# Multinational Phase III Clinical Trial of the Safety and Efficacy of Gadobenate Dimeglumine for Contrast-Enhanced MR Neuroimaging in Children

**M. J. Kuhn[1], E. Cianciulli[2], C. Fonda[3], M. Pasowicz[4], and P-Y. Gao[5]**

[1]Radiology, Southern Illinois University School of Medicine, Springfield, IL, United States, [2]Radiology, "Santobono Pausillipon" Children's Hospital, Naples, Italy, [3]Radiodiagnostics Unit, Anna Meyer Pediatric Hospital, Florence, Italy, [4]Radiology, Krakow Hospital John Paul II, Krakow, Poland, [5]Radiology, Beijing Tian Tan Hospital, Beijing, China, People's Republic of

**Purpose:** To evaluate the safety and efficacy of the high-relaxivity contrast agent gadobenate dimeglumine (Gd-BOPTA or MultiHance) in children ages 2 to 17 years with known or highly suspected CNS disease (brain or spine using an open label, multicenter, phase-III study design.

**Methods:** 92 children (2–17 yrs) referred for cranial/spinal contrast-enhanced MRI were enrolled at 17 centers in USA, Europe, or China as part of an open-label clinical study. Enrollment was stratified by age (2–5, 6–10, and 11–17 yrs). Sedation was performed at the discretion of the treating physician. Each subject received 0.1 mmol/kg gadobenate dimeglumine (0.2 mL/kg) at a rate of ≤2 mL/s (manually or by power injector), followed by a saline flush. T1wSE, T2wFSE, and FLAIR sequences were performed predose, and with T1wSE sequence repeated at 3-10 minutes after contrast injection. Brain images were acquired in either axial or coronal projections, and spine images were acquired in either axial or sagittal projections. Safety monitoring included incidence of AEs, changes in vital signs and serial 12-lead electrocardiograms (ECGs), urinanalysis, basic metabolic panel and complete blood count. Pathologies studied include malignant and benign neoplasms (germ cell tumor, high grade glioma, medulloblastoma, PNET, pineal cyst, pilocytic astrocytoma, fibrous meningioma, neurofibromatosis, etc.); vascular malformations (AVM & aneurysms); and other conditions (demyelinating processes, hemangiomas, pseudotumors). Images were evaluated by 3 blinded readers for lesion enhancement, border delineation, and visualization of internal morphology. Lesion-to-brain ratio (LBR) and contrast-to-noise ratio (CNR) were calculated from regions or interest placed by the readers. All subjects were monitored for AE for 72 hrs and followed up at 30 days to determine final diagnosis.

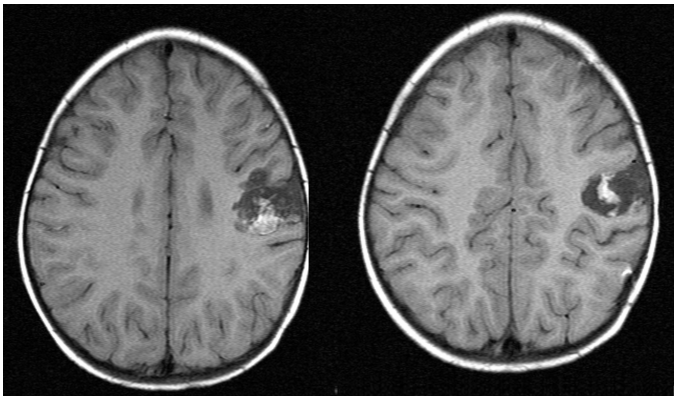

**Figure 1:** Biopsy proven primitive neuroectodermal tumor (PNET) of the left frontal lobe in a 4 year old girl

**Results:** 92 children (45 boys, 47 girls; mean age: 10.6 yrs [range: 2.0–17.8 yrs]) were enrolled and dosed with 89 children completing all safety evaluations (13 patients 2–5 yrs, 34 patients 6–10 yrs, and 45 patients were 11–17 yrs). The mean contrast dose was 8.4 mL (range: 2.0–22.8 mL). Diagnoses included: 28 (30.4%) nontumor, 60 (65.2%) tumor, and 4 (4.3%) normal parenchyma. Of the tumors, 43 (71.7%) were intra-axial and 17 (28.3%) were extra-axial; 25 (41.7%) were benign and 35 (58.3%) were malignant. A total of 9 AE were reported in 8 children (8.7%), including 3 AE in 2 patients considered possibly related to contrast injection (eyelid edema, abdominal discomfort, and vomiting). All AE were mild or moderate and resolved completely. Headache was reported in 2 patients with all other reported AE occurring once. No serious AE were reported. Modest vital sign changes (both increases and decreases) were recorded, but none of any clinical significance. No clinically meaningful changes in laboratory values or ECGs were observed.

Gadobenate dimeglumine provided clinically significant information which led to a greater understanding of the disease processes found on pre-dose images. In all children with enhancing lesions, gadobenate dimeglumine resulted in improved definition of disease extent, lesion border delineation, and visualization of lesion internal morphology. Readers blinded to clinical history judged that gadobenate dimeglumine provided additional diagnostic information over predose images in 83.7 - 96.7% of all patients. Quantitative assessments by the 3 readers showed gadobenate dimeglumine resulted in significantly greater mean lesion-to-brain ratio ($p<0.0001$) and contrast-to-noise ratio ($p<0.0016$). The mean changes across readers ranged from 0.9 to 1.1 for lesion-to-brain ratio and from 49.9 to 74.6 for contrast-to-noise ratio.

**Conclusions:** At a dose of 0.1 mmol/kg, gadobenate dimeglumine was found to be safe and efficacious for contrast-enhanced MRI of CNS lesions in children. The clinical advantages of greater signal intensity with gadobenate dimeglumine in children may include improved detection and/or diagnosis of small or poorly enhancing tumors and more precise definition of tumor borders.