745-8, in which approximately 1,509 patients were exposed to ferumoxytol), the most common adverse events following ferumoxytol administration included nausea, diarrhea, dizziness, headache, and peripheral edema. These adverse events were usually more common in the oral iron group than the ferumoxytol group (in Studies 62,745-5, 62,745-6, and 62,745-7, which utilized oral iron as a comparator). Hypotension was one of the more common adverse events in Study 62,745-7 and occurred more frequently in the ferumoxytol group (5.0%) than the oral iron group (1.4%). By contrast, preliminary data show that there have been lower rates of hypotension in Study 62,745-5 (1.8%, 1.7%, and 0% in the ferumoxytol 2x510 mg, ferumoxytol 4x255 mg, and oral iron groups, respectively); hypotension rates were similar between the ferumoxytol and placebo groups (1.3% vs. 0.8%) in the large safety study, Study 62,745-8; and there were no hypotension adverse events in Study 62,745-6. An independent Data Monitoring Committee met to review the clinical safety data for all Phase 3 studies in October 2005, February 2006, June 2006, October 2006, and March 2007, and they identified no safety concerns.

The dose of 510mg ferumoxytol has not been used in imaging studies before. The highest dose used was 4mg/kg (280mg for a 70kg patient). However 2 x 510mg dose was studied for iron replacement therapy in large number of patients without significant adverse effects. (Besarab et al 2007). If there is no history of iron over load, there is no need to screen for iron over load since 0.5 g will not hurt patients, even if they have asymptomatic iron over load. Phase 3 data by Besarab using two doses of 510 mg in a phase 3 trial showed no significant toxicity. A higher dose of ferumoxytol will result in a better contrast enhancement 24 hours after injection due to a higher plasma level.

2.6.2.2 From the Investigational brochure April 30, 2012:

Since approval, AMAG has conducted one clinical trial (Protocol Number FER-CKD-201). This was a randomized, open-label trial that compared the safety and efficacy of ferumoxytol to iron sucrose for the treatment of IDA in CKD subjects either on or not on dialysis. In this trial, 162 patients were randomized in a 1:1 ratio to either ferumoxytol or iron sucrose. Ferumoxytol was administered as a 1.02 g course given as a regimen of 2 x 510 mg within 2 to 8 (5±3) days. Related AEs experienced by ferumoxytol-treated subjects included one of each of the following (1.3%): anaphylactic reaction, dysgeusia, feeling hot, flushing, headache, injection site hematoma, injection site pain, and nausea.

There was 1 SAE considered related to ferumoxytol treatment. The subject experienced an anaphylactic reaction, described as a systemic allergic reaction, after receiving the first dose, and was treated with epinephrine, Benadryl, Solu-Cortef and IV normal saline on the day of the event. The event was subsequently resolved the same day.

2.6.3 Post-Marketing Program

In March of 2015 the FDA placed a black box warning on ferumoxytol stating:

WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS

Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving Feraheme. Initial symptoms may include hypotension, syncope, unresponsiveness, cardiac/cardiorespiratory arrest.

- Only administer Feraheme when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

- Observe for signs or symptoms of hypersensitivity reactions during and for at least 30 minutes following Feraheme infusion including monitoring of blood pressure and pulse during and after Feraheme administration.
- Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated.

In the black box warning the FDA updated their recommendations of how ferumoxytol should be given. The option to give ferumoxytol (510mg) as a fast undiluted injection in approximately 1 minute has been removed. It was recommended that ferumoxytol (510mg) be given over at least 15 minutes. To accommodate for this, the dose of ferumoxytol will be given in three separate, fractionated doses. The rate of administration of the second and third doses will be slowed down to no faster than 1 mL/s.

Based on communication with AMAG Pharmaceuticals, manufacturer of ferumoxytol, all recommendations apply to iron replacement therapy where infusion rate and dilution do not impact efficacy. However, for an imaging indication certain infusion parameters are required to gain information, such as dynamic imaging. Increased infusion rate will only affect the first injection of 1 mg/kg, which is a small fraction of the full therapeutic dose, and therefore may minimally increase the risk of adverse reactions. The next two injections are given at a slower rate. The recommended 15 minutes has no scientific basis, it has been chosen arbitrarily. For MR imaging stopping the scanner for 15 minutes would be disadvantageous. Applying multiple injections, which is not the case with iron replacement therapy, may increase safety, compared to continuous injection. This may contribute to the fact that in our patient population only minor adverse reactions have been reported.

2.6.4 OHSU Toxicity Data

As of April 1, 2015, a total of 621 infusions of ferumoxytol had been completed on 287 study subjects as part of OHSU's Blood Brain Barrier sponsored IRB approved protocols. The dose has ranged from 75 to 510 mg of ferumoxytol (0.5 to 11 mg/kg). Toxicities for this group as of April 1, 2015 show no grade 4 or 5 toxicities (CTCAE version 3) that were attributed to ferumoxytol. Two incidents of grade 3 toxicities were possibly attributable to ferumoxytol (one incident of constipation and one of neck pain). The most common adverse events associated with ferumoxytol were 20 (3% of total infusions) incidents of mild, transient hypertension and 5 (0.8% of total infusions) incidents of diarrhea. There have been no incidents of hypotension, syncope, unresponsiveness or cardiorespiratory arrest with these 621 administrations of ferumoxytol.

3 SUBJECT SELECTION

3.1 Eligibility Criteria

1) Subjects with radiographically suspected, histologically or cytologically confirmed primary brain tumors or brain metastasis are eligible.
2) Subjects may be enrolled at any point in diagnosis or treatment.
3) Subjects must have had radiographically evaluable or measurable disease with standard MR imaging.
4) .
5) Age $\geq$18 years. Both men and women and members of all races and ethnic groups will be included.
6) ECOG performance status $\leq$ 3 (KPS $\geq$ 30).

7) Ability to understand and the willingness to sign a written informed consent document, or have a representative able to consent for the subject.

8) Sexually active women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; or abstinence) prior to study treatment and for the duration of study treatment. Should a female become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

9) Subject agrees to complete follow up visit.

3.2 Exclusion Criteria

1) Subjects with clinically significant signs of uncal herniation, such as acute pupillary enlargement, rapidly developing motor changes (over hours), or rapidly decreasing level of consciousness.

2) Subjects who have a contraindication for MRI: metal in their bodies (a cardiac pacemaker or other incompatible device), are severely agitated, need monitored anesthesia for scanning, or have an allergy to Gd contrast material.

3) Subjects with known hepatic insufficiency or cirrhosis

4) History of allergic reactions attributed to compounds of similar chemical or biologic composition to ferumoxytol

5) Subjects with known or suspected iron overload (genetic hemochromatosis or history of multiple transfusions)

6) Subjects expecting to undergo surgery between the imaging sessions. Subjects may undergo surgery at any time before the first, or after the last imaging session. This exclusion only applies to each study visit (3 day scanning session), and does not apply to the time (at least 3 weeks) between each study visit.

7) Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

8) Pregnant or lactating women are excluded from this study because of possible risk to the fetus or infant.

9) Inability or unwillingness to undergo the complete series of imaging sessions. Inability or unwillingness to complete the one month follow-up.

10) HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ferumoxytol.

11) Subjects with GFR < 50.

12) Subjects with three or more drug allergies from separate drug classes.

4 CONTRAST AGENT FORMULATION AND PROCUREMENT

4.1 Gadolinium

Gadolinium is a standard contrast agent used in clinical practice and will be administered on day 1 as an I.V. bolus of 0.1 mmol/kg at a flow rate of up to 3 mL/s, followed by a saline flush. for dynamic MR imaging followed by routine MR imaging. The appropriate

volumes of contrast agents are based on the patient's weight (0.2 ml/kg gadoteridol + 20ml saline flush).

4.2 Ferumoxytol

4.2.1 Agent Accountability: The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent.

4.2.2 Availability: Ferumoxytol is purchased by the investigators from the manufacturer, AMAG Pharmaceuticals, Inc. (Cambridge, MA)

4.2.3 Product description: Ferumoxytol is a semi synthetic carbohydrate coated ultrasmall superparamagnetic iron oxide particle. The drug is formulated with mannitol; each vial contains 30 mg/mL of iron and 44 mg/mL of mannitol. A dose of 510 mg of iron is 17 mL. Ferumoxytol is isotonic: the osmolality is 270-330 mOsm. The amount of free (BDI) iron for ferumoxytol is approximately six - fold lower than for currently approved parenteral iron products at a similar dose. The product contains no preservatives. The pH is 6 to 9.

4.2.4 Preparation: The appropriate volume of drug is based on the subject's weight. The drug will be stored at room temperature (68-77 degree Fahrenheit) away from direct sunlight. The solution will be prepared and dispensed by the investigational drug pharmacist. The Ferumoxytol will be injected in the MR suite by either a nurse or technician.

The ferumoxytol will be diluted 1:1 to make a 15mg/ml solution. The total dose of ferumoxytol will be 4 mg/kg (to a maximum of 510 mg), and will be administered intravenously on day 2.

The dilution and injection parameters may be adjusted to obtain optimal signal changes. The total dose will not exceed 4 mg/kg or 510 mg.

See Section 5.3.4 for admistration.

4.3 Expected adverse events

As described in the Investigtor's Drug Brochure for ferumoxytol, a total of 1740 subjects (patients and healthy volunteers) were given one or more doses of ferumoxytol. Safety was determined in subjects through an analysis of changes in pre and post-dose blood chemistry, urinalysis, vital signs, results of physical examinations, electrocardiograms (ECG), and by the incidence of adverse events. There were no clinically significant changes noted by the investigators in ECG, vital signs, or clinical chemistries. There have been three serious adverse events considered related or possibly related to ferumoxytol. Two cases of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis, occurring 13 and 30 days after administration of ferumoxytol were considered 'possibly related'. Both patients had prior histories of peritonitis. One patient with a history of allergies had an anaphylactic reaction that was considered 'related' to ferumoxytol.

On June 20, 2009, the FDA approved ferumoxytol (Feraheme™) to treat iron deficiency anemia and adult chronic kidney disease patients. The recommended dose is an initial 510 mg IV injection followed by a second 510 mg IV injection three to eight days later. Ferumoxytol is now commercially available in the U.S.A.

4.4 Safety

The ferumoxytol clinical development program has been comprised of eleven studies. These included three Phase 1 studies (two dose-escalation studies and a study of the

electrocardiographic/QTC effects of ferumoxytol), two Phase 2 studies that evaluated the safety and efficacy of ferumoxytol for iron replacement in patients with CKD, and two Phase 2 imaging studies that assessed the feasibility of ferumoxytol as an MRI contrast agent. There were three open-label Phase 3 studies that examined the efficacy and safety of ferumoxytol relative to oral iron in patients with Chronic Kidney Disease (CKD) Stages 1-5 either on or not on dialysis. A fourth Phase 3 study in patients with any stage of CKD evaluated the safety of ferumoxytol relative to placebo in a cross-over, double-blind manner. Ferumoxytol has been evaluated at exposures up to 2 x 510 mg, including two courses of 2 x 510 mg in three of the four Phase 3 studies. Specifically, the following regimens of ferumoxytol were given during the clinical program:

- ≤4 mg Fe/kg
- 1 x 125 mg
- 1 x 250 mg
- 1 x 510 mg
- 8 x 128 mg
- x 255 mg
- x 510 mg

Approximately 1,740 patients have been exposed to ferumoxytol in the entire clinical program, and approximately 1,509 patients have been exposed to ferumoxytol in the Phase 3 studies. To date, only one patient (0.06% of all patients exposed to ferumoxytol) has experienced an anaphylacoid reaction following treatment with ferumoxytol; this patient had a history of multiple drug allergies and experienced an anaphylactoid reaction (hot flashes and itching, with no respiratory compromise) and severe hypotension a few minutes after receiving ferumoxytol. There have been no deaths that were considered to be related to ferumoxytol treatment. There were 28 deaths in the clinical program, all of which have occurred in Phase 3 studies, with 16 deaths among the 1,740 patients exposed to ferumoxytol (0.9%) and 8 deaths among the 296 patients exposed to oral iron (2.7%). Four deaths occurred in patients who had signed an informed consent for enrollment but did not receive any test article. All deaths in the clinical program have been in patients with CKD, who have a high risk of death due to cardiovascular disease and other causes. In completed studies that used oral iron as a comparator, there was a lower rate of SAEs among patients exposed to ferumoxytol than among patients exposed to oral iron: 4.4% of ferumoxytoltreated patients (64 of 1,451 patients) vs. 10.7% of oral iron-treated patients (17 of 159 patients). Patients exposed to placebo had the lowest rate of SAEs (1.7%; 13 of 780 patients). One patient each following ferumoxytol (0.1%), oral iron (0.6%), and placebo (0.1%) experienced an SAE that was considered by the investigator to be related to treatment. In Phase 3 Study 62,745-5, which enrolled CKD patients undergoing hemodialysis, 31 of 199 (15.6%) patients experienced an SAE following ferumoxytol administration and 8 of 70 (11.4%) patients experienced an SAE following oral iron administration. These data were taken from an unlocked database and therefore are preliminary and patient to final verification. In the Phase 3 studies in patients with CKD (62,745-5, 62,745-6, 62,745-7, and 62,745-8, in which approximately 1,509 patients were exposed to ferumoxytol), the most common adverse events following ferumoxytol administration included nausea, diarrhea, dizziness, headache, and peripheral edema. These adverse events were usually more common in the oral iron group than the ferumoxytol group (in Studies 62,745-5, 62,745-6, and 62,745-7, which utilized oral iron as a comparator). Hypotension was one of the more common adverse events in Study 62,745-7 and occurred more frequently in the ferumoxytol group (5.0%) than the oral iron group (1.4%). By contrast, preliminary data show that there have been

lower rates of hypotension in Study 62,745-5 (1.8%, 1.7%, and 0% in the ferumoxytol 2x510 mg, ferumoxytol 4x255 mg, and oral iron groups, respectively); hypotension rates were similar between the ferumoxytol and placebo groups (1.3% vs. 0.8%) in the large safety study, Study 62,745-8; and there were no hypotension adverse events in Study 62,745-6.

An independent Data Monitoring Committee met to review the clinical safety data for all Phase 3 studies in October 2005, February 2006, June 2006, October 2006, and March 2007, and they identified no safety concerns.

5 STUDY PROCEDURES AND SCHEDULE OF EVENTS

5.1 Enrollment

Targeted enrollment is 150 subjects for this study. Study length is 2 years. Subjects will be assigned to 3T or 7T magnet to maintain a balance within the subgroups (primary with or without prior treatment and metastatic with or without prior treatment).

A subset of 25 of the 150 subjects will only undergo MRIs on the 7T magnet. We have recently performed upgrades to the magnet and need to test these new upgrades in order to get the best images to compare with the 3T magnet in the remaining subjects.

5.2 Subject Registration

5.2.1 Informed consent will be obtained, refer to section 8.2.

5.2.2 New subject registrations will be submitted to the study coordinator, who will record study data on all patients entered into the study and complete subsequent forms.

5.2.3 A subject's tumor type (primary versus metastatic) and prior treatment status (yes or no) determine to which of four strata the subject will be assigned. Subjects will be assigned to either 3T or 7T groups in an effort to keep the subgroups balanced and/or possibly depending on MRI availability. We expect up to 20% of subjects will not be able to complete the imaging at the assigned magnet strength and, further, that the proportion may be somewhat higher in those assigned to the 7T magnet (as this magnet is more likely to not be available due to technical and, more rarely, subjects may not be able to tolerate the more confined space). This approach is designed to, as well as possible, maintain balance between the 3T and 7T subgroups .

5.3 Study Visits

5.3.1 Each study visit consists of 3 days. There may be up to 7 days between Day 1 and Day 2 visits. A study visit may be repeated up to four times, but not any more frequently than every 3 weeks.

5.3.2 The subject may be given Benadryl before MRI scanning to help with relaxation during the MRI scan and/or to prevent an allergic reaction to the Ferumoxytol. Subject's need for anti-anxiolytics for each MRI study visit will be evaluated and administered as needed. Common anti-anxiolytics include lorazepam and diazepam; diphenhydramine may also be used. The administration of a relaxing/anti-anxiolytic agent will be given at the treating physician or the PI's discretion and is considered routine prior to MRI and as such is not being evaluated on this study.

5.3.3 **Day 1**

Laboratory testing:

- creatinine to calculate GFR prior to gadolinium administration (may be done up to 3 weeks prior)

- Urine pregnancy test in women of child bearing potential.

Imaging:

- Anatomical imaging on 3T & 7T and dynamic MRI (with gadolinium, see section 4.1) on either 3T or 7T (dependent on which group subject is assigned and as described in section 5.1.3)
- Day 1 and Day 2 imaging sessions may be separated by up to 7 days.
- A subset of 25 of the 150 subjects will only undergo MRIs on the 7T magnet.

5.3.4 **Day 2**

Imaging

- Anatomical imaging on 3T & 7T and dynamic MRI (with ferumoxytol, see section 4.2). A subset of 25 of the 150 subjects will only undergo MRIs on the 7T magnet.
- Dynamic imaging will be performed on the same scanner as on which the dynamic the dynamic imaging was acquired on Day 1(as described below on Section: 6.0). Ferumoxytol Administration:
- The ferumoxytol will be diluted 1:2 to make a 10mg/ml solution. The dose of ferumoxytol will be 4 mg/kg (to a maximum of 510 mg), and will be administered intravenously on day 2.
- Dose 1: Give 1/4th of the total dose (1mg/kg); inject at up to 3 ml/sec followed by a saline flush. This rate is required for adequate signal change during the dynamic imaging.
- Dose 2: Give 3/4th of the total dose (3mg/kg); inject no faster than 1 ml/sec and followed by a saline flush
-
- The dilution and injection parameters of the ferumoxytol may be adjusted to obtain optimal signal changes on MRI/MRA and to decrease the possibility of an allergic reaction. Injection rate can be varied based on the participant's IV site, but the total dose will never exceed 510mg.

Monitoring

- A clinical examination will be performed before and after the MRI session on Day 2.. Blood pressure and pulse will be monitored before the first dose of ferumoxytol and after each dose of ferumoxytol, and at 30 minutes after the initial dose of ferumoxytol.

5.3.5 **Day 3**

Imaging:

- Post-ferumoxytol MR imaging at both 3T and 7T (as described below in section: 6.0). No contrast agent will be administered on this day. A subset of 25 of the 150 subjects will only undergo MRIs on the 7T magnet.

5.4 Adverse Events

Toxicities and adverse experiences will be assessed using the NCI Common Terminology Criteria for Adverse Events v3.0. . Adverse events related to or potentially related to the administration of ferumoxytol will be recorded; adverse events related to

the MRI's experience itself, such as claustrophobia/anxiety, nausea with GBCA injection, or discomfort due to positioning, is not being studied and will not be reported. Adverse events that will be monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, flushing, dizziness, pruritis/rash, and any other symptoms that could be secondary to an anaphylactoid type reaction.

5.5 5.5 Follow-up:

The subject will be seen in an outpatient clinic or have a telephone follow up interview approximately 4-6 weeks after the study visit to assess for adverse events.

5.6 Subject Evaluability

Subjects who are assigned to either the 3T or the 7T magnet strength MRI instruments may not be able to complete the imaging on the assigned strength on a given day. This will most likely be due to an MRI technical issue on the day the subject has been assigned. The 7T MRI is more likely to experience technical difficulties as this is a research instrument and is not a standard clinical product. In addition, a few subjects may not be able to tolerate an MRI examination on a particular day. If one MRI instrument is unavailable and the other one is available, the subject will be "crossed-over" for that day. For Primary Aims 1 and 2, crossing a subject on either day 1 or day 2 (but not both) will mean that the subject will be evaluable for one aim (corresponding to the non-crossover day) but not for the other. The sample size is adequate to allow up to 20% of subjects to be crossed over on at least one day. If one MRI instrument is not available on Study Day 3, data will be collected from that subject on only one instrument and these data will be used only to describe the range of values for that magnet strength.

5.7 Criteria for early termination from the protocol

- Voluntary subject withdrawal
- Investigator's decision that is in the subject's best interest to withdraw
- Subject becomes pregnant
- Noncompliance
- Significant protocol violation
- For any reason, at the Sponsor or Investigators discretion

6 IMAGING SCHEMA AND ACQUISITION

6.1 Schema

<u>Day 1</u>

1. Standard precontrast anatomical MRI sequences at 3T and/or 7T: sagittal T1, coronal FLAIR, MPRAGE, axial T1, T2, T2*, PD weighted images and DWI.
2. TOF angiography
3. Quantitative T1 images
4. DSC MRI (T2* weighted) for perfusion with Gd bolus administration dose: 0.1mmol/kg)
5. Quantitative T1 images for permeability measurement will be performed 4 times
6. TOF angiography (postgadolinium)
7. Standard postgadolinium imaging at 3T and 7T:MPRAGE, axial T1, T2, T2* weighted images.

A subset of 25 of the 150 subjects will only undergo MRIs on the 7T magnet.

[Section 6.1 and 6.2 numbers 4 and 5 will be assigned to either 3 or 7 Tesla. 1, 2, 3, 6 and 7 will be performed on both magnet fields, the order of the scanners will be balanced, see Study Procedures section 5.2.3.] In subjects who cannot tolerate long MRI study either 3T or 7T (MRI with no dynamic imaging) pre-contrast sequences 1, 2 and 3 maybe acquired on Day 2 (dash line in the figure below).

Day 2

1. Standard MRI sequences: axial T1, (MPRAGE, T2, T2*, PD, DWI images will be acquired only when quality of images are not good or if they were not acquired for some reason in first session)
2. TOF angiography (only when quality of image is not good or was not acquired for some reason on first session)
3. Quantitative T1 images
4. DSC MR (T2* weighted) for perfusion with ferumoxytol bolus (maximum dose: 1mg Fe/kg) the remaining 3mg/kg to be administered after this series)
5. Quantitative T1 images for permeability measurement will be performed 4 times
6. TOF angiography (post ferumoxytol)
7. Standard MRI sequences (post contrast): MPRAGE, axial T1, T2, T2* weighted images.

Day 3

1. (24±6h post-ferumoxytol administration in both magnets.)
2. Standard MRI sequences (post contrast): sagittal T1, coronal FLAIR, axial MPRAGE, T1, T2, T2* weighted images, TOF angiography and Quantitative T1 images.

6.2 Schema Options

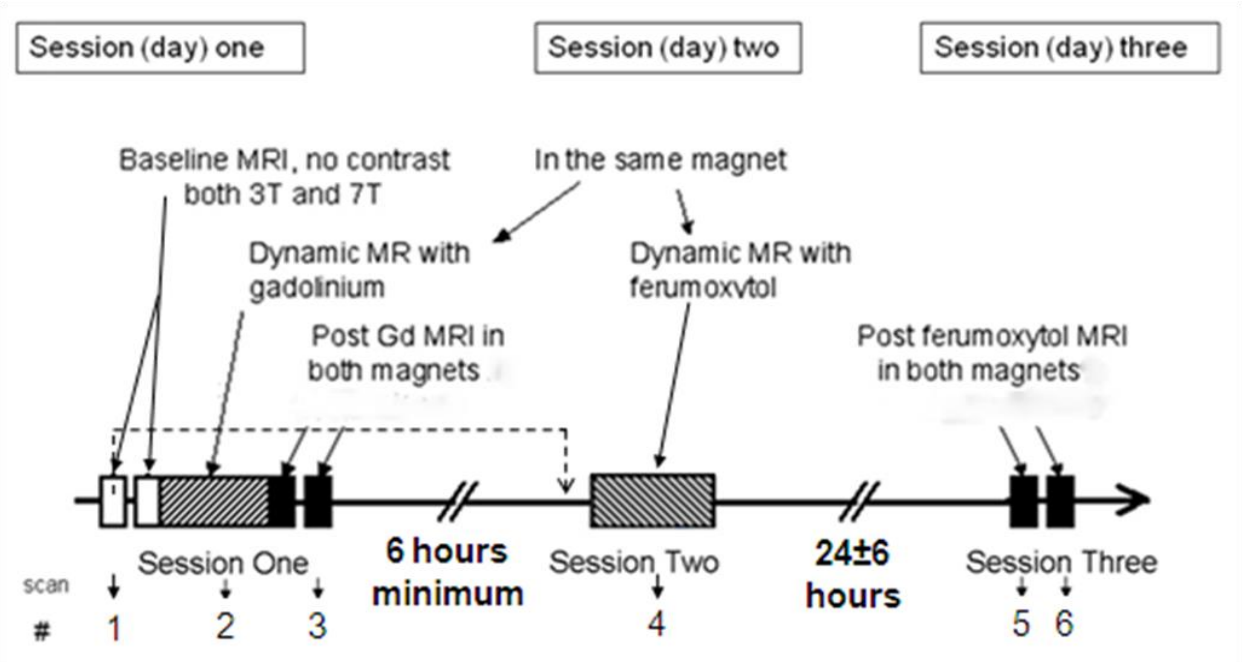
There are two schema options | Duration (min)

6.2.1 Option A

Three times in MRI on Day 1 (3T-7T-3T or 7T-3T-7T)	150
One time on MRI scanner Day 2 (3T or 7T)	90
Two times on MRI scanner Day 3 (3T and 7T)	100

6.2.2 Option B

Two times on MRI scanner Day1 (3T and 7T)	100
Two times on MRI scanner Day 2 (3T and 7T)	130
Two times on MRI scanner Day 3 (3T and 7T)	100



6.3 MR Acquisition Parameters

Images will be acquired at 3T (Siemens TIM) using a 12-channel receive only phased array RF head coil and at 7T (Siemens MAGNETOM) using an 8 channel phased array transmit/receive RF head coil.

3T acquisition parameters:

Scan type	***Scan time (min)***
0. Setup/localizer/B_0 shimming/B_1 mapping	3
1. T1-w sagittal (TE 2.5/TR 300/FA 60)	
220mm x 220mm FOV 256 x 256 matrix 4 mm contiguous	2
2. FLAIR coronal (TE 9000/TR 95/TI 2500)	
230mm x 172mm FOV 256 x 205 matrix 3 mm contiguous	4
3.. T1-w axial TSE (TE14/TR700 TSE factor 4 4NEX; PAT=2)	
180mm x 240mm FOV 192 x 256 matrix 3 mm contiguous, interleaved	4
4. MPRAGE axial (TE 2300/TR 3.4/FA 12)	
256 mm x 192 mm FOV 256 x 256 matrix 1 mm contiguous	7
5. T2-w axial TSE (TE72/TR9000 TSE factor 9 PAT=2)	
180mm x 240mm FOV 192 x 256 matrix 3 mm contiguous, interleaved	2
6. PD-w axial TSE (TE14/TR9000 TSE factor 9 PAT=2)	
180mm x 240mm FOV 192 x 256 matrix 3 mm contiguous, interleaved	2
7. Diffusion weighted MRI axial (TE90/TR6000 SE EPI b=0, 500, 1000 s/mm^2)	
220mm x 220mm FOV 128 x 128 matrix 3 mm contiguous, interleaved	4
8. MRA 3D-TOF (TE3.2/TR18/FA20; PAT=2)	
170mm x 200mm x 150 mm FOV 200 x 400 x 140	5
9. Quantitative T_1 axial (3D GRE TE3/TR15/FA5,20)	
180mm x 240mm x 144 FOV 192 x 256 x 48 matrix 3 mm contiguous, 3D	5
10. T_2*-w axial; GEPI (TE25/TR2000/FA50; PAT=2) x 45 volumes	
220mm x 220mm FOV 128 x 128 matrix 3 mm contiguous, interleaved	6
11. PWI Echo-Planar Gradient Echo and Spin Echo 20- 90 ° Flip Angle	
TR=2000 msec/TE=28 msec 3mm Slices in Axial Plane	3

7T acquisiton parameters:

0. Setup/localizer/B_0 shimming/B_1 mapping.....3
1. MPRAGE axial (TE2.7/TR26.5/FA8)180mm x 220mm x 160mm FOV
   320mm x 256mm x 224mm matrix 0.7mm contiguous, 3D .....
2. Quantitative T_1 axial (EPI GRE TE16/TR10000) 256mm x 256mm FOV
   128mm x 128mm matrix 2 mm contiguous, interleaved.....
3. T2-w axial TSE (TE91/TR10000; ETL 11) 240mm x 180mm FOV
   512mm x 384mm matrix 3 mm contiguous, interleaved.....
4. SWI axial (TE12/TR26) 240mm x 180mm FOV
   512mm x 384mm matrix 1.5mm contiguous, interleaved.....
5. T2*-w High Resolution axial (TE20/TR950) 220mm x 160mm FOV
   960mm x 704mm matrix 1.5 mm contiguous, interleaved .....
6. Diffusion weighted MRI axial (TE90/TR6000 SE EPI b=0, 500, 1000 s/mm2)
   220mm x 220mm FOV 128 x 128 matrix 3 mm contiguous, interleaved.....
7. DSC: T2*-w axial; GEPI (TE20/TR1500/FA30) x 90 volumes
   200mm x 200mm FOV 64mm x 64mm matrix 3 mm contiguous, interleaved.....

The above detailed sequences are subject to change in order to acquire the best imaging results on the applied field strength.

7 CRITERIA FOR EVALUATION USING MRI

7.1 Lesion assessment methodology and volumetrics

To be eligible for this study, subjects must have had a radiographically evaluable or measurable lesion on standard MRI. Anatomical images acquired pre- and post contrast, including T1-w, T2-w, FLAIR, PD images will be assessed. Lesions should be measurable on at least two dimensions. Depending on the MR mophological abnormality of the lesion, volumetric measurement maybe performed using T1-w, T2-w,

FLAIR, PD images. MR signal abnormality refers to:

1. T1 signal abnormality on precontrast images
2. Abnormal hyperintensity on T1-w postcontrast images
3. T2/FLAIR signal abnormality

7.2 Perfusion MR

7.2.1 T_2* weighted MR images will be collected during contrast agent administration to obtain a dynamic susceptibility contrast (DSC) data set.

7.2.2 Time-intensity curves, cerebral blood volume (CBV) parametric maps and relative CBV (rCBV) values (as area under the signal intensity curve, normalized by area under the curve for control region) will be obtained. Relative mean transit time (rMTT) values will be obtained by gamma variate fitting the time-intensity curves,[50] using Matlab environment

(Mathworks, Natick, MA). The relative perfusion values will be plotted as a function of time with both agents.

7.3 Vascular Permeability measurement

T_1 weighted MR data will be collected before and after contrast agent administration. Permeability will be evaluated by applying dynamic contrast enhanced (DCE) scans for quantitative T1 measurements 4 times over 45 minutes and also 24±6 hours after contrast administration. Using the R_1 (=1/T_1) values, K^{trans} will can be calculated in the selected ROIs, (i. tumor core, ii. tumor rim, iii. ipsilateral control region iv. contralateral control region).

7.4 Ferumoxytol delayed MRI enhancement

3 T and 7 T T_1-w scans acquired 24±6 hours post-ferumoxytol administration will be compared. Scans will be evaluated by two radiologists, measuring the enhancing volume from a volumetric T_1-w image set using a manual trace technique. Total delayed enhancement volumes will be calculated by multiplying the enhancing pixel area by the pixel volume. Volume measurements will be compared between 3T and 7 T.

7.5 Diffusion weighted imaging

For diffusion evaluation, the same ROIs will be defined as were done for perfusion evaluation. (i. tumor core, ii. tumor rim, iii. ipsilateral control region iv. contralateral control region). Apparent diffusion coefficient (ADC) values will be calculated using Matlab environment (Mathworks, Natick, MA).

7.6 Time of flight angiography (TOF)

Time of Flight angiography will be evaluated semi quantitatively by two radiologists. Vascular density will be compared between ferumoxytol and gadolinium and also between time points. We expect more visible vessels than without contrast agent. In our previous study TOF angiography was done after the injection of 4mg Fe/kg ferumoxytol. We hypothesize that the reduced dose of ferumoxytol also allows good visualization of blood vessels without leakage artifact.

7.7 Susceptibility weighted imaging:

The size of the vascular structures within the tumor bed will be semi-quantitively analyzed. The size of the tumor vessels will be compared to that of the normal penetrating vessels. Ttumor vessels are considered to be small if their diameter is smaller than the diameter of the penetrating vessels. If the diameter is equal to or larger, they are determined to be medium and large respectively. The presence of tortuous vessels within the tumor bed is also recorded as present or absent. The resulting images will be evaluated in a blinded fashion by two neuroradiologists.

8 ETHICAL AND REGULATORY REQUIREMENTS

8.1 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and appropriate Institutional Review Board (IRB) prior to any subject being registered on this study.

8.2 Informed Consent

Written informed consent will be obtained from all subjects, or the legally authorized representative of the subject, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a subjects signature cannot be obtained, the investigator must ensure that the informed consent is signed by the subject's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the subject's medical record.

8.3 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

8.4 Maintenance of Records

If the investigator relocates or, for any reason, withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to the OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained according to sponsor or FDA requirements.

8.5 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site

http://www.ohsu.edu/research/rda/irb/policies.shtml.

Fatal and life-threatening UP will be reported to OHSU IRB within 7 days of notification of the event. All other UP reports will be submitted to OHSU IRB no later than 15 days of occurrence or notification of the event. Copies of the report documents will be kept in the study regulatory binder.

UP and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU Knight Cancer Institute and IRB. Monthly accumulative reports will be reviewed by a DSMC Oncologist and forwarded to the CRRC.

8.6 MedWatch Reporting

For this investigator-initiated study, the investigator is considered the sponsor. The investigator/sponsor is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package label), serious adverse experiences with a suspected association to the study drug.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using the FDA 3500A Mandatory Reporting form, which is available online at:
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm

This is available as a .pdf document for printing. (At this time, MedWatch does not have a 3500A form that can be submitted electronically).

When the serious adverse event is reported to the FDA, copies of the MedWatch 3500A form and supporting materials will be submitted to the OHSU Knight Cancer Institute and the IRB. A copy of the MedWatch 3500A form and supporting materials will be kept on file in the study regulatory binder.

8.7 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited anytime after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan.

8.8 Inclusion of Women, Minorities and Children

8.8.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 5: Population Demographics - Oregon (%)

Ethnic Category	Sex/Gender		
	Femal	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6
More than one race			3.8
Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Table 6: Projected Accrual for the Present Study *(enter actual estimates, not percentages).*

Ethnic Category	Sex/Gender			
	Femal	Males	Unkn own	Total
Hispanic or Latino	9	9		18
Not Hispanic or Latino	66	66		132
Unknown				
Ethnic Category: Total of all subjects*	75	75		150*
Racial Category				
American Indian or Alaskan Native	1	1		2
Asian	3	3		6
Black or African American	2	1		3
Native Hawaiian or other Pacific Islander				0
White	62	63		125
More than one race	3	3		6
Unknown	4	4		8
Racial Category: Total of all subjects*	75	75		150*

Source: Investigator projections based on Table 5*Totals must agree.

8.8.2 Inclusion of Children

This protocol does not include children for the following reason:

the number of children with this type of cancer is limited and limited dosing and adverse event data are currently available on the use of ferumoxytol in subjects <18 years of age, therefore, children are excluded from this study.

9 STATISTICAL CONSIDERATIONS

9.1 Study Objectives

Refer to section 1.

9.2 Baseline Summaries

Descriptive statistics will be provided for all baseline characteristics including demographic variables (age, gender, race), disease characteristics (prior treatment, baseline KPS and steroid use), tumor characteristics (size and permeability) and pre-imaging variables. For continuous data, mean and standard deviation and minimum, median and maximum will be estimated. For categorical variables, the number and percent for each category will be estimated.

Data from those subjects already enrolled will be summarized both separately from the rest of the subjects and combined with the other subjects. These first eleven subjects will be considered as feasibility subjects. Summaries of imaging measures will include data on relative normalized signal intensity changes (CNR) for dynamic MRI data sets, cerebral blood volume and relative mean transit time for the perfusion data and K^{trans} for vascular permeability.

9.3 Descriptive Statistical Analyses

All analyses described are viewed as descriptive in nature to better understand the variation in these parameters and not to provide definitive results as would be expected in a Phase III trial. The statistical analyses provide appropriate frameworks for assessing the relative magnitudes of effects while potentially controlling for other parameters of interest. Results will be used to plan for future definitive studies of the parameters that have appropriate power calculations and sample sizes. These analyses will be performed when target sample sizes are achieved and not on as interim analyses.

For Primary Aim 1, the primary descriptive comparisons are paired sample t-tests comparing the normalized signal intensity changes (CNR) for T_1-weighted MRI signal at 3T and at 7T. Secondary analyses will use a repeated measures analysis of variance (ANOVA) model to compare 3T and 7T while adjusting for other factors including tumor type, prior therapy, and, potentially, important baseline factors that differ between the subjects assigned to the two field strengths. These tests are descriptive in nature and are not powered to provide a complete answer. Subjects who are scheduled to be imaged by a magnet of one field strength but are “crossed-over” to the other magnet or who otherwise fail to complete the scheduled imaging will not be included in these analyses. For the baseline characteristics, if two-sample tests of hypotheses indicate a significant difference ($p<0.10$) between 3T and 7T signal intensity changes for a particular variable, that variable will be included in the ANOVA model as a covariate. Normality will be assessed graphically and, if needed, a transformation (e.g. the logarithmic transform) will be applied. These analyses will be performed for Gd T1-weighted MRI data only

For Primary Aim 2, the analyses will be similar to those for Aim 1 above using normalized (CNR) signal intensity decreases in the DSC data sets. . The same factors and analyses will be used. This objective assesses only Ferumoxytol.

For the first Secondary Aim, mixed model repeated measures ANOVA’s will be fit. The outcomes will be relevant dynamic MRI (DCE and DSC) signal intensity changes for permeability and for perfusion. Factors will include imaging agent (Gd or ferumoxytol)

and field strength (3T and 7T). Each subject will contribute one measure for each combination of imaging agent and field strength (4 measures total). This will not be a definitive analysis as the power cannot be determined *a priori*. The mixed model allows for estimation of the means and confidence intervals for imaging agent and field strength (57). These data will be used to plan future comparative studies. For the second Secondary Aim, blood volumes will be compared using repeated measures ANOVA to compare the imaging agents. For the third Secondary Aim, analyses will add covariates of prior therapy to the analyses listed above. For the comparisons between treated and untreated subjects, means and confidence intervals will be estimated for each group for the perfusion and permeability measures and for the baseline characteristics listed above. Since prior treatment is likely confounded with other variables (e.g. disease severity), these comparisons will also be descriptive in nature and mainly be used to plan future studies.

For Secondary Aim five, the pathology will be analyzed qualitatively for the presence of iron staining. The amount and localization of the staining will be assessed, with attention paid to whether the tumor cells themselves or reactive cells in and around the tumor demonstrate iron uptake.

9.4 Sample Size

There is no statistical justification for the sample size used in this study. This study plans to enroll 150 subjects with either primary or metastatic tumors. Subjects may or may not have had previous treatment.

9.5 Schema to maintain balance between 3T and & 7T groups

Subjects will be assigned to a subgroup (with or without prior treatment) and will be assigned to undergo dynamic MR imaging at either 3T or 7T in an attempt to balance the subgroup. We expect up to 20% of subjects will not be able to complete the imaging at the assigned magnet strength and, further, that the proportion may be somewhat higher in those assigned to the 7T magnet (as this magnet is more likely to not be available due to technical and, more rarely, subjects may not be able to tolerate the more confined space. This approach is designed to, as well as possible, maintain balance between the 3T and 7T groups with respect to tumor type and prior treatment. This schema is not intended to provide the same validity as randomization within a Phase III trial as this is an exploratory study and not a definitive trial.

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IRB#: 2864
Protocol Approval Date: 4/7/2016

CO1450

OHSU Knight Cancer Institute Consent and Authorization Form

Title: ***A Phase II study of ferumoxytol and gadolinium magnetic resonance imaging at 3T and 7T in patients with primary or metastatic brain tumor either before or after treatment.***

Funded by: The Walter S. and Lucienne Driskill Foundation
Supported by: AMAG Pharmaceuticals, Inc. and the National Cancer Institute (NCI)

Conflict of Interest Statement: Dr. Rooney and Dr. Li are inventors of a technology that may be used in this research and that has been licensed to Imbio, Inc. If this study and others like it are successful, then Imbio, OHSU and Drs. Rooney and Li could financially benefit. The nature of this financial interest and the design of the study have been reviewed by two committees at OHSU. They have put in place a plan to make sure this research study is not affected by the financial interest. If you would like more information, you may contact the OHSU Research Integrity Office at (503) 494-7887

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STUDY CONTACT INFORMATION

Purpose	Role	Contact Name	Contact Phone Number	Email
For medical questions about the study	Principal Investigator	Edward A. Neuwelt, M.D.	503-494-5626	neuwelte@ohsu.edu
	Co-Investigator	Joao Prola Netto, MD Csanad Varallyay, MD Jenny Firkins, RN Prakash Ambady, MD Jessica Jensen, NP Kirsten Johansson, FNP Tricia White, RN	503-494-5626 503-494-5626 503-494-5626 503-494-5626 503-494-5626 503-494-5626 503-494-5626	
	Research Nurse	Jenny Firkins, RN	503-494-5626	firkinsj@ohsu.edu
For non-medical questions about the study	Study Coordinator	Amy Huddleston, MPA	503-494-5626	huddlesa@ohsu.edu

INTRODUCTION

This is a clinical trial (a type of research study). Clinical trials include only subjects who choose to take part. Please take your time to make your decision. Discuss it with your friends, family and/or your primary care provider.

You have been asked to take part in this research study because you have or are suspected to have a primary brain tumor or a brain metastasis – cancer that has spread to the brain from another part of your body. Your brain tumor(s) can be seen on a MR scan.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the standard treatment
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for your brain lesion, but you may want to receive comfort care to relieve symptoms.

PURPOSE

WHY IS THIS STUDY BEING DONE?

This is a clinical trial, a type of research study. Medical personnel who carry out research studies are called

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"investigators." The investigator will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You can discuss your decision with your friends and family. You can also discuss it with your health care team or another doctor. If you have any questions, ask the investigator.

Your participation will enable us to compare the standard magnetic resonance (MR) contrast agent, gadolinium, with the study agent, ferumoxytol. The study agent consists of small iron particles which are taken by the blood stream to your brain and to the area of the tumor. Because it is highly visible on the MR scans, we hope it will help us to look at the blood flow going through your tumor, evaluating the size, number, and integrity of the blood vessels feeding your tumor in a different way than the standard contrast agent, gadolinium.

We are also studying the newer, more sensitive and faster MR 7 tesla (7T) magnet. Standard MR magnets are 1.5 to 3T strength. If you choose to participate in this study, your images on the 7T magnet will allow us to optimize the 7T magnet so we can most effectively compare images from the 7T magnet to those from the 3T magnet.

The study agent is approved by the Food and Drug Administration (FDA) for iron replacement therapy but is considered investigational as used in this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

As many as 25 subjects will take part in this study at Oregon Health & Science University (OHSU).

PROCEDURES

HOW LONG WILL I BE IN THIS STUDY?

You may be in the study for up to 2 years. At the investigator's discretion, you may be asked to repeat additional study visits; up to a total of 4 study visits. Each "study visit" would consist of 3trips to the study site. You would be repeating Day 1, 2, and 3, for each additional "study visit". The "study visit" may be repeated at the discretion of the investigator. There must be at least 3 weeks between study visits.

WHAT TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

Before you begin the study:

As part of your regular care, you will have a brief clinical exam and your medical history will be reviewed. The investigator will evaluate your eligibility for the study based on your medical history, kidney function, evidence of tumor on MR scan, your present physical condition, and your ability to tolerate multiple MR scans.

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During the study:
Your MRs will take place at the Advanced Imaging Research Center (AIRC).

The study will last for up to 2 years or until you have completed up to 4 of the 3 day MR study visits. The 3 day study visit may not occur any more often than once every 3 weeks. Each study visit will be the same as the first one.

Study Visit
A study visit consists of 3 days of MR scanning days as follows:
Day 1:

- An IV will be placed in your arm and you will be asked to give less than a teaspoon of blood prior to exposure of the gadolinium. The blood test checks how well your kidneys are working. For women, you may be asked to take a urine pregnancy test. This preparation time will take approximately 20 – 30 minutes. During the MR, gadolinium contrast agent will be injected in the standard dose and will be given through the IV by either the study nurse or the MR technician. You will be in the MR for about 60 minutes.
- Day 1 and Day 2 imaging sessions may be separated by up to 7 days.

Day 2:

- You will have a clinical examination before and after the MR. An IV will be placed in your arm. We will give you the study agent through your IV. You will have your blood pressure and heart rate checked before and after each infusion. You will receive IV injections of the study agent; the total dose given is based on your weight and is given IV in several smaller doses during the MR (total dose 4 mg/kg).
- You will be in the MR scanner for about 90 minutes.
- You will be monitored for 30 minutes after receiving the final dose of the study agent. When the investigator thinks you are stable, you will be discharged.

Day 3:

- You will not receive any contrast agent during this MR.
- You will be in the MR scanner for about 45 minutes.

After the Study:
Approximately 4-6 weeks after receiving the study agent, you will be evaluated during a routine clinic visit or be contacted by telephone to see if you experienced any side effects after receiving the study agent.

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Any complaints or problems potentially related to the infusion of the study agent will be recorded.

SCHEDULE OF EVENTS:

Test / Procedure	Day 1	Day 2	Day 3	Final
Inclusion/Exclusion Criteria	X[a]			
Consent	X[a]			
Clinical Exam/Assessment	X[a]	X[c]		
Laboratory Monitoring	X[a, b]			
MR scan with and without gadolinium as contrast agent	X			
MR scan with the study agent as contrast agent		X		
MR scan without contrast, 24 hrs after the study agent infusion			X	
Blood pressure/heart rate		X[d]		
Monitor for side effects				X

[a] May be done prior to visit 1
[b] Creatinine to check GFR (may be done within the previous 3 weeks) and urine pregnancy test if female of child bearing potential
[c] Before and after the day 2 MR
[d] Before and after each study agent injection and 30 minutes after the final study agent injection

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RISKS

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?
While you are in the study, you are at risk for a number of side effects. You should discuss these with the researchers and/or your regular doctor. There may also be side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable if they occur.

Here are important points about side effects:

- The investigators do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.
- You may have some side effects we do not expect because we are still learning about ferumoxytol.
- There may be unanticipated risk to an embryo or fetus if you or your partner becomes pregnant.

Here are important points about how you and the investigator can make side effects less of a problem:

- Tell the investigator if you notice or feel anything different so they can see if you are having a side effect.
- The investigator may be able to treat some side effects.

The most common and the most serious side effects that researchers know about are explained below. There might be other side effects that researchers do not yet know about. If important new side effects are found, the investigator will discuss these with you.

PHYSICAL RISKS
Study agent ferumoxytol
In March 2015, the FDA updated the risks of the study agent, ferumoxytol. They placed a “black box” warning on ferumoxytol due to reports of severe allergic reactions (anaphylaxis) in patients receiving ferumoxytol for iron replacement therapy. There are data to show that people with multiple drug allergies may be at higher risk for anaphylaxis (a severe, whole body allergic reaction) following study agent administration. Please tell the investigator if you have any known drug allergies. It is important to note that an allergic reaction can occur even if you have received the study agent previously, with no reaction. If an allergic reaction were to happen during a study visit, you might experience low blood pressure, breathing difficulties, and/or a rash. There is a very small possibility that serious hypersensitivity (allergic) reactions may be life threatening.

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A nurse or physician will be present and monitor you during, and for at least 30 minutes after, you receive the study agent.

A total of 1700 subjects have received one or more doses of the study agent. There have been 3 serious adverse events possibly related to the administration of the study agent—two cases of peritonitis (the inflammation of the lining the abdomen) that were possibly related and one case of serious allergic reaction related to the study agent.

The reactions that have been observed during the infusion include discomfort, pain and/or bruising at the IV injection site. More common but less severe side effects include a metallic taste in your mouth, which usually resolves quickly.

Other reported side effects (reported in 1-2 % of patients) are: gastrointestinal (GI) discomfort (including

- Nausea
- Vomiting
- Constipation and/or diarrhea
- Viral infection of the digestive tract
- Upper respiratory infection (cold)
- High blood sugar
- Changes in vision
- Joint pain
- Tingling in the limbs or body
- Dizziness and hypotension (low blood pressure)
- Flushing
- Chills
- Abnormal liver function tests
- Pruritus (itching) and rash

There is an increased risk of infection in subjects with weakened immune systems. If you have a weakened immune system it means you have an increased risk of infection, whether or not you participate in this study.

You may have some side effects we do not expect because we are still learning about the study agent.

In March of 2015, the FDA updated how the study agent should be given based on its use in patients with low iron levels. The FDA recommendation is to give 510 mg over 15 minutes. In this study, your dose is calculated by

your weight and will likely be less than 510 mg. For this study, you will receive 4 mg per kilogram (so a 68 kilogram [150 pound] individual would receive 272 mg of the study agent, a 90 kilogram [200 pound] individual would receive 360 mg). The study agent will be divided up and given in three doses, and MR images will be taken in between. The time between the doses will be about 5 minutes.

The first smaller dose will be given quickly, over about 5 seconds, and the other two doses will be given more slowly, over about 10-20 seconds. This first dose is less than 20% of the FDA approved 510 mg. The first dose will be given faster than the FDA's recommended rate because this allows special images, which are not possible when the study agent is given at a slower rate. This gives information about blood supply of the tumor and normal brain. The increased rate may increase your risk of adverse reactions.

The remaining two doses will be given slowly, but not as slow as the FDA recommends because of the timing of the images. The FDA recommended timing may not be applicable to this study population because the total dose is injected in three smaller doses, which may help to decrease the risk of adverse events.

***For pregnancy/risk to fetus (for women*):** We do not know whether the study agent is safe for a developing fetus or a nursing infant. You should not become pregnant or nurse an infant while you are in this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use a method of birth control that works well or you must not have intercourse. The investigator will talk to you about the types of birth control that are acceptable. You will have to use birth control or abstain from intercourse the whole time you are in this study. If you become pregnant during the research study, please tell the investigator and your doctor immediately.

For pregnancy/risk to fetus (for men): We do not know whether the study agent can damage sperm. You should not father a child while in this study. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method of birth control that works well or you must not have intercourse. The investigator will talk to you about the types of birth control that are acceptable. You will have to use birth control or abstain from intercourse the whole time you are in this study. If a female partner becomes pregnant during the research study, please tell the investigator and ask your partner to tell her doctor immediately.

For potential drug interactions: Potential drug interactions (prescription and non-prescription) when taken with the study agent are unknown at this time. The investigator will carefully review all of the drugs you are taking before giving you the study agent. If any other health care provider prescribes any new drug(s) for you while you are in this study, please tell the investigator before you take the new drug. You could also have that

provider talk to the investigator before prescribing the new drug. Do not take any new over-the-counter drugs while you are in this study unless you first check with the investigator.

There are data to show that people with multiple drug allergies may be at higher risk for anaphylaxis (a severe, whole body allergic reaction) following administration of the study agent.

For blood draw*:* We will draw blood from your arm. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, or an infection.

For MR: The magnetic resonance (MR) machine is a powerful magnet. This magnet may cause any metal in your body to move. If you know of any metal in your body, you will need to tell the investigator right away. Otherwise, there are no known risks of MR. Some individuals with claustrophobia (fear of closed spaces) may find the MR equipment too confining. In that case, you can request to be removed from the scanner and this will be done immediately. The MR scanner makes a loud beeping sound. You will be asked to wear protective earplugs during scanning.

The standard dye (gadolinium) that is injected into your IV for the scan is generally well tolerated. Some people feel dizzy or queasy or get a headache with it or notice a cold feeling near the injection site. There is a rare chance of having an allergic reaction to the dye that very rarely can be serious and life threatening. However, if you have kidney problems or your kidneys don't work, there is chance the dye could cause a disease known as Nephrogenic Systemic Fibrosis (NSF). NSF causes your skin to harden due to formation of too much scar tissue. This can lead to your joints not being able to move. In some people with NSF this scaring can affect the internal organs and will lead to death. Currently there is no treatment for NSF. Blood work will be done prior to the MR to check your kidney function. Multiple exposures to GBCA might increase the risk of developing nephrogenic systemic fibrosis, especially in patients with kidney problems.

The study coordinator will discuss with you if you need to have any medication to help you better tolerate the MR. The medication would be given to help you relax and is not intended to cause you to go to sleep or sedate you. These medications are often given prior to an MR and may include lorazepam (Ativan) or diazepam (Valium) or even an anti-histamine such as diphenhydramine (Benadryl). All of these medications will make you drowsy and for this reason you would need to have someone available after the MRI to drive you home. The risk of taking these types of medications is that they can cause problems with your breathing or heart function, for this reason, the MR technician will be talking with you throughout the MR and you will be visually monitored also.
Let your investigator know of any questions you have about possible side effects. You can ask the investigator questions about side effects at any time.

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BENEFITS

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

PRIVACY

WHO WILL SEE MY MEDICAL INFORMATION?

We will take steps to keep your personal information confidential, but we cannot guarantee total privacy.

We will create and collect health information about you as described in the WHY IS THIS STUDY BEING DONE and the WHAT TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study. We may release this information to others outside of OHSU who are involved in conducting or overseeing this research, including:

- The funder of this study, The Walter S. and Lucienne Driskill Foundation, and the funder's representatives
- The Food and Drug Administration (FDA)
- The Office of Human Research Protections (OHRP), a federal agency that oversees research in humans
- The National Cancer Institute (NCI)
- AMAG, the manufacturer of the study drug

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.

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When we send specimens or information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your specimens or information could be used and re-released without your permission.

We may continue to use and disclose your information as described above indefinitely. Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. Ask the investigator if you have questions about what study information you will be able to access, and when it will be available.

PARTICIPATION

CAN I STOP TAKING PART IN THIS STUDY?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the investigator know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the investigator continue to provide your medical information to the organization running the study.

The investigator will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
The investigator may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the IRB or FDA.

WHAT ARE MY RIGHTS IN THIS STUDY?

Your participation in this study is voluntary. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. If you have any questions, concerns, or complaints regarding this study now or in the future, contact the principal investigator listed at the beginning of the form.

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team
- You want to talk to someone besides the research team

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- You have questions about your rights as a research subject
- You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, seven days a week).

You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study.

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study.

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:
Knight Clinical Trials Office, ATTN: KCTO Manager
3303 SW Bond Ave, CH15R, Portland, OR 97239
trials@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already taken action based on your authorization.

Your health care provider may be one of the investigators of this research study and, as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your physician.

You will be told of any new information that might make you want to change your mind about continuing to be in the study.

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WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
You will not be billed for the cost of any procedures solely related to the study. This includes the MR scans without or with contrast agents (gadolinium and the study agent) and the blood tests to check your kidney function. You or your insurance company will be billed for the outpatient clinic visits which are medically related to your treatment. The screening for the study will always be done during a clinically indicated visit with your doctor and therefore will be billed to you or your insurance. You are not offered any payment for taking part in this study.

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?
If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact Dr. Edward Neuwelt at 503-494-5626.

If you are injured or harmed by the study agent, you will be treated. OHSU, the Walter S. and Lucienne Driskill Foundation and AMAG Pharmaceuticals, Inc. do not offer any financial compensation or payment for the cost of treatment if you are injured or harmed as a result of participating in this research. Therefore, any medical treatment you need may be billed to you or your insurance. However, you are not prevented from seeking to collect compensation for injury related to negligence on the part of those involved in the research. Oregon law (Oregon Tort Claims Act (ORS 30.260 through 30.300)) may limit the dollar amount that you may recover from OHSU or its caregivers and researchers for a claim relating to care or research at OHSU, and the time you have to bring a claim.

If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

WHAT IS COMMERCIAL DEVELOPMENT AND HOW DOES IT AFFECT ME?
Samples and information about you or obtained from you in this research may be used for commercial purposes, such as making a discovery that could, in the future, be patented or licensed to a company, which could result in a possible financial benefit to that company, OHSU, and its researchers. There are no plans to pay you if this happens. You will not have any property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your samples or information.

WHERE CAN I GET MORE INFORMATION?
You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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If you want more information about this study, ask your investigator.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to the investigator about any questions or concerns you have about this study or to report side effects or injuries. Outside of regular clinic hours, you can speak with the neuro-oncologist on-call. Refer to the beginning of this consent form for contact names and phone numbers.

SIGNATURE

MY SIGNATURE AGREEING TO TAKE PART IN THE MAIN STUDY

Your signature below indicates that you have read this entire form and that you agree to be in this study
We will give you a copy of this signed form.

OREGON HEALTH & SCIENCE UNIVERSITY
INSTITUTIONAL REVIEW BOARD
PHONE NUMBER (503) 494-7887
CONSENT/AUTHORIZATION FORM APPROVAL DATE

APR. 7, 2016

Do not sign this form after the expiration date of: APR. 06, 2017

Participant Printed Name	Participant Signature	Date

Person(s) Obtaining Consent Printed Name	Person(s) Obtaining Consent Signature	Date

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Use of an Interpreter: Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only. If the interpreter is affiliated with the study team, the signature of an impartial witness is also required.

Print name of interpreter: _____

Signature of interpreter: _____ Date: _____

An oral translation of this document was administered to the participant in _____ (state language) by an individual proficient in English and _____ (state language).