Presence of Gadolinium (Gd) in the Brain and Body

Presentation to the

Medical Imaging Drugs Advisory Committee

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Background: Bayer Experience with MRI Contrast

- Estimated 450 million doses with gadolinium based contrast agents (GBCAs) worldwide have been administered to patients since the introduction of the first GBCA by Bayer in 1988

Bayer´s GBCA	FDA Approval	Administrations*
Magnevist® (gadopentetate dimeglumine) 1st multi-purpose linear GBCA	1988	> 148.8 million
Eovist® (gadoxetate disodium) 1st liver specific linear GBCA	2008	> 4.3 million
Gadavist® (gadobutrol) 1st high relaxivity macrocyclic GBCA	2011	> 40.8 million
Total		**~ 194 million**

*Worldwide

- Clear clinical benefit: GBCAs provide crucial medical information

Background: Safety Profile of GBCAs
(>450 Million Patient Administrations)

- Overall, GBCAs demonstrate a favorable safety experience and very low reporting rate of adverse events (AEs)
  - The most frequently reported reaction for all GBCAs is hypersensitivity
- GBCA label updates have effectively addressed past safety observations partially related to stability:
  - Interference with colorimetric calcium testing (2003)
  - Nephrogenic systemic fibrosis (NSF) (2006)
    - In patients with severe renal impairment only
- Latest observations of increased signal intensity (SI) / presence of Gd in the brain in patients with normal renal function (2013)
  - Clinical significance unknown

Signal Intensity Studies Demonstrate Differences Based on Chemical Structure

- 39 signal intensity (SI) studies demonstrate differences based on chemical structure, associated with different molecule stabilities of GBCAs:
  - **Multi-purpose linear GBCAs:** SI increase in the brain after multiple (generally ≥5) injections (Magnevist, MultiHance®, Omniscan™); and a dose dependent SI increase (after standard dose of 0.1 mmol Gd/kg BW)
    - All multi-purpose linear agents behave similarly at ≥5 injections
  - **Liver-specific linear GBCA:** SI increase visible only after a significantly higher number (>20) of administrations (Eovist)
    - 1/4 of the standard dose, most stable linear agent, 50% hepatobiliary excretion
  - **Macrocyclic GBCAs:** No visual proof of a SI increase in the brain even after a high number (>50) of injections (Dotarem®, Gadavist, ProHance®)
- No clinical effects associated with these findings have been confirmed

Traces of Gd Can Be Found in Bone and Brain

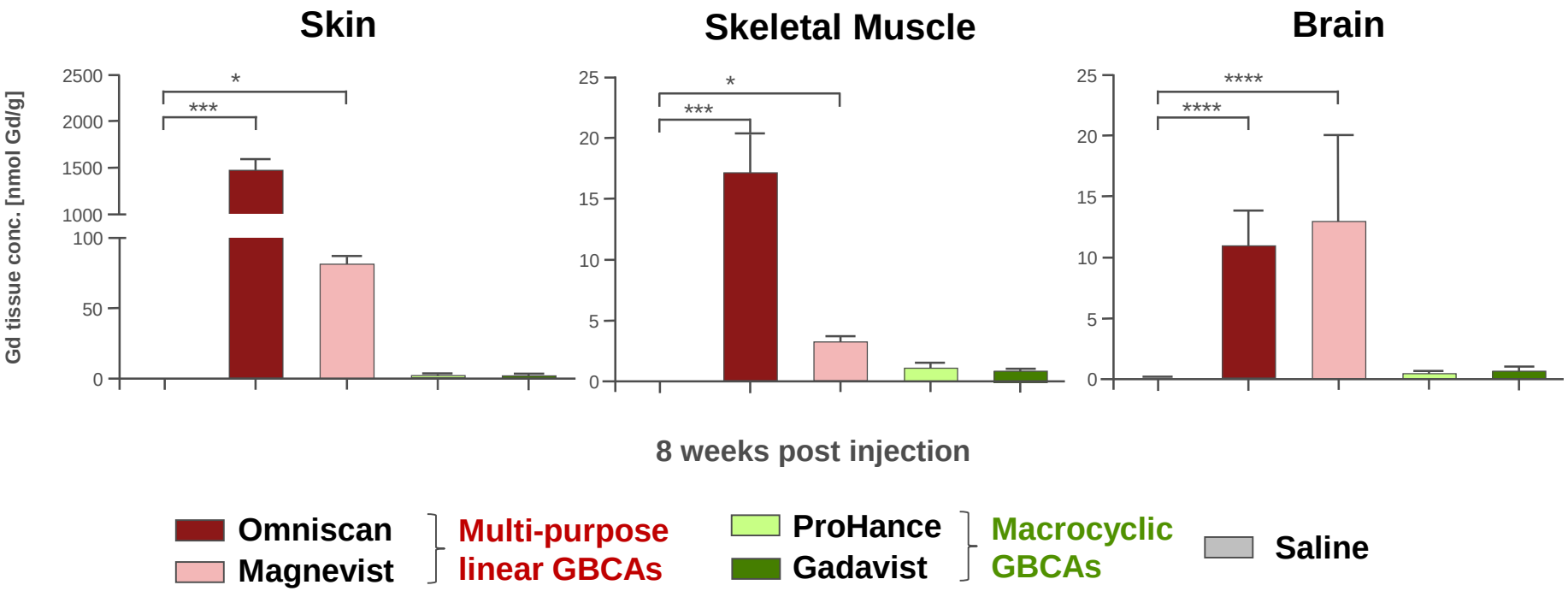
- Traces of Gd can be found in bone and brain for both linear and macrocyclic GBCAs, however quantitative comparisons are limited by methodological constraints
  - 4 tissue studies - Gd in the bone and skin with macrocyclic & linear GBCAs
    - *Gibby et al. (2004) / Darrah et al. (2009):* Gd measured from patients receiving Omniscan or ProHance
    - *Murata et al. (2016):* Gd concentrations in the bone were 23 times (median) higher than in the brain
    - *Roberts et al. (2016):* Gd measured in skin (case report)
  - 6 post mortem studies - traces of Gd in the brain
    - 2/6 studies indicated traces of Gd in the brain from patients receiving macrocyclic GBCAs *(Kanda et al. 2015, Murata et al. 2016)*
    - 6/6 studies showed Gd after linear GBCAs
- The (trace) concentration of Gd measured in the brain is not enough to explain the observed SI increase

Bayer´s Extensive Non-clinical Research

Reproduction of imaging findings? Jost et al., 2016 Investigative Radiology	Confirmed
How do GBCAs enter the brain? Jost et al., 2016 European Radiology	Blood-CSF Barrier
Histopathological changes in the brain? Lohrke et al., 2017 Investigative Radiology	No tissue changes
Molecular structure of Gd in the brain? Frenzel et al., 2017 Investigative Radiology	Macromolecular formation: Linear GBCAs only
Kinetic - elimination or accumulation?	Elimination: Macrocyclic GBCAs only
Does Gd presence in the brain influence neurological capabilities or behavior of animals?	Studies ongoing

Gd Presence in the Rat Brain and Body

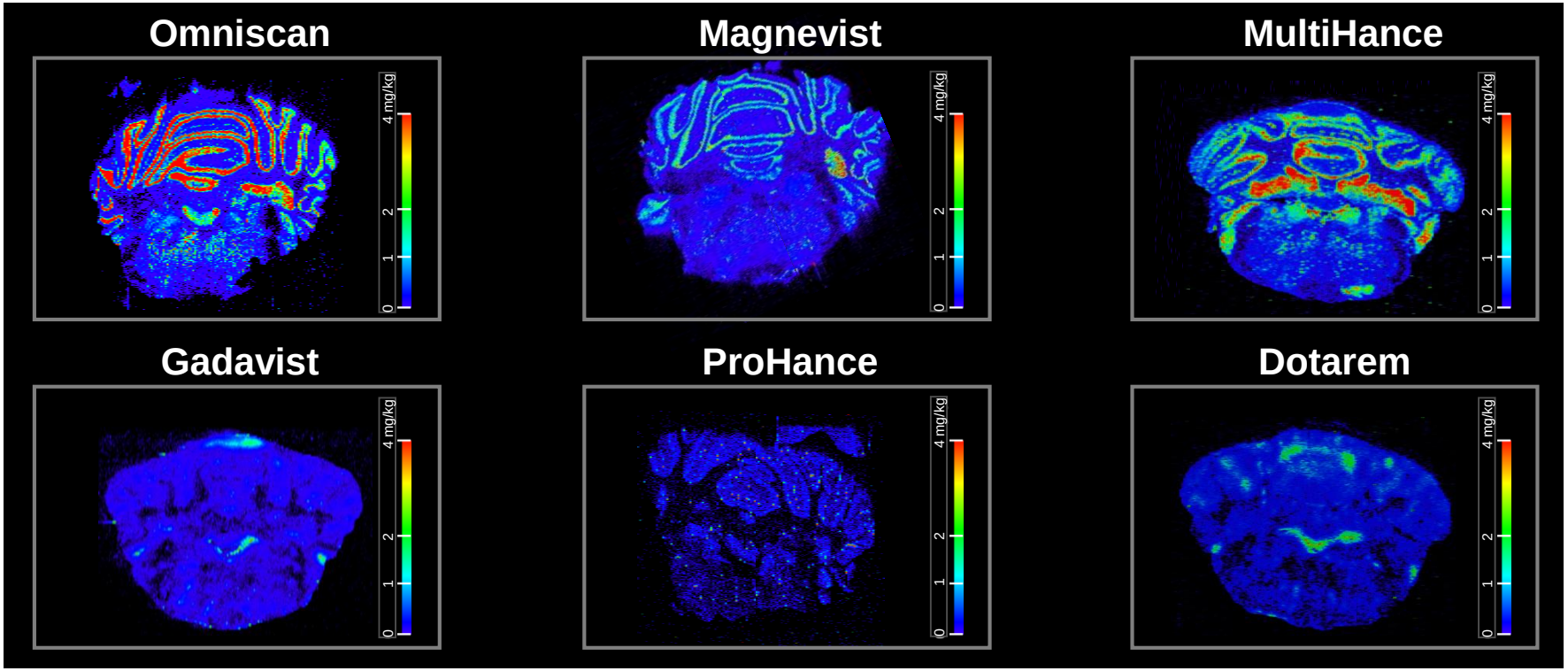
- Gd concentrations in the brain are higher for linear than macrocyclic GBCAs
- Gd can be detected in other organ systems
  - Gd concentration in skin is about factor 100 higher compared to brain and muscle



J. Lohrke, A.-L. Frisk, T. Frenzel, L. Schöckel, M. Rosenbruch, G. Jost, A. Küppers, H. Pietsch Investigative Radiology 2017 Mar 20.

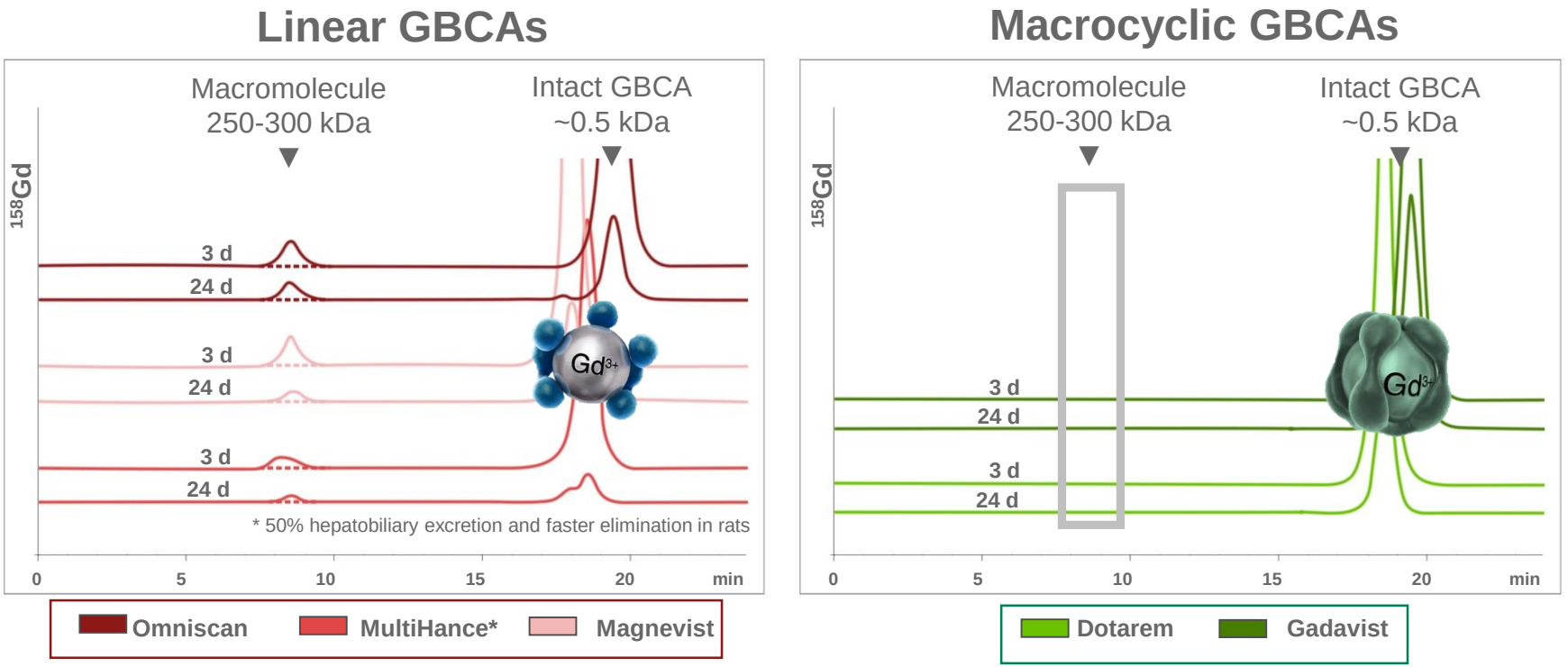
Localization of Gd in the Rat Brain Seen with Linear Agents Only

- All multi-purpose linear GBCAs show
  - Comparable concentrations of Gd in the brain (slightly higher concentrations for Omniscan)
  - Comparable distribution & localization of Gd in the brain (nuclei & granular layers)



- No Gd-trapping in the nuclei & granular layers after macrocyclic GBCAs (Gadavist, ProHance, Dotarem)

Partial Gd Release & Binding to Macromolecules in the Rat Brain Seen with Linear Agents Only



- Linear agents release some Gd from the intact GBCA which binds to soluble macromolecules and insoluble complexes
  - Control experiments exclude the possibility of intact GBCAs binding to macromolecules
- Macrocyclic GBCAs do not appear to dissociate or bind to macromolecules

Quantification and Assessment of the Chemical Form of Residual Gadolinium in the Brain After Repeated Administration of Gadolinium-Based Contrast Agents: Comparative Study in Rats. T. Frenzel, C. Apte, G. Jost, L. Schöckel, J. Lohrke, H. PietschInvestigative Radiology 2017 Jan 25.

Stability Plays an Important Role in Understanding SI Increase / Gd Presence in the Brain

- Release and binding of Gd to macromolecules for linear GBCAs are related to lower stability of linear GBCAs

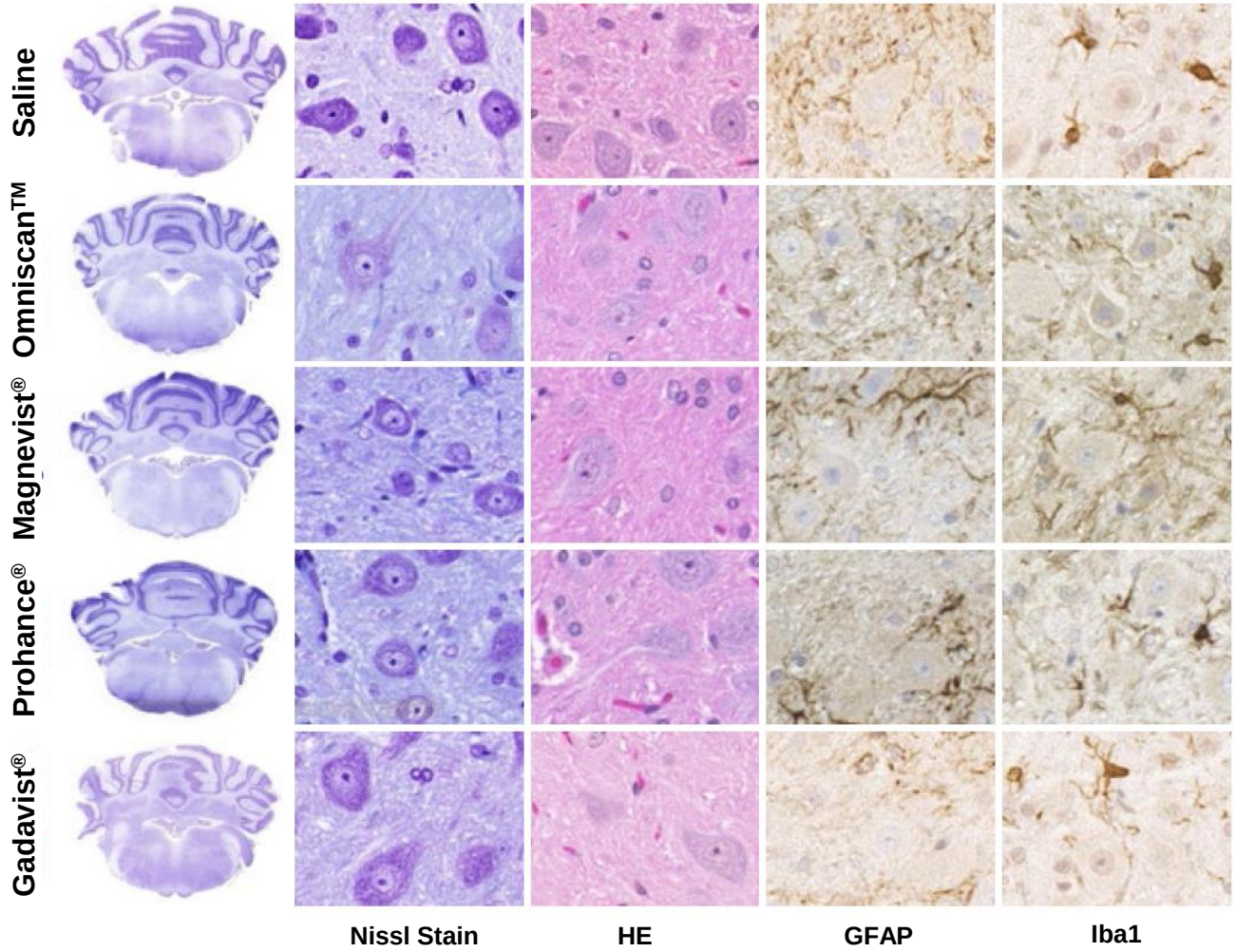
	GBCA	Gd-release after 15d*
Non-ionic linear agents	Omniscan, OptiMark®	20%
Ionic linear agents	Magnevist, MultiHance	2%
Ionic linear liver agent	Eovist	1%
Macrocyclic agents	Gadavist, Dotarem, ProHance	0%

*Measured in human serum at body temperature

- Stability: Nonionic linears < ionic linears < macrocyclics (kinetically inert)
  - Linear GBCAs characterized by **thermodynamic stability**
  - Macrocyclic GBCAs characterized by **kinetic stability** only

Frenzel et al. Investigative Radiology, 2008

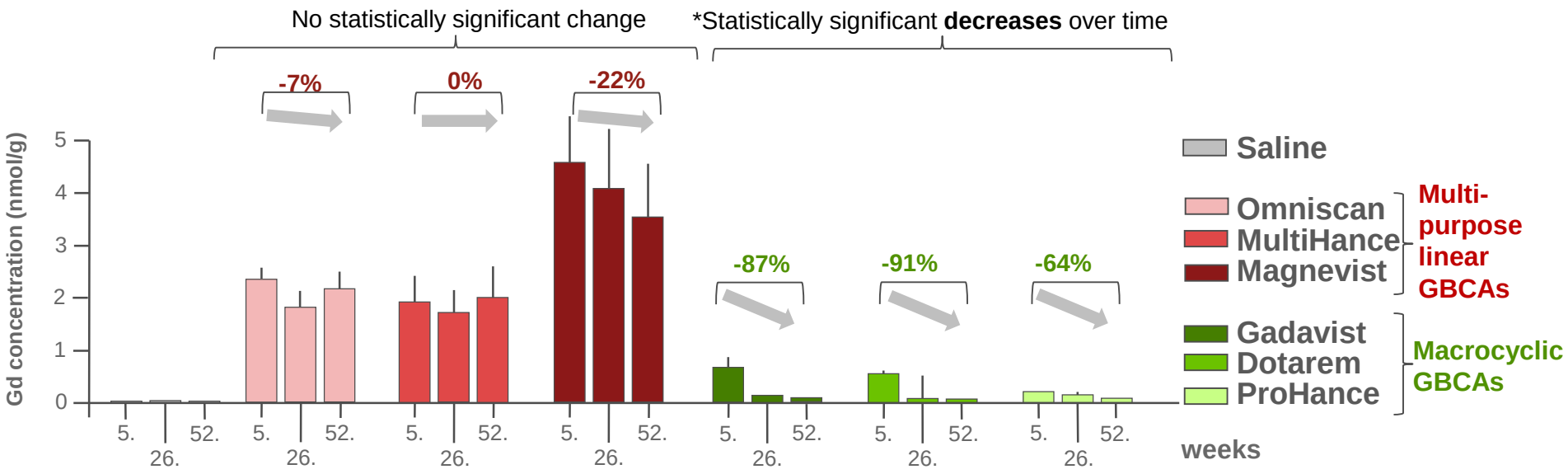
No Histopathological Changes in Rat Brain Tissue for any of the GBCAs



Histology and Gadolinium Distribution in the Rodent Brain After the Administration of Cumulative High Doses of Linear and Macrocyclic Gadolinium-Based Contrast Agents. Lohrke J, Frisk AL, Frenzel T, Schöckel L, Rosenbruch M, Jost G, Lenhard DC, Sieber MA, Nischwitz V, Küppers A, Pietsch H.

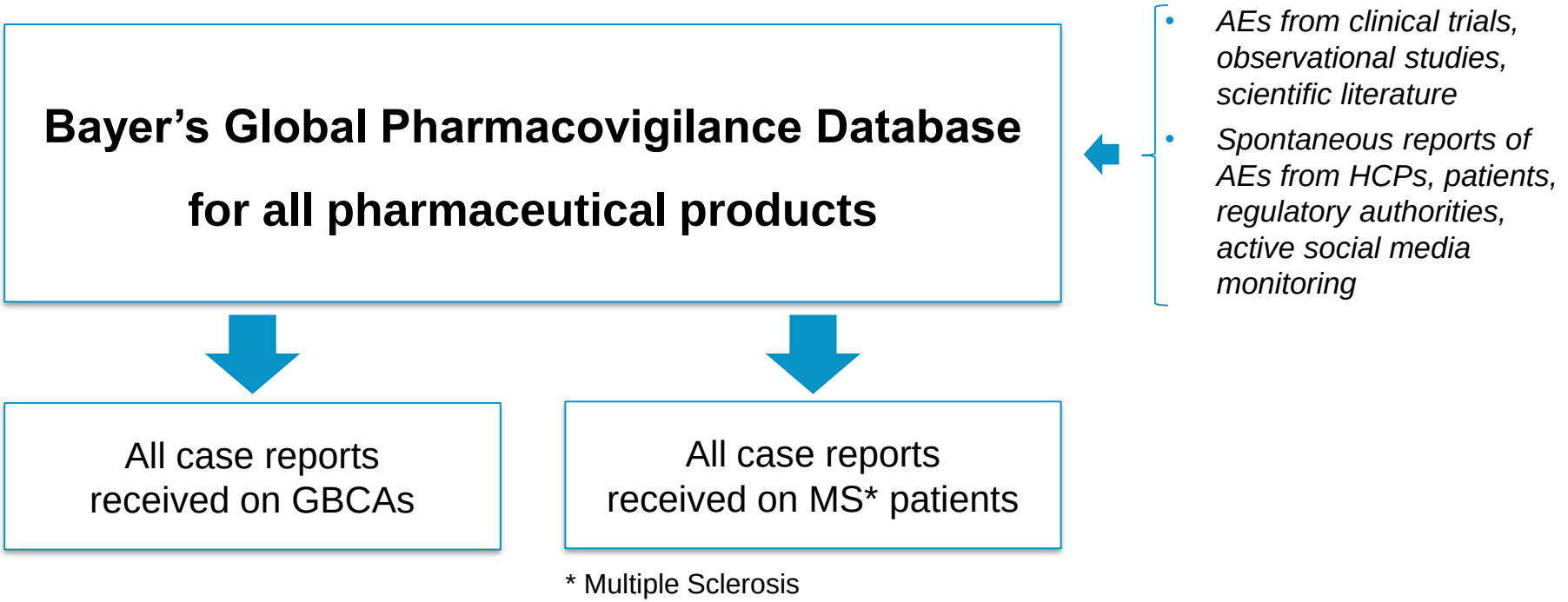
Elimination of GBCAs from the Rat Brain Between 5-52 weeks Seen with Macrocyclic Agents Only

Change of Gd concentration in the brain between 5-52 weeks post injection



- After 52 weeks, significantly higher Gd concentration in the brain for linear GBCAs
- No elimination observed for linear GBCAs between 5-52 weeks
- Continuous elimination of all macrocyclic GBCAs

Bayer's Comprehensive Pharmacovigilance (PV) Approach



- Ongoing evaluation of reported AEs
- Ongoing quantitative signal detection using computerized database screening

PV Search for Clinical Relevance: Brain

- Initial search focused on brain and any potential neurological symptoms related to GBCAs
- Safety observations from literature:
  - *Welk et al. (2016):* No association of GBCAs with Parkinson's disease
  - *Forslin et al. (2017):* "Lower verbal fluency scores" observed in association with SI increase (exposed MS patients vs. unexposed healthy controls)
  - *Terashima et al. (2017):* No effect on disease progression in MS patients
- Expansion of PV search to include Bayer's entire PV database (incl. ~300,000 case reports regarding patients with MS)
- Based on PV data: no adverse health effects confirmed to be associated with increased SI / presence of Gd in the brain

PV Search for Clinical Relevance: Body (except NSF)

- Safety observations from literature:
  - *Gathings et al. (2016):* Gd associated plaques
  - *Semelka et al. (2016), Burke et al. (2016):* **"**Gadolinium Deposition Disease" – term assigned by the authors to patients with normal renal function who experience persistent symptoms not attributable to other causes
- Bayer's PV database*: 40 reports noting persistent or elevated Gd levels in the body (blood, hair, nails, skin, urine)
  - 21 reports describing a wide variety of symptoms reportedly associated with elevated levels of Gd
- 13 reports describing similar symptoms without evidence of Gd measurements
- Many reports are not medically confirmed and most contain insufficient information for causality assessment
- Bayer continues to investigate these reports with a targeted questionnaire

*from Bayer's database (includes literature and spontaneous reports, excludes NSF reports); DLP August 31, 2017

Options For Further Signal Detection in Patients with Multiple Exposures to GBCAs

- Retrospective screening studies in large population-based longitudinal healthcare databases evaluating for any clinical signal detection in patients with multiple GBCA exposures, compared to unexposed controls
- **Exposed cohort:**
  - Women with multiple contrast-enhanced breast MRIs, without breast cancer (e.g. screening in high risk patients for breast cancer)
  - Patients with asymptomatic benign pancreatic tumors/cysts undergoing monitoring with CE-MRI for surveillance
- **Comparison cohort:**
  - Age, sex and comorbidity-matched population without MRI contrast exposure
- **Challenges:**
  - Relies on what is recorded and coded in routine clinical practice
  - Multiple comparisons/random error, unknown or residual confounding
  - Signals found need to be interpreted as data-derived hypotheses

Risk Mitigation

- Communication with HCPs about Gd presence in the brain and body
  - Label updates: class approach addressing the differences between linear and macrocyclic GBCAs. Important points to include:
    - Description of the signal intensity increase and Gd presence in the brain and body after repeated use, and its potential risk
    - Higher tissue concentrations of Gd seen for linear GBCAs compared to macrocyclics
    - No adverse clinical consequences have been confirmed
    - No histopathological changes detected in an animal model
  - “Dear Healthcare Professional” Letter
  - Ongoing medical education
- Continued non-clinical research
- Consideration of epidemiologic studies

Patient Safety and Continuing Research Remain our Focus

- **GBCAs play a vital role in diagnosis and disease monitoring**
  - Scientific and medical evidence to date demonstrate a favorable benefit-risk profile of Bayer's GBCAs in the vast majority of patients
  - Bayer is committed to furthering our investigation into Gd presence in the body and whether there are any clinical implications through:
    - Non-clinical research
    - Pharmacovigilance surveillance, follow-up and analysis
    - Potential epidemiologic study
- **As we move forward Bayer will continue to:**
  - Actively communicate with healthcare providers about the presence of Gd in the brain and body
  - Work with the FDA on proposed label updates to inform patients and healthcare providers about Gd presence