Gadolinium Retention in Brain and Body Tissues: Safety Considerations

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Introduction

Bracco Position

- Bracco is a global pharmaceutical group, with Clinical, Medical and Regulatory operations headquartered in the United States
- The recent findings on long-term retention of gadolinium (Gd) complexes in tissues following exposure to gadolinium-based contrast agents (GBCAs) are taken very seriously by Bracco
- Although much is still unknown (e.g., risk factors, potential association with adverse health effects), it is prudent and appropriate to further inform health care professionals and the public about the finding of retention in the brain and other organs

Bracco Position

- Bracco fully supports FDA's initiatives for:
  - Updating/enhancing the labeling of gadolinium-based contrast agents (GBCAs) based on their individual benefit-risk profile
  - Developing a collaborative effort to better understand this phenomenon and mitigate any potential risk of Gd retention in patients
    - Including ways to reduce exposure through dose reduction without compromising efficacy (as for example has been effective in radiation exposure in CT – the "As Low As Reasonably Achievable", ALARA principle)

Bracco Position

- When looking at nephrogenic systemic fibrosis (NSF), the only serious medical condition associated with Gd retention in tissues to date, it is clear that the response of FDA has been extremely effective at significantly reducing the risk of its occurrence:
  - Introduced agent-specific warnings and restrictions in patients at risk, based on clinical evidence
  - Did not segregate the approved products merely on the basis of their chemical structure, or based upon results of animal experiments
- Eight years later, a large amount of new clinical evidence, in part derived from FDA-requested post-marketing safety studies, further validates the Agency's 2009 evidence-based approach

Incidence of Nephrogenic Systemic Fibrosis in High-Risk Patients – Evidence from Clinical Studies

2017

GBCA	Incidence of NSF (N of NSF cases / N of high-risk patients [a])	Upper Bound of 95% Confidence Interval (Clopper-Pearson Exact Method)	Upper Bound of 95% Confidence Interval (Wilson Score Interval Approximate Method)
MultiHance®	0/8486	0.0435%	0.0452%
Dotarem®	0/502	0.7321%	0.7594%
Gadavist®	0/284	1.2905%	1.3346%
ProHance®	0/153	2.3822%	2.4493%
Eovist®	0/85	4.2470%	4.3239%
Optimark®	Not Available	Not Available	Not Available
Magnevist®	12/498 (2.4%)	4.1713%	4.1642%
Omniscan™	79/1673 (4.7%)	5.8506%	5.8463%

[a] Patients with end-stage renal disease or eGFR <30 mL/min/1.73 m^2, and/or during the perioperative liver transplantation period

Source: Bracco Briefing Material, Section 3.2.2.1, Table R

Linear GBCA

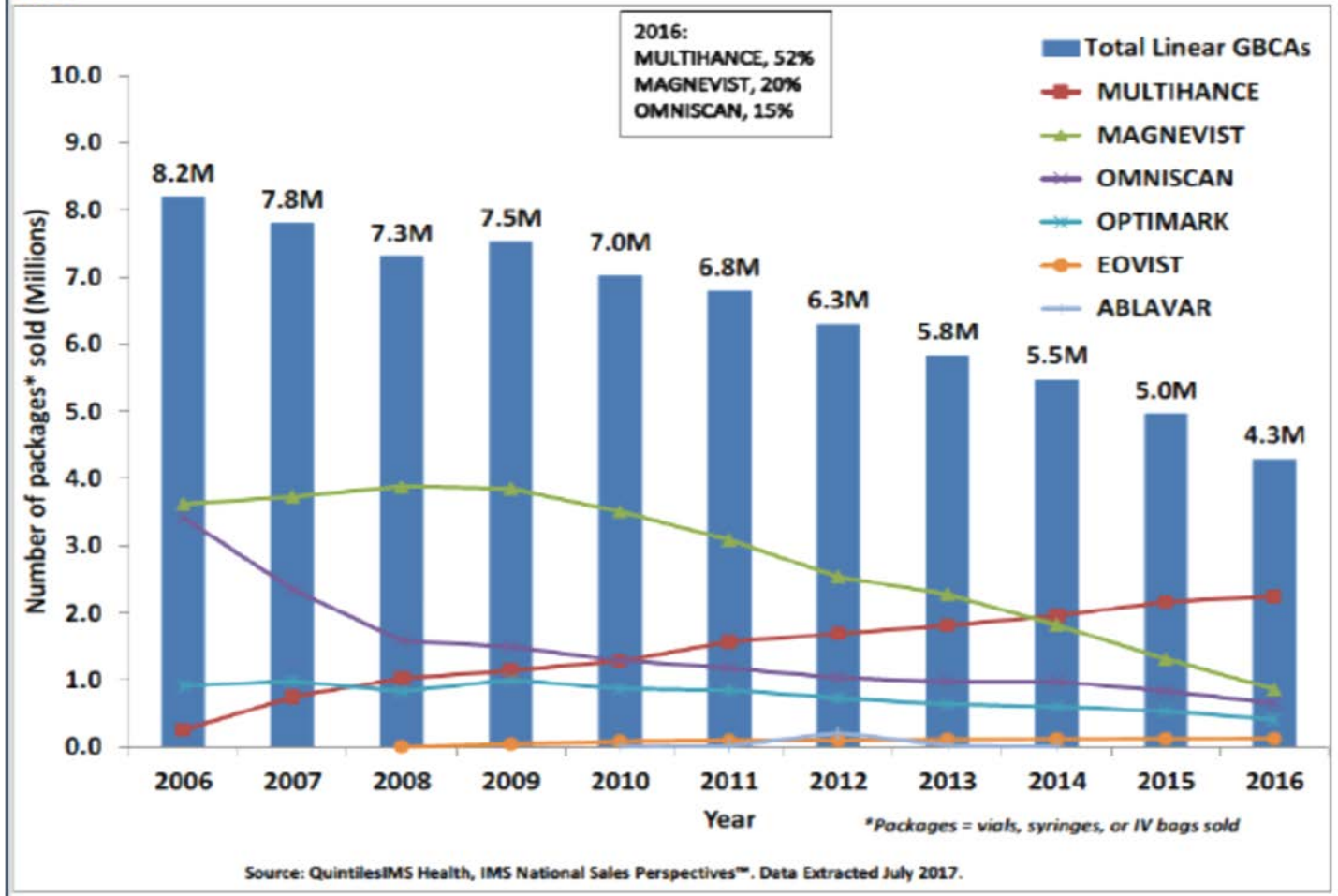
Macrocyclic GBCA

Differences Among Linear GBCAs Recognized By Health Care Providers

- Marked and steady decrease in the use of the 3 linear agents affected by higher rates of NSF (Magnevist®, Omniscan™, OptiMARK®)
- But, progressive and marked increase in the use of MultiHance®, due to its more favorable benefit-risk profile

Source: FDA Briefing Material, Page 107

Figure 3. National estimates of sales (in packages sold) for linear gadolinium-based contrast agents from US manufacturers to non-retail channels of distribution, 2006 – 2016*



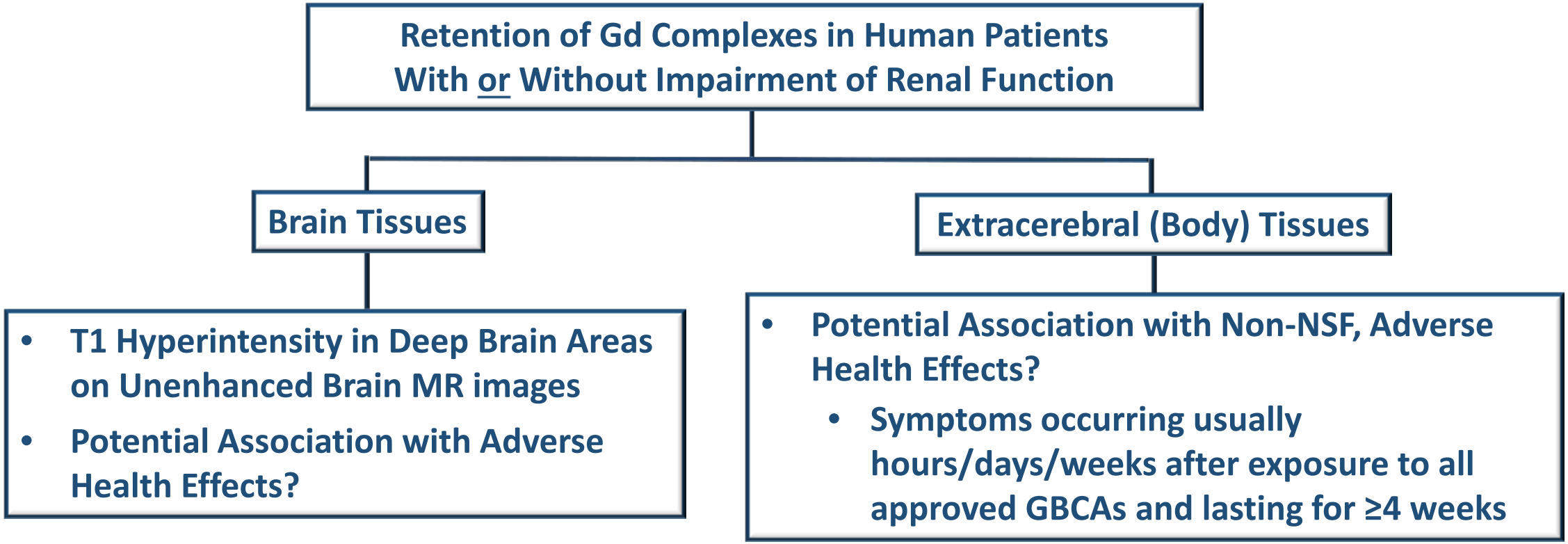
Problem Statement

Benefit-Risk Balance of Use of Gadolinium-Based Contrast Agents

Benefit	Risk
GBCAs provide critical medical information [1-2] • Part of standard clinical practice to enhance the diagnostic effectiveness of magnetic resonance imaging (MRI) for over 30 years in more than 300 million patients • Their use is an essential component in the diagnosis, monitoring and follow-up of a variety of clinical conditions	**Known Risk** [3-4] • Acute (immediate-type) adverse events • Breath-holding difficulty with gadoxetate disodium (Eovist®) • Extravasation • Retention of gadolinium (Gd) in tissues and association with Nephrogenic Systemic Fibrosis (NSF) **Potential (Unknown) Risk** • Non-NSF adverse events reported in conjunction with Gd retention in brain and body tissues?

1. ACR-ASNR Position statement on the use of gadolinium contrast media. https://www.acr.org/Quality-Safety/Resources/Contrast-Manual, pages 78-79.; 2. RSNA Statement on Gadolinium-Based MR Contrast Agents. Reviewed 3/17/2017.: http://www.rsna.org/uploadedfiles/rsna/content/role_based_pages/media/rsna-gadolinium-position-statement.pdf; 3. ACR (American College of Radiology) Manual on Contrast Media Version 10.3, 2017. Chapter 14. Adverse reactions to gadolinium-based contrast media. Available at: https://www.acr.org/Quality-Safety/Resources/Contrast-Manual, pages 80-83; 4. ACR (American College of Radiology) Manual on Contrast Media Version 10.3, 2017. Chapter 15. Nephrogenic systemic fibrosis. Available at: https://www.acr.org/Quality-Safety/Resources/Contrast-Manual, pages 84-92

Gd Retention – Risk Assessment Beyond NSF



Summary of Available Evidence

Evidence of Long-Term Gd Retention: Hierarchical Framework – 1

Highest level of evidence: Direct demonstration of presence, levels and localization of Gd complexes in HUMAN TISSUES using highly reliable, specific and sensitive methods

Key findings: [1]

- Retained Gd levels extremely small, especially in brain tissues (10 to >100 times lower than in body tissues)
- **Brain tissues:**
  - Not a clear demarcation between all macrocyclic GBCAs and linear GBCAs :
    ProHance< Gadavist/MultiHance/Magnevist < Omniscan [2] (no data with Dotarem and OptiMARK)
- **Body Tissues (e.g., skin, bone, liver):**
  - Observed following exposure to all GBCAs, linear and macrocyclic

1. Bracco Briefing Material, Sections 2.1.1.2 and 2.2.2; 2. Murata et al. Invest Radiol 2016; 51: 447-53

Brain Retention – Post-Mortem, Tissue-Sample Data

TABLE 3. Gd Deposition Ratio Amount per Gram Tissue per Millimole Administered

Case ID	GBCA	No. of CEMRI	Total Dose, mL	Total Dose, mmol	Gd Deposition, µg/g Tissue			Gd Deposition Ratio, µg/g/mmol			Last-First CEMRI Before Death, d
					GP	DN	Bone	GP	DN	Bone	
1*	Gadobutrol (Gadovist)	1	5	5	0.625	1.070	NA	0.125	0.214	—	5
2	Gadobutrol (Gadovist)	2	20	20	0.188	0.111	5.280	0.009	0.006	0.264	392–441
3	Gadoteridol (ProHance)	1	24	12	0.066	0.078	0.754	0.006	0.007	0.063	15
4	Gadoteridol (ProHance)	11	126	63	0.039	NA	1.620	0.001	—	0.026	19–318
5	Gadoteridol (ProHance)	3	57	28.5	0.023	NA	0.428	0.001	—	0.015	53–818
6	Gadoteridol (ProHance)	1	18	9	0.008	<0.004	0.098	0.001	<0.001	0.011	118
7	Gadoteridol (ProHance)	1	20	10	<0.005	<0.005	0.094	<0.001	<0.001	0.009	90
8	Gadoxetate (Eovist)	10	100	25	0.148	NA	1.300	0.006	—	0.052	90–819
9	Gadobenate (MultiHance)	1	20	10	0.052	0.078	2.380	0.005	0.008	0.238	83

Murata et al., Invest Radiol. 2016; 51: 447-453

Evidence of Long-Term Gd Retention: Hierarchical Framework – 2

Lower level of evidence: Direct demonstration of presence, levels and localization of Gd complexes in ANIMAL TISSUES

Key findings:

- Retained Gd levels extremely small after very high cumulative doses (brain tissues << body tissues)
- **Brain tissues:**[1]
  - ProHance < Dotarem/Gadavist < MultiHance < Magnevist << Omniscan
- **Body Tissues (e.g., skin, bone, liver, kidney):**[2]
  - Observed following exposure to all GBCAs, with differences in Gd retention among individual GBCAs dependent on animal species, individual organs tested, and experimental models used
  - Studies with Dotarem and MultiHance in juvenile animals did not show remarkable differences in body retention between the two agents

1. Bracco Briefing Material, Section 2.1.1.1; 2. Bracco Briefing Material, Section 2.2.1

Evidence of Long-Term Gd Retention: Hierarchical Framework – 3

Lowest level of evidence (for brain retention only): Studies aimed at detecting changes in signal intensity (SI) on unenhanced T1-weighted images or r1 relaxation rate (R1) in deep brain areas

- **Dependent on: a) the method used for quantitative analysis of changes in SI, and b) individual readers**
- **Cannot determine levels of retained Gd in brain tissues**

Key findings: [1]

- A systematic trend observed for ProHance (no effect on SI) and Omniscan and Magnevist (always determining significant changes in SI in the dentate nucleus, DN, and globus pallidus, GP)
- Mixed results observed after Eovist, MultiHance, Gadavist and Dotarem (with a majority of studies not showing a significant effect in the DN and GP)
- Visible T1 hyperintensity in deep brain areas more robustly associated with previous administration of certain linear GBCAs (Magnevist, Omniscan) compared with other GBCAs

1. Bracco Briefing Material, Section 2.1.2

Summary of Results of Clinical Imaging Studies

(Source: Bracco Briefing Material, Section 2.1.2, Table B, Pages 39-40)

Linear GBCA

Macrocyclic GBCA

GBCA	Significant effect on SI or relaxation rate a. Adult patients b. Pediatric patients	No significant effect on SI or relaxation rate a. Adult patients b. Pediatric patients
ProHance		a. Kanda et al., 2015 b. Tibussek et al, 2017
Magnevist	a. Kanda et al, 2014; Kanda et al, 2015; Adin et al, 2015; Radbruch et al, 2015a; Radbruch et al, 2015b; Tedeschi et al, 2016; Cao et al, 2016a; Tanaka et al, 2016; Radbruch et al, 2016; Cao et al, 2016b; Zhang et al, 2017; Schlemm et al, 2017; Kuno et al, 2017; Bae et al, 2017; Radbruch et al, 2017b; Forslin et al, 2017 b. Hu et al, 2016; Roberts et al, 2016a; Flood et al, 2017	
Omniscan	a. Kanda et al, 2014; Errante et al, 2104; Quattrocchi et al, 2015; McDonald et al, 2015; Ramalho et al, 2015; Ramalho et al, 2016a; Tanaka et al, 2016; Ramalho et al, 2016b; Cao et al, 2016b; Zhang et al, 2017; Bae et al, 2017; Ichikawa et al, 2017; Radbruch et al, 2017b; Forslin et al, 2017 b. No data available	
Dotarem	a. Tedeschi et al, 2016 b. Rossi-Espagnet et al, 2017	a. Radbruch et al, 2015b; Eisele et al, 2016; Bae et al, 2017; Radbruch et al, 2017b; Eisele et al, 2017b b. Tibussek et al 2017
Eovist	a. Kahn et al, 2017 b. No data available	a. Ichikawa et al 2017; Conte et al 2017 b. No data available
Gadavist	a. Stojanov et al, 2016; Tedeschi et al., 2016; Bjornerud et al , in press a. No data available	a. Radbruch et al, 2015a; Cao et al, 2016a; Radbruch et al, 2016; Schlemm et al, 2017; Kromrey et al, 2017; Bae et al, 2017; Radbruch et al, 2017b; Langner et al, 2017; Müller et al, 2017; Yoo et al, 2017 b. No data available
MultiHance	a. Weberling et al. 2015	a. Ramalho et al. 2015; Ramalho et al 2016b b. Schneider et al. 2017
OptiMARK	No data available	No data available

Assessment of Potential Toxicity in Animals

- **Data from animal experiments did not show histological or clinical signs of neurotoxicity deriving from brain Gd retention in adult and juvenile animals** [1]
  - No histological changes ever observed in animals treated up to 50 mmol/kg (still a no-effect dose), corresponding to 83 standard doses of 0.1 mmol/kg, with assessments performed up to 50 weeks after dosing
  - Longitudinal neuro-behavioral assessments did not show any abnormality
  - As no toxic effects were observed (any cumulative dose, any Gd level in brain tissues), no threshold for toxic levels could be established
- **Body retention: skin lesions observed following repeated doses of Omniscan or OptiMARK (but not of any other GBCAs)** [2]
  - The observed skin changes were characterized by dermal fibrosis and infiltration of different cells, including mononuclear cells and CD34-positive cells

1. Bracco Briefing Material, Section 3.1.2; 2. Bracco Briefing Material, Section 3.2.1

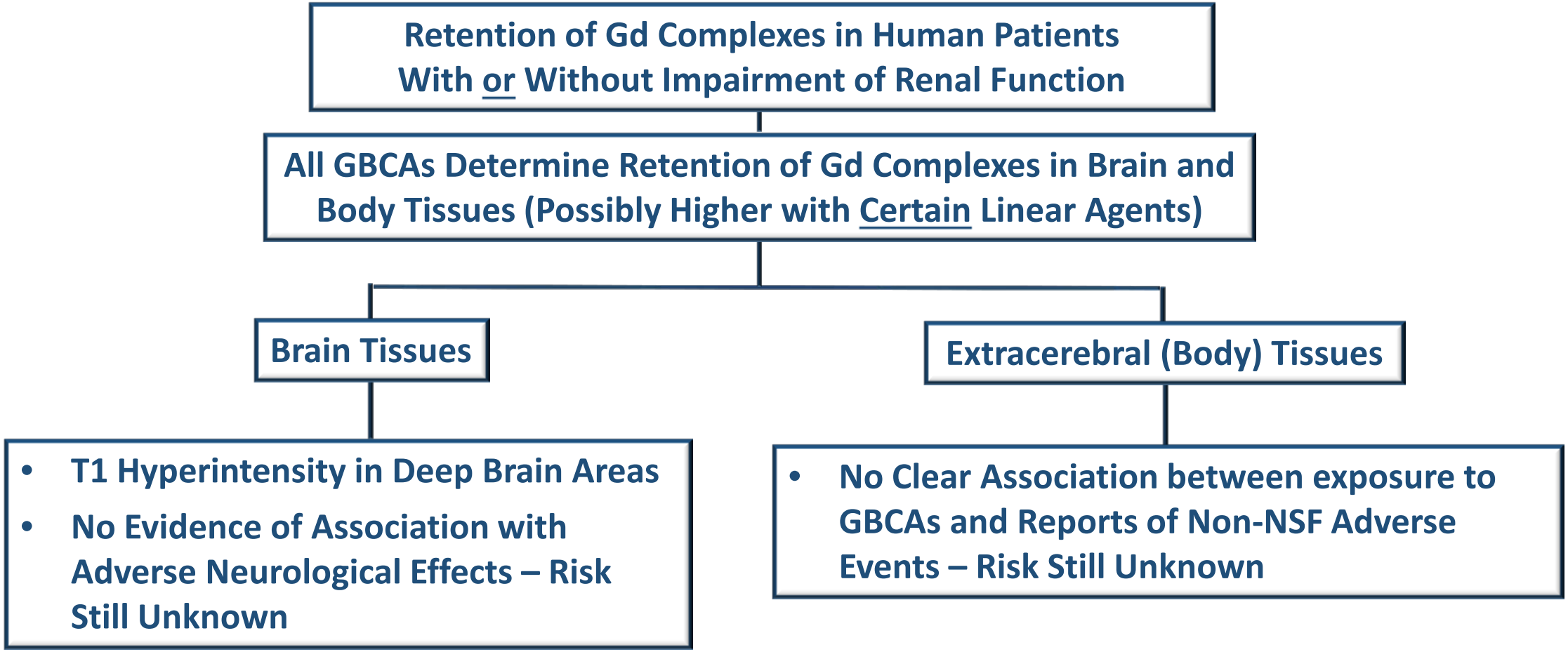
No Evidence of Adverse Health Effects of Gd Retention in Humans

- **No evidence of neurotoxicity from tissue-sample studies in human patients** [1]
- **No association between exposure to GBCAs and neurological adverse effects** [2]
  - No association between exposure to GBCAs and development of parkinsonism in patients >65 years of age (Welk et al., JAMA 2016; follow-up: approx. 4 years)
  - Results of a prospective cohort study (Mayo Clinical Study of Aging) in 4,261 patients, with 2,946 controls and 1,315 patients >70 yrs of age exposed to Omniscan (742 ≤4 doses, and 573 ≥5 doses; median follow-up: 5.6 years) and undergoing periodic monitoring of cognitive function and motoric skills
    - Omniscan exposure was not a predictor of excess cognitive decline or altered motor performance compared to controls
- **No clear association between body Gd retention and sporadic non-NSF adverse events** [3]

1. Bracco Briefing Material, Section 3.1.3.1; 2. Bracco Briefing Material, Section 3.1.3.2; FDA Briefing Material , Section 2: Pharmacovigilance

Risk Assessment

Gd Retention – Risk Assessment Beyond NSF



Proposal For Risk Mitigation Measures

Labeling Enhancement and Education

- In order to minimize the risk of Gd retention, the prescribing information for each GBCA (including MultiHance and ProHance) should contain tailored, clear warnings regarding the potential for:
  - Gd retention in tissues also in patients with normal renal function, to a) make the health care professionals aware, and b) reduce exposure (ALARA principle)
  - Visible T1 hyperintensity in deep brain areas on unenhanced brain MR images, to increase awareness and avoid any potential, even if unlikely, effect of abnormal T1 shortening on image interpretation
  - Late-onset symptoms in patients with normal renal function (even if the association of these events and exposure to GBCAs is still unknown)
- FDA-approved information to healthcare professionals (e.g., Dear Health Care Provider Letters) and educational programs validated by FDA

Conclusions

- The recent findings on long-term Gd retention following exposure to GBCAs are taken very seriously by Bracco
- Gd retention has been associated with all of the GBCAs available, regardless of their chemical structure
  - It is neither possible nor appropriate to draw a demarcation line between groups of agents only based on their chemical structure
  - It is important to look attentively at differences (or absence of differences) between individual GBCAs (not classes)
- Bracco fully supports FDA's sensible position to adjust labeling, to inform health care providers and the public about Gd retention, and to encourage more research in this area

Thank you