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News Release

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Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS):

Bayer's Gadovist™ (Gadobutrol) at a Reduced Dose Demonstrates Non-Inferiority Compared to a Standard Dose of Gadoterate for CNS Imaging

- Phase IV LEADER-75 study showed 25 percent reduction in standard dose of gadobutrol is non-inferior to gadoterate full dose in improvement of visualization imaging parameters
- Diagnostic equivalence of the two contrast regimens was confirmed by a post-hoc analysis

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Berlin, October 1, 2021 – Bayer published today the results of its LEADER-75 (**L**ow**E**r **A**dministered **D**ose with high**E**r **R**elaxivity) study, demonstrating the clinical efficacy of a reduced dose of gadobutrol compared to a standard dose of gadoterate in patients undergoing a steady-state contrast-enhanced MRI of the CNS. The Phase IV, multicenter, controlled, cross-over study with corresponding blinded image evaluations met its primary endpoint, showing that a 75 percent dose of gadobutrol (0.075 mmol/kg) is non-inferior to a 100 percent dose of gadoterate (0.1 mmol/kg) for CNS imaging. The total number of lesions detected by mean reading was 301 for gadobutrol versus 291 for gadoterate. The study data was presented at this year's hybrid annual meeting of the European Society for Neuroradiology (ESNR), taking place in Geneva, Switzerland, from September 29 to October 3, 2021.

"The LEADER-75 study showed that a reduced dose of Gadovist™, given its high relaxivity, may achieve essentially equivalent diagnostic efficacy as a standard gadoterate dose in CNS imaging," said Dr. Benjamin P. Liu, Division of Neuroradiology, Northwestern Memorial Hospital, Chicago, Illinois, USA, and the LEADER-75 coordinating investigator.

Gadobutrol is an approved and commonly used macrocyclic gadolinium-based contrast agent (GBCA) for CNS imaging and several other indications. MRI provides a radiation-free, non-invasive means to obtain detailed images of the body. The administration of GBCAs during MRI helps physicians answer critical medical questions in the diagnosis and monitoring of disease. Currently, the standard dose for all marketed GBCAs, including gadobutrol and gadoterate, is 0.1 mmol/kg body weight.

“At Bayer, we are constantly striving to provide the best possible therapeutic and diagnostic options for physicians and patients,” said Prof. Dr. Olaf Weber, Head of Radiology Research and Development at Bayer. “LEADER-75 underlines our commitment to developing contrast agents that provide physicians with the image enhancement required for optimal diagnosis while continuing to explore opportunities to reduce the dose for patients as best as possible.”

About LEADER-75

The LEADER-75 study analysis included 141 male and female adult patients at least 18 years of age, of any ethnic group with known or highly suspected contrast enhancing CNS pathologies. All patients were referred for contrast-enhanced MRI of the CNS based on current clinical symptoms or on a previous imaging procedure. The primary objective of the study was to demonstrate the non-inferiority of a reduced dose of gadobutrol compared to a standard dose of gadoterate based on blinded readers’ evaluation of three primary variables: degree of lesion contrast enhancement, assessment of lesion border delineation, and internal morphology of lesions. In a post-hoc analysis, mean reading for these three primary variables differed by less than 1% between gadobutrol and gadoterate, supporting equivalence of all measures using a narrow ±5% margin ($p \leq .025$). Safety was evaluated by analyzing the frequency of treatment-emergent adverse events (TEAE). There were five patients (3.2%) with TEAEs, which were non-serious and mild. There were three patients (1.9%) with drug-related TEAEs – one on gadobutrol (paresthesia) and two on gadoterate (pruritus, urticaria).

The study results were featured online by the American Journal of Roentgenology (AJR) recently, and will be published in the print version of the journal in November 2021.

About Gadovist™ (gadobutrol)
Gadobutrol was first approved for contrast enhanced (CE) MRI of the central nervous system (CNS) in 1998 and is currently approved for several indications in more than 100 countries, including the European Union (EU), Australia, Canada, China, South Africa, Mexico, New Zealand, Turkey, Japan, and several Asian countries. Approved indications include CE MRI of the CNS, CE-MRA (2003), CE MRI of the liver and kidneys (2007), and CE MRI of all body regions (whole body, 2012) in the EU and other countries.

Gadobutrol injection was first approved in the U.S. in March 2011 for intravenous use in diagnostic magnetic resonance imaging in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system. It was further approved in the U.S. in 2014 for MRI of the breast to assess the presence and extent of malignant breast disease and for pediatric patients less than 2 years of age, including term neonates, to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system. In 2016, it was approved in the U.S. for use with magnetic resonance angiography (MRA) to evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including term neonates).

Gadovist™, also known as Gadovist™1.0 and Gadavist™ in other regions, is an aqueous solution of gadobutrol, a gadolinium (Gd)-based extracellular contrast agent for MRI with a macrocyclic structure.

Over 75 million gadobutrol-enhanced MRI procedures have been performed worldwide to date.

About Radiology at Bayer
Everyone deserves clear answers about their health, starting with an early and accurate diagnosis. As a true life-science company with a heritage of around 100 years in Radiology, Bayer is committed to providing excellence, from innovative products to high-quality services. The portfolio includes contrast media for computed tomography (CT), X-Ray, and magnetic resonance imaging (MRI), devices for their precise administration, informatics solutions to support efficient and optimal patient care, as well as acknowledged educational programs. In addition, Bayer is strongly committed to research and development and leverages artificial intelligence, thus further driving innovation in

medical imaging. Each of these offerings helps radiologists in their mission to deliver answers and a clear direction – from diagnosis to care.

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to drive sustainable development and generate a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2020, the Group employed around 100,000 people and had sales of 41.4 billion euros. R&D expenses before special items amounted to 4.9 billion euros. For more information, go to www.bayer.com.

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