Objective: The aim of this study was to provide a systematic safety analysis of gadobutrol after more than 29 million applications in clinical routine.

Materials and Methods: Forty-two clinical development phase II to IV studies on gadobutrol or comparator and the postmarketing safety surveillance database for gadobutrol (1998–2015) were analyzed. Adverse events (AEs) and drug-related AEs were evaluated in the clinical development database and spontaneous adverse drug reactions (ADRs) in the postmarketing database. Subgroup analyses were run on patients with special medical history and on patients of different age groups.

Results: In the clinical development studies, 6809 and 2184 patients received gadobutrol or comparators, respectively. The incidence of drug-related AEs was 3.5% for both groups. With the exception of nausea (0.7% related cases in both groups), all other drug-related AEs were 0.3% or less in both groups. Hypersensitivity reactions were sporadic (<0.1%). Patients with history of allergies to contrast agents experienced slightly more drug-related AEs. No differences were seen between age groups.

The overall reporting rate of ADRs from postmarketing surveillance was 0.05%. The most frequent ADRs were anaphylactoid/hypersensitivity reactions, nausea, vomiting, and dyspnea.

Conclusions: Gadobutrol is well tolerated and has a favorable safety profile for patients of all age groups.

Key Words: gadobutrol, GBCA, contrast agent, MRI, safety

Gadobutrol (Gadovist, Gadavist; Bayer Pharma AG, Leverkusen, Germany) is a gadolinium-based contrast agent (GBCA) for magnetic resonance imaging (MRI), approved for a broad range of indications in all age groups. In Europe and a number of other countries, gadobutrol is indicated for all body regions in adults and children including term newborns. However, the range of approved indications and the age range depend on the country-specific label.

Gadobutrol is a second-generation extracellular, macrocyclic, nonionic GBCA2,3 with particular physicochemical properties that enable the unique formulation of a 1 mol/L solution,2,4 twice the gadolinium concentration of other currently licensed extracellular GBCAs.

Thus, gadobutrol's 1 mol/L concentration halves the injection volume compared with 0.5 mol/L agents. In addition, Gadobutrol features a 20% to 30% higher relaxivity at 1.5 T compared with other macrocyclic agents.2,4,5 The macrocyclic structure of gadobutrol provides greater chelate stability and therefore a lower propensity of gadolinium release compared with linear GBCAs.5,6 In this context, it is important to understand that for macrocyclic GBCAs, thermodynamic stability (ie, equilibrium between chelate and ligand + free gadolinium) is an inadequate and irrelevant parameter to assess the stability. The only relevant parameter is kinetic inertness (ie, the dissociation half-life to reach the equilibrium).6,7 It can only be measured under extreme conditions such as pH 1, and the dissociation half-lives have been extrapolated from these measurements to pH 7.4.7 As a result, at physiological pH, all macrocyclic GBCAs—also irrespective of their ionicity—show half-lives exceeding 1000 years,7 which by far exceeds the elimination time even in patients with severe renal impairment of approximately 15 days. The stability of GBCAs is clinically important because the release of gadolinium ions has been associated with the development of nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment.8,9 In view of these characteristics, gadobutrol has been placed in the lowest risk category for development of NSF.10–12

The recommended standard dose of gadobutrol for intravenous injection is 0.1 mmol/kg body weight (bw), with doses up to 0.3 mmol/kg bw approved in Europe and some other countries for specific indications in adults. At these doses, the efficacy and safety of gadobutrol have been demonstrated in numerous clinical studies in adults and children, including term newborns.13–17

Gadobutrol was first introduced in Switzerland in February 1998. Through December 31, 2015, more than 29.6 million patients worldwide are estimated to have received gadobutrol. While monitoring safety continuously, passing the 29 million landmark was the trigger for this comprehensive review of gadobutrol's safety data.

Data Sources
This comprehensive retrospective safety analysis was based on 2 data sets: (1) an integrated safety analysis database of 42 clinical development phase II to IV studies and (2) the global postmarketing surveillance database for gadobutrol.

Clinical Development Phase II to IV Studies
The 42 interventional studies, conducted globally between 1993 and 2014, encompassed 13 phase II studies, 27 phase III studies (including 2 phase I/III studies in pediatric population 0–18 years), and 2 phase IV studies. Twenty-three clinical phase II to IV were single-arm gadobutrol studies, 13 had a parallel group design with either different gadobutrol doses or gadobutrol and a comparator contrast agent, and 6 were crossover studies with either different gadobutrol doses or gadobutrol and a comparator contrast agent. Comparators were either gadopentetate dimeglumine (Gd-DTPA, Magnevist), gadodiamide (Omniscan), gadoversetamide (OptiMark), gadoteridol (ProHance), or gadoterate meglumine (Gd-DOTA, Dotarem).
Most studies were conducted for MRI of the central nervous system (CNS). Other studies were conducted for the indications of MR angiography (MRA) (the second most common) as well as MRI of the liver, kidney, breasts, and various other body regions.

All clinical studies were conducted in accordance with International Conference on Harmonization Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed.

The global postmarketing surveillance database is run by the Bayer HealthCare Global Pharmacovigilance Department. This department receives reports on adverse drug reactions (ADRs) from worldwide sources, not only from health care professionals (physicians, pharmacists, nurses) but also from scientific publications, regulatory authorities, and patients or lay persons. During the period from the first marketing authorization in Switzerland on February 26, 1998, through December 31, 2015, nearly 30 million patients worldwide are estimated to have received gadobutrol.

### Study Population

The study population of the 42 clinical phase II to IV studies consisted of patients of all ages (term newborns up to patients older than 90 years) with a clinical need for various diagnostic contrast-enhanced MRI. Special attention was paid to patients with specific risk factors, for example, renal impairment, reduced liver function, cardiovascular disorders, general history of allergies, and specific history of allergies to contrast agents. Two studies recruited children aged 0 to 18 years. All patients (or their legal representatives) gave written informed consent before the start of the study.

No selection criteria were applied for patients for whom ADRs were reported to the Pharmacovigilance Department.

### Treatments

In the 42 clinical development phase II to IV studies, a total of 6809 patients received gadobutrol, and 2184 received one of the following comparators: Gd-DTPA (n = 1097), gadodiamide (n = 150), gadoversetamide (n = 227), gadoteridol (n = 555), and Gd-DOTA (n = 155). All contrast agents were administered by a single intravenous bolus injection followed by a saline chaser.

Gadobutrol was administered at a dose range from 0.01 mmol/kg to 0.51 mmol/kg bw. Most subjects (n = 4765) received the standard dose of 0.1 mmol/kg bw. Two hundred ninety-two subjects received a dose between 0.01 and less than 0.09 mmol/kg, and 47 patients received 0.31 to 0.51 mmol/kg bw, a dose above the approved dose. The dose for comparators was mainly 0.1 mmol/kg bw.

### Study Procedures

In all clinical phase II–IV studies, demographic data and medical history (in particular history of renal, liver, cardiovascular diseases, and allergies) were recorded. Once contrast-enhanced MRI was performed, patients were asked about their well-being in an unsolicited way to gather information about adverse events (AEs). The follow-up period lasted from just the examination day up to 72 hours.

### Target Variables

The key target variables of this analysis were the number of patients with and the characteristics of AEs, drug-related AEs, and serious AEs for the clinical phase II to IV studies and ADRs for the postmarketing surveillance part. All events were coded using MedDRA version 17.0. An AE was defined as any illness, sign or symptom, or unfavorable change in the clinical status that had appeared or worsened after study start, whether or not it was considered to be related to contrast agent administration. All AEs were evaluated for seriousness and potential relationship to contrast agent administration by experienced health care professionals in each institution. Drug-related AEs comprised the categories “possibly,” “probably,” and “definitely” related to contrast agent administration. A serious AE was defined as any AE that (1) resulted in death, (2) was life-threatening, (3) required subject hospitalization or prolongation of existing hospitalization, (4) resulted in a persistent or significant disability/incapacity, (5) resulted in a congenital anomaly/birth defect, or (6) was considered an otherwise medically significant event.

### Postmarketing Surveillance

In the postmarketing surveillance database, all AE reports received by the company (drug-related or unrelated) and reports attributed to the product derived from the scientific literature are recorded. The global pharmacovigilance database also contains serious events occurring in clinical trials and from other studies. For regulatory and reporting purposes, a causal association is assumed for individual spontaneous reports of ADRs. However, these reports are assessed individually and in aggregate for causality by the Pharmacovigilance Department of Bayer HealthCare. During this process, the temporal relationship of the AE to drug administration, the known pharmacological properties of the product, confounding factors (eg, patient’s medical history and concurrent conditions, concomitant medications), the epidemiology of the disease state and the reported event, possible reporting biases, and previous experience with the product and comparators are taken into account.18

### Statistics

All patients who received at least 1 dose of gadobutrol or comparator were included in this safety analysis. Subjects who got multiple doses within less than 1 hour, the doses were summed up and counted once. Patients in crossover studies with different contrast agents were included only once per comparator.

#### TABLE 1. Demographic Data of Study Population of Clinical Studies Phase II–IV

| No. Patients, n (%) |
|---------------------|
| **Gadobutrol**      |
| 6809 (100)          |
| **Comparators**     |
| 2184 (100)          |

| Sex               | Male | 3444 (50.6) | 1140 (52.2) |
|--------------------|------|------------|-------------|
| Female             | 3365 (49.4) | 1044 (47.8) |
| Age, y            |      |            |             |
| Mean ± SD         | 55.6 ± 16.4 | 55.1 ± 14.8 |
| Min, Max          | 7, 93 y   | 18 y, 89 y  |
| <18               | 184 (2.7)  | 0           |
| ≥65               | 4383 (64.4) | 1549 (70.9) |
| Weight, kg        | 69.4 ± 17.3 | 69.2 ± 16.6 |
| Mean ± SD         | 2.8, 145.2 | 30.9, 145.0 |
| Min, Max          |        |             |
| Other             | 177 (2.6)  | 94 (4.3)    |
| Region            |        |             |
| Europe            | 3812 (56.0) | 944 (43.2)  |
| United States/Canada | 562 (8.3) | 194 (8.9)   |
| South/Central America | 446 (6.6) | 184 (8.4)   |
| Asia              | 1961 (28.8) | 853 (39.1)  |
| Australia         | 28 (0.4)   | 9 (0.4)     |

*Gadopentetate dimeglumine (n = 1097), gadodiamide (n = 150), gadoversetamide (n = 227), gadoteridol (n = 555), and gadoterate meglumine (n = 155). SD indicates standard deviation; Min, minimum; Max, maximum.
TABLE 2. Incidence of AEs, Clinical Studies Phase II–IV

| No. Patients, n (%) | Gadobutrol 6809 (100) | Comparators* 2184 (100) |
|---------------------|------------------------|--------------------------|
| AEs total           | 663 (9.7)              | 216 (9.9)                |
| Drug-Related        | 241 (3.5)              | 77 (3.5)                 |
| SAEs total          | 20 (0.3)               | 4 (0.2)                  |
| Drug-Related        | 1 (<0.1)               | 0 (0.0)                  |
| Death               | 1 (<0.1)               | 1 (<0.1)                 |
| Drug-Related        | 0 (0.0)                | 0 (0.0)                  |

Most frequent AEs

- Headache: 100 (1.5) total, 21 (0.3) drug-related
- Nausea: 75 (1.1) total, 48 (0.7) drug-related
- Dizziness: 34 (0.5) total, 9 (0.1) drug-related
- Injection site reactions: 30 (0.4) total, 18 (0.3) drug-related
- Feeling hot: 26 (0.4) total, 22 (0.3) drug-related
- Vomiting: 26 (0.4) total, 9 (0.1) drug-related
- Dysgeusia: 24 (0.4) total, 23 (0.3) drug-related
- Rash: 19 (0.3) total, 14 (0.2) drug-related
- Erythema: 11 (0.2) total, 4 (<0.1) drug-related
- Dyspnea: 11 (0.2) total, 4 (<0.1) drug-related
- Pruritus: 10 (0.1) total, 7 (0.1) drug-related
- Paresthesia: 8 (0.1) total, 5 (<0.1) drug-related
- Hypersensitivity: 2 (<0.1) total, 2 (<0.1) drug-related

*Gadopentetate dimeglumine (n = 1097), gadodiamide (n = 150), gadoversatamide (n = 227), gadoteridol (n = 555), and gadoterate meglumine (n = 155).

AE indicates adverse event; SAE, serious adverse event.

TABLE 3. Incidence of AEs by MRI Indication of Clinical Studies Phase II–IV

| Indication | No. Patients (100%) | Total AEs, n (%) | Drug-Related AEs, n (%) | No. Patients (100%) | Total AEs, n (%) | Drug-Related AEs, n (%) |
|------------|---------------------|-----------------|------------------------|---------------------|-----------------|------------------------|
| CNS        | 2671                | 319 (11.9)      | 112 (4.2)              | 1316*               | 163 (12.4)      | 60 (4.6)               |
| MRA        | 1548                | 135 (8.7)       | 57 (3.7)               | 81†                 | 7 (8.6)         | 4 (4.9)                |
| Body       | 2408                | 155 (6.4)       | 63 (2.6)               | 787†                | 46 (5.8)        | 13 (1.7)               |
| Children   | 182                 | 54 (29.7)       | 9 (4.9)                |                     |                 |                        |

*Gadopentetate dimeglumine (n = 229), gadodiamide (n = 150), gadoversatamide (n = 227), gadoteridol (n = 555), and gadoterate meglumine (n = 155).
†Gadopentetate dimeglumine.

AE indicates adverse event; MRI, magnetic resonance imaging; CNS, central nervous system; MRA, magnetic resonance angiography.

RESULTS

Clinical Development Phase II to IV Studies

A total of 6809 and 2184 patients were included in the database for gadobutrol and comparators, respectively. The demographic data were very similar with the exception that patients younger than 18 years were only included in the gadobutrol group (Table 1).

The incidence of drug-related AEs was 3.5% in the gadobutrol and the comparator group. Serious AEs (including deaths) were similarly low (<0.1%) in both groups. For gadobutrol, the most frequent drug-related AEs were headache, nausea, dizziness, injection site reactions, feeling hot, and dysgeusia. With the exception of nausea, 0.7% drug-related cases in both groups, all other drug-related AEs were 0.3% or less. Hypersensitivity reactions were sporadic, that is, less than 0.1% (Table 2).

The most frequent indication for MRI was CNS imaging, followed by MRA and all other single body regions. Drug-related AEs were recorded in 4.2% and 4.6% for CNS and 3.7% and 4.9% for MRA in the gadobutrol and the comparator group, respectively. In 9 of 182 children (4.9%), drug-related AEs were reported (Table 3).

There were no remarkable differences in the incidence of drug-related AEs between patients with or without renal impairment, elevated liver enzymes, or cardiovascular diseases. Patients with history of allergies in general—or specifically allergies to contrast agents—experienced slightly more drug-related AEs. Within the small number of 25 patients with history of allergies to contrast agents, 3 (12%) showed a drug-related AE (Table 4).

The incidence of drug-related AEs by age group is shown in Figure 1. The rates of 4.9%, 4.0%, and 2.6% for the age groups younger than 18 years, 18 to 65 years, and 65 years or older, respectively, were not statistically significantly different.

Postmarketing Surveillance

Patient exposure to gadobutrol (per year) increased steadily from 416 patients in 1999, the year after market introduction, to more than 5.7 million in 2015. The ADR reporting rate in the postmarketing surveillance was highest in the years 2001 and 2002, reaching 0.09%. Lowest rates of 0.04% were seen in 2003, 2006, and 2013. The average from 1999 to 2014 was 0.05% (Fig. 2).

Through December 31, 2015, approximately 6000 AE reports have been received by the Pharmacovigilance Department, containing nearly 15,000 AEs. Most of these (approximately 75%) are nonserious. The reports were in males (31%), females (56%), and patients of unknown sex (13%) ranging in age from younger than 1 year to 94 years. There is no discernible difference in the nature and intensity of events by age group. The reports came from 61 countries, with the highest numbers of reports received from the United States (24%), Germany (16%), Canada (12%), France (7%), Great Britain (6%), and Italy (5%). The most frequently reported ADRs in the postmarketing surveillance database were anaphylactoid/hypersensitivity reactions featuring a reporting rate of 0.019%. As with most other GBCAs, fatal anaphylactoid reactions are exceedingly rare. Less frequent were nausea, vomiting, and dyspnea with rates of 0.005%, 0.004%, and 0.002%, respectively. All other single ADRs were analyzed by period. An analysis by age was performed, looking at 3 age brackets as follows: younger than 18 years, 18 to 65 years, and 65 years or older.

All variables were analyzed by descriptive statistical methods. Adverse event incidence rates were calculated by dividing the number of patients reporting 1 specific AE by the number of patients exposed times 100 to receive percentages. The same was done for the ADR reporting rates in the postmarketing surveillance part. All analyses were performed post hoc. The statistical evaluation was performed using the software package SAS release 9.2 for UNIX (SAS Institute Inc, Cary, NC).

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Dosing was not a factor in the reports; where the information was provided, most patients appeared to be dosed appropriately.

As of December 2015, a total of 12 reports of NSF or NSF-like symptoms in patients who reportedly were administered gadobutrol have been received. Four of these are “single-agent reports”; that is, in which patients reportedly received only gadobutrol, 3 of the 4 single-agent reports were derived from literature.19,20 The other 8 reports are confounded by the administration of other GBCAs (“multiple-agent reports”). In assessing these reports, Bayer utilizes the criteria developed by Girardi et al21 and applies the criteria very conservatively. Not having direct access to the patient, the patient’s past contrast use, or even to the biopsy report in most cases, thus often having to rely on minimal information, Bayer gives the report the highest possible score based on the information available. Using this conservative “worst-case scenario” approach, 3 of the 4 single-agent reports meet the criteria for being diagnostic of or consistent with NSF,21 and a possible association with gadobutrol cannot be excluded. The fourth single-agent report contained information that was insufficient for evaluation. All 3 patients were multimorbid. The largest single dose administered to any patient with reported NSF was 0.49 mmol/kg bw. Onset of NSF-like symptoms in these 3 reports occurred in 2006, 2008, and 2009. Onset latency ranged from 14 days to 18 months.

**DISCUSSION**

This publication is a systematic analysis of safety data on gadobutrol reported in 42 prospective clinical phase II to IV studies performed all over the world complemented by reports from 17 years of postmarketing surveillance. The rate and quality of AEs, drug-related AEs, and ADRs was consistent with those of other GBCAs.14,22-24 The findings did not give rise to any specific safety concerns regarding gadobutrol.

**Clinical Development Phase II to IV Studies**

The incidence of drug-related AEs was 3.5% in the gadobutrol and the comparator group. However, the comparator group, consisting of 5 agents, was not as homogeneous as it appears. The incidence rates for drug-related AEs of the comparators varied between 1.9% and 7.4%. We did not present these data because the single comparator groups were markedly smaller and the number of patients varied between n = 150 and n = 1097. Unfortunately, a direct comparison with the pertinent literature is difficult as there is no published overall safety

![FIGURE 1. Incidence of drug-related AEs by age group, clinical studies phase II to IV (percent and 95% confidence intervals*)](image)
evaluation of phase II to IV studies for other GBCAs. However, some data from phase III and IV studies are available. A recent phase III study by Gutierrez et al25 compared gadobutrol with gadoteridol and recorded rates for treatment-related AEs of 10.0% and 9.7%, respectively. When focusing on phase IV studies, data for gadobutrol, gadoterate meglumine, and gadobenate dimeglumine are available. Forsting et al28 reported on 14,299 patients on gadobutrol a rate of drug-related AEs of 0.55%, Ishiguchi and Takahashi26 on 3,444 patients on gadoterate a rate of drug-related AEs of 0.93%, and Fakhri et al27 on 132,252 administrations of gadobenate a rate of drug-related AEs of 0.18%.

The most frequent drug-related AEs were headache, nausea, and dizziness. This is in line with other publications, although for other GBCAs, some different AEs were also in the group of most frequent reactions, for example, hives and dyspnea, vomiting and hives, vomiting and urticaria, and vomiting and feeling hot.26

No increase in the incidence of drug-related AEs was seen in special risk populations, such as patients with renal impairment, elevated liver enzymes, or cardiovascular diseases. In addition, Maurer et al28 did not report a higher risk for developing drug-related AEs in patients with renal failure, liver dysfunction, or β-blocker in their study of 84,621 patients on gadoteric acid.28 In contrast, patients with liver and kidney disorders showed a significantly higher (P < 0.0001) rate of experiencing drug-related AEs in the gadoterate study by Ishiguchi and Takahashi.26 In a large multinational and multiethnic study on 37,788 patients who got contrast-enhanced cardiovascular MR, Bruder et al29 investigated the safety of different GBCAs in this special risk population. Data were captured from 7-day old newborns to elderly up to 93 years; however, only for gadobutrol but not for comparators. The incidence of drug-related AEs in children younger than 18 years was 4.9%, not statistically significantly different from the other age groups. Hahn et al15 evaluated 138 children 2 to 17 years (2–6 years, n = 46; 7–11 years, n = 47; 12–17 years, n = 48) on gadobutrol and reported 8 children (5.8%) with drug-related AEs. Kunze et al16 analyzed findings on newborns and toddlers younger than 2 years and found 1 (2.8%) of 44 case of drug-related AE. In an observational study also in children younger than 2 years, Bhargava et al17 did not find any drug-related AE in 60 patients while Glutig et al18 reported a rate of drug-related AEs of 0.5% in 1,142 children younger than 18 years in another observational study. For gadobenate dimeglumine, no drug-related AEs were identified in a retrospective study of 200 children 4 days to 15 years of age.19 The other end of the age range was evaluated by Endrikat et al who used 3 databases (clinical trials, postmarketing surveillance, and pharmacovigilance reports) to investigate the impact of age on safety in elderly patients. They conclude that gadobutrol has a favorable safety profile also in patients aged 65 years or older.20

### Postmarketing Surveillance

While annual patient exposure to gadobutrol increased steadily from 416 patients in 1999 to more than 5.7 million in 2015, the postmarketing surveillance ADR reporting rate averaged approximately 0.05%. As the highest rates were documented in the early years in 2001–2002, a trend toward lower rates over time could be postulated. This is in line with the Weber effect, that is, increasing reporting rates toward the end of the second calendar year after market introduction followed by a decline.33 The spikes in between might be caused by the sequential market introduction of gadobutrol over the whole world, for example, approval in 1998 in Switzerland, 1999 in Canada, 2000 in Germany, 2009 in China, 2011 in the United States, and 2015 in Japan. Thus, the initial increase and subsequent decrease is not as clear as described by Knopp et al,34 who evaluated the safety of Gd-DTPA after 45 million applications. They reported an initial rate of 0.016%, declining to 0.002% after 14 years.34 Likewise, Matsumura et al,35 also looking into Gd-DTPA over 25 years, recorded a decline from 0.021% to 0.014%. Although Gd-DTPA was the first MR contrast on the market (1988), the average AE reporting rate is lower than the 0.05%, reported here for gadobutrol. Matsumura et al36 recorded an AE rate of 0.0144%. This might be caused by an increasing vigilance and preparedness of health care professionals to report safety results to authorities. This hypothesis is supported by figures for gadobenate dimeglumine (Gd-BOPTA), introduced in 1998, approximately at the same time as gadobutrol (1999). Gd-BOPTA featured an overall ADR reporting rate of 0.05%,36 nearly similar to gadobutrol. Gadobutrol’s overall ADR spectrum was comparable with Gd-DTPA35 and Gd-BOPTA.34

Finally, pharmacovigilance databases generally yield lower ADR rates compared with results from clinical development phase II to IV studies, as reporting is voluntary, and the motivation to report depends on a number of factors.

As of Dec 2015, pharmacovigilance has received 3 single-agent reports consistent with the clinicohistopathological definition of NSF. This classification was rigorously performed by Bayer scientists after the most stringent and conservative approach according to the criteria by Girardi21; that is, the assessment/classification represents a worst-case scenario. This needs to be considered when data and numbers regarding NSF reports from different sources are compared as the interpretation and the use of a categorical score when assessing non-categorical biological parameters leaves some room for interpretation and may introduce variance. Bayer continues to follow a policy of total

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**FIGURE 2.** ADR reporting rate and patient exposure by year, 1999 to December 31, 2015.
### TABLE 5. ADRs From Postmarketing Surveillance (Exposure n = >29.6 million); Cutoff at 25 Events (≥0.0001%)

| ADR                                      | No. Events | Reporting Rate, % |
|------------------------------------------|------------|-------------------|
| Anaphylactoid/hypersensitivity reactions*| 5811       | 0.019             |
| Nausea/retching                          | 1626       | 0.005             |
| Vomiting                                 | 1208       | 0.004             |
| Dyspnea                                  | 542        | 0.002             |
| Throat irritation                        | 360        | 0.001             |
| Cough                                    | 252        | 0.0007            |
| Paresthesia                              | 174        | 0.0006            |
| Feeling hot                              | 168        | 0.0006            |
| Dizziness                                | 167        | 0.0006            |
| Malaise                                  | 158        | 0.0005            |
| Chest pain                               | 148        | 0.0005            |
| Sweating                                 | 141        | 0.0005            |
| Loss of consciousness                    | 137        | 0.0005            |
| Flushing                                 | 123        | 0.0004            |
| Tachycardia/heart rate increased         | 116        | 0.0004            |
| Headache                                 | 111        | 0.0004            |
| Syncope                                  | 87         | 0.0003            |
| Injection site reaction                  | 86         | 0.0003            |
| Hypoesthesia                             | 85         | 0.0003            |
| Feeling cold/chills                      | 77         | 0.0003            |
| Upper respiratory congestion/irritation  | 77         | 0.0003            |
| Abdominal pain                           | 67         | 0.0002            |
| Convulsions/seizures                     | 61         | 0.0002            |
| Edema/localized edema                    | 61         | 0.0002            |
| Burning sensation                        | 56         | 0.0002            |
| Lacrimation increased                    | 56         | 0.0002            |
| Hypertension/blood pressure increased    | 51         | 0.0002            |
| Rash pustular                            | 51         | 0.0002            |
| Difficulty swallowing                    | 49         | 0.0002            |
| Tremor                                   | 46         | 0.0002            |
| Medication error                         | 44         | 0.0001            |
| Pallor                                   | 44         | 0.0001            |
| Peripheral edema                         | 44         | 0.0001            |
| Lack of drug effect                      | 42         | 0.0001            |
| AE/ADR NOS                               | 41         | 0.0001            |
| Cardiac arrest                           | 41         | 0.0001            |
| Skin reaction                            | 39         | 0.0001            |
| Feeling abnormal                         | 36         | 0.0001            |
| Pain in extremity                        | 36         | 0.0001            |
| Taste disorders/dysgeusia                | 35         | 0.0001            |
| Vertigo                                  | 33         | 0.0001            |
| Cardiac disorder                         | 32         | 0.0001            |
| Asthenia                                 | 31         | 0.0001            |
| Dysphonia/hoarseness                     | 31         | 0.0001            |
| Pain/discomfort                          | 31         | 0.0001            |
| Sensation of foreign body                | 31         | 0.0001            |
| Respiratory arrest                       | 30         | 0.0001            |
| Pulmonary edema                          | 29         | 0.0001            |
| Cyanosis                                 | 28         | 0.0001            |
| Bradycardia/heart rate decreased         | 27         | 0.0001            |
| Increased salivation                     | 27         | 0.0001            |
| Dermatitis                               | 26         | 0.0001            |

### TABLE 5. (Continued)

| ADR                                      | No. Events | Reporting Rate, % |
|------------------------------------------|------------|-------------------|
| Hypoxia/oxygen saturation decreased      | 26         | 0.0001            |
| Speech disorders                         | 26         | 0.0001            |

*Angioedema, anaphylactic/anaphylactoid reaction/shock, hypotension, bronchospasm, conjunctivitis, hypersensitivity reaction, erythema, rash, pruritus, laryngeal edema, sneezing, and urticaria.

ADR indicates adverse drug reaction; AE, adverse event; NOS, not otherwise specified.

A safety review as presented with this study has mainly 2 limitations: (1) the comparator groups of the phase II to IV clinical studies are too small for a reasonable comparison, so that only pooling these agents allowed for a meaningful assessment; and (2) data on newborns and children are only available for gadobutrol because no head-to-head studies were carried out on safety in this vulnerable population.

There are many limitations to postmarketing reporting, including underreporting (more seen for mild and delayed contrast media reactions than for very severe acute contrast reactions) and differences in reporting behavior, which have been described previously.40 For these reasons, data from postmarketing surveillance can only be represented by reporting rate and not by incidence.

### CONCLUSIONS

Gadobutrol is a well-tolerated macrocyclic GBCA with higher relaxivity and higher concentration, which has a good safety profile as shown from results of 42 clinical phase II to IV studies and postmarketing surveillance over 17 years and more than 29 million applications.

### ACKNOWLEDGMENTS

The authors thank all investigators and patients who participated in the study program.
