

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201277Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: DARRTS Set #1743-1 A study that will examine the safety of Gadavist in new born and neonates animals, following a single dose and limited repeated dose administrations. The study will provide safety data assessing mortality, toxicities, and potential reversibility of observed clinical and histopathological findings. The study will also examine the pharmacokinetics of Gadavist including tissue deposition of Gadolinium.

| | | |
|------------------------------|----------------------------|----------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>May, 2011</u> |
| | Study/Trial Completion: | <u>January, 2012</u> |
| | Final Report Submission: | <u>June, 2012</u> |
| | Other: | _____ |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval (I removed this check on the nonclinical form)
- Prior clinical experience indicates safety
- Small subpopulation affected (I removed this check on the nonclinical form)
- Theoretical concern
- Other

Proposed nonclinical study will evaluate the safety of Gadavist in a non clinical animal model prior to clinical exposure in view of known risk of NSF in adults especially those with renal impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To evaluate the safety of Gadavist in newborn and neonate animals.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Basic study design: The study should include four dosage levels to demonstrate potential dose-response relationship, a control, the intended clinical dose as the low dose, a mid dose, and the maximal tolerated dose. A single dose and a repeated dose for example once per week for four weeks designs are desirable to fully evaluate the potential risks considering the fact that clinical studies demonstrated that Gd can be accumulated in the tissues for long time. A recovery phase with appropriate recovery duration should be included to demonstrate the reversibility of potential findings. In addition to traditional toxicity observations and examinations, Gd depositions in tissues especially in skin, kidneys, bone, heart, and liver should be monitored. If feasible, the analytical method used should be able to differentiate between the chelated and free Gd. Calcium deposition in tissues especially in skin, kidneys, liver and cardiovascular system and potential tissue mineralization should also be monitored. The sample collection should be carefully designed to adequately evaluate the liver and renal functions.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Nonclinical study, safety related
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENE C TYSON
03/14/2011

IRA P KREFTING
03/14/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: DARRTS Set#1743-2 Study that will examine patients 0-23 months of age who are referred for a contrast-enhanced MRI exam of the central nervous system. At least 40 subjects will be studied to adequately characterize the pharmacokinetics of the product in this age group. The study will include a sufficient number to adequately assess the efficacy of Gadavist for central nervous system MRI.

| | | |
|------------------------------|----------------------------|----------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>July, 2012</u> |
| | Study/Trial Completion: | <u>March, 2014</u> |
| | Final Report Submission: | <u>January, 2015</u> |
| | Other: | _____ |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Immature kidneys of proposed population; in order to assess safety in normal and renally impaired patients and to assess risk of nephrogenic systemic fibrosis, required full Pharm/Tox and Clin/Pharm review in addition to Clinical review. Proposed study is similar to study submitted to the NDA for ages 2-17 years, needed to assess safety in this age group and to assure adequacy of the PK model.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To evaluate pharmacokinetics and safety of gadobutrol in children ages 0-23 months. Proposed study risk is Nephrogenic Systemic Fibrosis (NSF).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open-label study in pediatric subjects (term newborn to 23 months) referred for an MRI with contrast for routine diagnostic purposes. Subjects must be clinically stable, have no contraindications to MRI exam, and have no evidence of renal insufficiency, (eGFR < 80% of age-adjusted normal value calculated based on the Schwartz formula.)

Study initiation: Study to proceed after completion of a limited repeat dose administration (pre-clinical) study.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
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Continuation of Question 4

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Agreed upon:

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/s/

RENE C TYSON
03/14/2011

IRA P KREFTING
03/14/2011

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

| Application Information | | |
|--|--|------------------------------|
| NDA # 201-277 BLA# | NDA Supplement #:S- BLA STN # | Efficacy Supplement Type SE- |
| Proprietary Name: Gadovist Established/Proper Name: Gadobutrol Dosage Form: Injection Strengths: 1M | | |
| Applicant: Bayer Healthcare Agent for Applicant (if applicable): | | |
| Date of Application: May 13, 2010 Date of Receipt: May 14, 2010 Date clock started after UN: | | |
| PDUFA Goal Date: March 14, 2011 | Action Goal Date (if different): March 10, 2011 | |
| Filing Date: July 23, 2011 | Date of Filing Meeting: June 24, 2010 | |
| Chemical Classification: (1, 2, 3 etc.) (original NDAs only) 1 | | |
| Proposed indication(s)/Proposed change(s): Gadovist is indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i> | | |
| Review Classification: | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted | |
| <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i> | | |
| Resubmission after withdrawal? No | Resubmission after refuse to file? No | |
| Part 3 Combination Product? No <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device | |
| <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical | |

| | | | | |
|--|---|-----------|-----------|----------------|
| Other: | benefit and safety (21 CFR 314.610/21 CFR 601.42) | | | |
| Collaborative Review Division (if OTC product): | | | | |
| List referenced IND Number(s): | | | | |
| Goal Dates/Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | x | | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | x | | | |
| Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i> | x | | | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | | x | | |
| If yes, explain in comment column. | | | | |
| If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified: | | | | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | x | | | |
| <u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i> | Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required | | | |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i> | Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears | | | |
| <i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i> | | | | |

| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | YES | NO | NA | Comment | | | | | | | | | | | | | | | | |
|--|-----------------|------------------|------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | | x | | | | | | | | | | | | | | | | | | |
| Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). | | x | | | | | | | | | | | | | | | | | | |
| Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i> | | x | | | | | | | | | | | | | | | | | | |
| Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below: | | x | | | | | | | | | | | | | | | | | | |
| <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
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| <i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i> | | | | | | | | | | | | | | | | | | | | |
| Exclusivity | YES | NO | NA | Comment | | | | | | | | | | | | | | | | |
| Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm | | x | | | | | | | | | | | | | | | | | | |
| If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i> | | | | | | | | | | | | | | | | | | | | |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | x | | | | | | | | | | | | | | | | | | | |

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|--|--|---|--|--|
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)? | | x | | |
| If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i> | | | | |

| Format and Content | | | | |
|---|---|-----------|-----------|----------------|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format? | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted). | x | | | |
| Index: Does the submission contain an accurate comprehensive index? | x | | | |
| Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain. | x | | | |
| Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i> | | x | | |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA # | | | | |

| Forms and Certifications | | | | |
|--|------------|-----------|-----------|----------------|
| <p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> | | | | |
| Application Form | YES | NO | NA | Comment |
| <p>Is form FDA 356h included with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> | x | | | |
| <p>Are all establishments and their registration numbers listed on the form/attached to the form?</p> | x | | | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>Is patent information submitted on form FDA 3542a?</p> | x | | | |
| Financial Disclosure | YES | NO | NA | Comment |
| <p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> | x | | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| <p>Is form FDA 3674 included with authorized signature?</p> | x | | | |
| Debarment Certification | YES | NO | NA | Comment |
| <p>Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> | x | | | |

| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
|---|------------|-----------|-----------|----------------|
| <p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | | | X | |

| Pediatrics | YES | NO | NA | Comment |
|---|------------|-----------|-----------|----------------|
| <p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | X | | | |
| <p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> | | X | | |
| <p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p> | X | | | |
| <p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p> | X | | | |
| <p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p> | | X | | |

| Proprietary Name | YES | NO | NA | Comment |
|--|--|-----------|-----------|--|
| Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i> | x | | | Was submitted for review under the IND |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i> | x | | | |
| Is the PI submitted in PLR format? | x | | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i> | | | x | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC? | | x | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i> | | x | | |
| REMS consulted to OSE/DRISK? | | x | | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA? | x | | | |
| OTC Labeling | x Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | x | | | |

| | | | | |
|---|------------|-----------|-----------|----------------|
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | | | | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | | | | |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | | | | |
| Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: Through QT Study August 6, 2010</i> | x | | | |

| Meeting Minutes/SPAs | YES | NO | NA | Comment |
|---|------------|-----------|-----------|----------------|
| End-of Phase 2 meeting(s)? Date(s): August 28, 2007 <i>If yes, distribute minutes before filing meeting</i> | x | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): February 4, 2010 <i>If yes, distribute minutes before filing meeting</i> | x | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | x | | | |

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 24, 2010

BLA/NDA/Supp #: 201-277

PROPRIETARY NAME: Gadovist

ESTABLISHED/PROPER NAME: Gadobutrol

DOSAGE FORM/STRENGTH: 1M

APPLICANT: Bayer Healthcare

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Gadovist is indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

BACKGROUND: This is another gadolinium based contrast agent that will be used to visualize the CNS. The IND was received by the Division on July 16, 1998. The proposed population for use is ages 2 years to adult. A deferral request for pediatric studies for ages (0-23 months) was submitted in the NDA. An End-of-Phase 2 meeting was held on August 28, 2007 and a Pre-NDA Meeting on February 4, 2010. On April 14, 2008, an SPA was approved by the Division for Bayer to study patients referred for contrast-enhance MRI of the central nervous system using Gadovist in a Phase 3 trial

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|--------------------|--------------------|-------------------------------------|
| Regulatory Project Management | RPM: | James Moore | |
| | CPMS/TL: | Kyong Kang | |
| Cross-Discipline Team Leader (CDTL) | Alexander Gorovets | | |
| Clinical | Reviewer: | Barbara Stinson | |
| | TL: | Alexander Gorovets | |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | | N |
| | TL: | | N |
| OTC Labeling Review (<i>for OTC</i>) | Reviewer: | | NA |

| | | | |
|--|-----------|--|----|
| <i>products)</i> | | | |
| | TL: | | |
| Clinical Microbiology (<i>for antimicrobial products)</i> | Reviewer: | | NA |
| | TL: | | NA |

| | | | |
|---|-----------|------------------|----|
| Clinical Pharmacology | Reviewer: | Christy John | |
| | TL: | Young Moon Choi | |
| Biostatistics | Reviewer: | Anthony Mucci | |
| | TL: | Jyoti Zalkikar | |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Olayinka Dina | |
| | TL: | Adebayo Lanionu | |
| Statistics (carcinogenicity) | Reviewer: | NA | |
| | TL: | NA | |
| Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) | Reviewer: | NA | |
| | TL: | NA | |
| Product Quality (CMC) | Reviewer: | David Sasserman | |
| | TL: | Eldon Leutzinger | |
| Quality Microbiology (<i>for sterile products</i>) | Reviewer: | Jessica Cole | |
| | TL: | Stephen Langille | |
| CMC Labeling Review (<i>for BLAs/BLA supplements</i>) | Reviewer: | | NA |
| | TL: | | NA |
| Facility Review/Inspection | Reviewer: | | NA |
| | TL: | | NA |
| OSE/DMEPA (proprietary name) | Reviewer: | Catherine Carr | |
| | TL: | | |
| OSE/DRISK (REMS) | Reviewer: | | |
| | TL: | | |
| Bioresearch Monitoring (DSI) | Reviewer: | | |
| | TL: | | |

| | | |
|-----------------|--|--|
| Other reviewers | | |
| Other attendees | | |

FILING MEETING DISCUSSION:

| | |
|---|---|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p> | <p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p> | <p><input type="checkbox"/> Not Applicable</p> |
| <p>CLINICAL</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p> |
| <ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <p><input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p> |

| | |
|---|--|
| <ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

| | |
|--|--|
| <p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable</p> <p>x YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>x YES <input type="checkbox"/> NO</p> |
| <p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable</p> <p>x YES <input type="checkbox"/> NO</p> |
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable</p> <p>x YES <input type="checkbox"/> NO</p> <p>x YES <input type="checkbox"/> NO</p> |
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <p>x Not Applicable FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p> | <p><input type="checkbox"/> Review issues for 74-day letter</p> |

| REGULATORY PROJECT MANAGEMENT | |
|---|---|
| Signatory Authority: Kyong Kang | |
| 21st Century Review Milestones (see attached) (optional): | |
| Comments: | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| x | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>x Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p>x Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |
| ACTIONS ITEMS | |
| <input type="checkbox"/> | Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system. |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |
| <input type="checkbox"/> | <p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier) |
| <input type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input type="checkbox"/> | Other |

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE
03/08/2011

KYONG A KANG
03/08/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: March 3, 2011

Application Type/Number: NDA 201277

To: Rafael Rieves, MD, Division Director
Division of Medical Imaging Products

Through: Zachary Oleszczuk, PharmD, Team Leader
Kellie Taylor, Pharm.D., MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, MPH, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): (b) (4) (Gadobutrol) Injection
1 mmol Gadobutrol/mL (equivalent to 604.72 mg/mL)

Applicant/sponsor: Bayer Healthcare Pharmaceuticals, Inc.

OSE RCM #: 2010-2533

CONTENTS

| | | |
|------|---|----|
| 1 | INTRODUCTION | 3 |
| 1.1. | Regulatory History | 3 |
| 1.2. | Product Information | 4 |
| 2 | METHODS AND Materials | 6 |
| 2.1. | Adverse Event Reporting System (AERS) selection of cases..... | 6 |
| 2.2. | Applicant Post-Marketing Experience of ‘Gadovist’ in Europe | 6 |
| 2.3. | Labels and Labeling | 7 |
| 3 | Results..... | 7 |
| 3.1. | AERS Results..... | 7 |
| 3.2. | Applicant Post-Marketing Experience of ‘Gadovist’ in Europe | 7 |
| 3.3. | Labels and Labeling | 7 |
| 4 | discussion..... | 8 |
| 5 | CONCLUSION AND RECOMMENDATIONS..... | 9 |
| 5.1. | Comments to the Division..... | 10 |
| 5.2. | Comments to the Applicant..... | 11 |
| 6 | References..... | 12 |
| | Appendices | 13 |

1 INTRODUCTION

This review evaluates the proposed labels and labeling for (b) (4) (Gadobutrol Injection, (NDA 201277) for areas of vulnerability that could lead to medication errors. These labels and labeling were submitted by the Applicant on December 2, 2010, in conjunction with a request for review of the proposed proprietary name, (b) (4) which is reviewed separately in OSE #2010-2532.

1.1. REGULATORY HISTORY

Gadobutrol was first approved in Switzerland in February 1998 under the proprietary name, Gadovist. Since 2000, the product has been marketed in most of Europe using the proprietary name, Gadovist, totalling 65 countries. In many countries, '1.0' or '1.0 M' follows the proprietary name, Gadovist, to further emphasize the higher concentration of Gadobutrol compared to other Gadolinium-Based Contrast Agents (GBCAs).

The Applicant submitted a request for review of the proposed names, Gadovist 1.0 and Gadovist, during the IND phase of the development of this product (IND 056410). These names were found unacceptable by DMEPA in OSE-RCM Review #2010-457, dated August 13, 2010, (b) (4)

On November 22, 2010, the Applicant submitted a briefing document to DMIP in preparation for a teleconference scheduled for December 6, 2010, which included pending issues regarding the product review and potential topics to be discussed at the pending January 21, 2011 Advisory Committee meeting. The Applicant's questions included a request for feedback from the Agency on revising the labels and labeling for the product, in an effort to emphasize the higher concentration that this product has compared to other GBCAs.

In response to the Applicant's inquiry, the Division of Medical Imaging Products (DMIP) met with DMEPA on November 30, 2010, to discuss the unique features of the product, along with potential for medication errors due to the higher concentration and the subsequent challenges that may occur as a result of a new Gadolinium-based contrast agent (GBCA). This product requires half the volume administered compared to currently marketed GBCA products for central nervous system imaging indications. DMIP and DMEPA discussed differentiating labels and labeling features proposed by the Applicant in their original application, along with discussing additional options to better differentiate this product from other GBCAs and minimize the potential of wrong dose medication errors in clinical practice.

On December 1, 2010, the Applicant submitted a request for review of the proposed proprietary name, (b) (4) along with draft labels and labeling that incorporated features discussed during November 2010 discussions with DMIP.

On December 3, 2010, DMIP sent an information request communication to the Applicant which included preliminary labels and labeling recommendation discussed by

DMIP and DMEPA. These recommendations, along with other areas for improvement, will be discussed in this review.

On January 21, 2011, the Peripheral and Central Nervous Systems Drug Advisory Committee of the FDA met to discuss Gadobutrol Injection (NDA 201277). The committee provided recommendations with regard to this product and pending approval, including recommendations for minimizing the potential for medication errors with this product. (See Section 4 Discussion).

On February 8, 2011, DMIP and DMEPA conducted a teleconference with the Applicant to discuss concerns raised by DMIP about the proposed name (b) (4)

On February 10, 2011, the Applicant withdrew their request for review of the proposed name, (b) (4)

On February 18, 2011, the Applicant submitted a request for the review of the proposed proprietary name, Gadavist, which was reviewed separately in found acceptable in OSE Review#2010-2532 dated February 28, 2011. We note that although labels and labeling evaluated in this review are presented with the previously proposed name, (b) (4) the Applicant will need to submit revised labels and labeling that are presented with the name, Gadavist, and these labels and labeling will need to be reviewed prior to approval.

1.2. PRODUCT INFORMATION

(b) (4) is a Gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age or older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

(b) (4) is a macrocyclic GBCA, formulated at a higher concentration (1 mmol/mL) compared to other extracellular Gadolinium-based contrast agents (0.5 mmol/mL). This results in half the volume needed for administration per kg body weight (0.1 mL/kg) for central nervous system (CNS) indications compared to currently marketed GBCA products used for CNS indications (0.2 mL/kg).

In their original submission, the Applicant stated that the higher concentration was used due to the physico-chemical properties of Gadobutrol, including solubility, hydrophilicity and osmolarity and is the only GBCA which can be formulated in a 1 Molar concentration while maintaining acceptable viscosity similar to other available extracellular GBCAs. Table 1 below outlines currently marketed GBCA products with CNS indications.

Table 1. Five Marketed GBCAs With CNS Indications

| Trade Name | Molar | Dosing Regimen (mmol/kg) | |
|-----------------|------------|------------------------------------|--------------------------|
| | | Adults | Pediatrics |
| Magnevist | 0.5 | 0.1 | 0.1 (> 2 y.o.) |
| Prohance | 0.5 | 0.1 CNS (optional 2nd dose 0.2) | 0.1 (> 2 y.o.) |
| Omniscan | 0.5 | 0.1 | 0.1 (> 2 y.o.) |
| Optimark | 0.5 | 0.1 | N/A |
| Multihance | 0.5 | 0.1 | 0.1 (> 2 y.o.) |
| Gadovist | 1.0 | 0.1 | 0.1 (> 2 y.o.) |

Table 2 below illustrates the volume of (b) (4) to be administered based on body weight. (b) (4) should be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL per second.

Table 2: (b) (4) dosed at 0.1 mL/kg body weight

| VOLUME OF TRADENAME INJECTION BY BODY WEIGHT | | |
|--|-----|-------------------|
| BODY WEIGHT | | Total Volume, mL* |
| lb | kg | |
| 22 | 10 | 1 |
| 33 | 15 | 1.5 |
| 44 | 20 | 2 |
| 55 | 25 | 2.5 |
| 66 | 30 | 3 |
| 77 | 35 | 3.5 |
| 88 | 40 | 4 |
| 99 | 45 | 4.5 |
| 110 | 50 | 5 |
| 132 | 60 | 6 |
| 154 | 70 | 7 |
| 176 | 80 | 8 |
| 198 | 90 | 9 |
| 220 | 100 | 10 |
| 242 | 110 | 11 |
| 264 | 120 | 12 |
| 286 | 130 | 13 |
| 298 | 140 | 14 |

(b) (4) is supplied in 7.5 mL, 10 mL and 15 mL single-dose vials and pre-filled disposable syringes, long with pharmacy bulk packages of 30 mL multiple-dose vials and 65 mL multiple-dose infusion bottles. (b) (4) should be stored at 25°C (77°F).

An important safety consideration with this product, along with other GBCA products, is the adverse event Nephrogenic Systemic Fibrosis (NSF) associated with product use. These products subsequently carry a boxed warning in labeling to alert practitioners about the use of these products in vulnerable populations with impaired elimination of the drug unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

2 METHODS AND MATERIALS

Because (b) (4) has been marketed in Europe for over ten years under the proprietary name, Gadovist, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify any medication errors relevant to the labels or labeling of the product. (See Appendix E) We considered these errors as we evaluated the proposed container labels and carton labeling submitted by the Applicant for vulnerabilities that may contribute to medication errors. Additionally, DMEPA reviewed postmarketing data on medication errors that were submitted by the Applicant to DMIP via email on December 1, 2010. This data summarizes postmarketing overdose medication error reports of Gadovist, since it has been marketed in Europe.

2.1. ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

The AERS search conducted on January 27, 2011, used the search terms: tradename “Gadovist”, active ingredients “Gadobutrol” and verbatim term “Gadovist%,” and “Gadobutrol%.” The reactions in the search included the HLGTT term, “Medication Errors,” and the HLGTT term, “Product Quality Issues.”

Reports are manually reviewed to determine if a medication error occurred. Reports that do not describe a medication error or do not describe an error applicable to the referenced product are excluded from further analysis. If an error has occurred, the reports are categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports are reviewed to determine if the error could be applicable to the labels and labeling of the referenced product and thus pertinent to our review.

2.2. APPLICANT POST-MARKETING EXPERIENCE OF ‘GADOVIST’ IN EUROPE

On December 3, 2010, the Applicant submitted postmarketing maladministration and overdose reports for Gadobutrol, marketed under the proprietary name, Gadovist, in Europe. The Applicant provided reports cover the time period of the time of approval in Europe in 1998 through September 30, 2010.

2.3. LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA)¹, the principals of human factors, and postmarketing experience the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, and insert labeling submitted by the Applicant on December 2, 2010. (See Appendices A through D).

3 RESULTS

The following sections describe our findings from AERS and evaluation of the labels and labeling.

3.1. AERS RESULTS

The AERS search conducted on January 27, 2011 did not yield any medication errors reports.

3.2. APPLICANT POST-MARKETING EXPERIENCE OF ‘GADOVIST’ IN EUROPE

The Applicant reported that no spontaneous reports of dose maladministration were retrieved from the safety database.

Three single case reports of “overdose” were identified by the Applicant. In two of the cases, (200718109GPV) and (200831547GPV), doses that exceeded the labeled milliliter per kilogram body weight [(35 mL) and (47 mL)], were administered. The reports lacked information regarding patient weight and any contributing factors for the misdosing. Therefore, no conclusions could be drawn about the root cause of the overdose. The third case (201037790GPV) did not provide any details about the patient, events that lead to the error, dates, or the outcome of the event. (See Appendix E for details on all cases)

3.3. LABELS AND LABELING

Our labels and labeling risk assessment identified the following deficiencies:

- The prominence of the volume on the single-use vials and syringes (7.5 mL, 10 mL and 15 mL) are presented with equal or greater prominence than other important product characteristics such as the proprietary name, the established name and the strength.
- The graduation markings on the syringe labels do not include the unit of measure (mL), and the graduations markings do not include (b) (4) volumes nor are they labeled with the total volume (i.e., the 7.5 mL syringe label is marked with numbers (b) (4) but do not include a measurement for the total volume of 7.5 mL).
- The error-prone abbreviation (b) (4), is used for the route of administration.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- The unit of measure (b) (4) rather than ‘1 mmol/mL’ is used throughout the insert labeling. This inconsistency may contribute to confusion that could cause medication errors.

Additionally, DMEPA believes that an education plan should be directed to practitioners at the time of product launch, in order to educate physicians, pharmacists and radiology technicians about the unique qualities of this product compared to other GBCAs, particularly the variation in the volume of product required for administration compared to other GBCA products currently marketed for CNS indications.

Moreover, because the proposed proprietary name, (b) (4) was found unacceptable, we will need to review labels and labeling that incorporate the proprietary name that is found acceptable prior to approval.

4 DISCUSSION

We recognize that (b) (4) has been marketed in Europe for over ten years under the proprietary name ‘Gadovist’, and that the data submitted by the Applicant reports that limited medication error reports for the product exist. Nonetheless, both DMIP and DMEPA remain concerned that the variation in the milliliter per kilogram dose for this product (half the volume of product compared to other GBCAs for CNS indication) creates the potential for wrong dose medication errors in clinical practice in the U.S.

Additionally, the Peripheral and Central Nervous System Drugs Advisory Committee (PCNSDAC) convened on January 21, 2011 to discuss this NDA expressed similar concerns about the potential for medication errors that may lead to overdoses. The Advisory Committee provided many recommendations that align with those identified by DMEPA and are outlined in Section 5. DMEPA notes, however, that one recommendation provided by the Advisory Committee included a recommended revision of the dosing guidelines to include infants weighing less than 22 pounds. The proposed dosing chart begins with 22 pounds as the lowest weight which aligns with CDC child growth statistics for a 24 month². The labeled population for this product at this time is children two years or older. Therefore, DMEPA does not agree with this recommendation to expand the current weight chart to weights below 22 pounds. However, if future development of this product includes an expansion of the patient population to include neonates and infants, DMEPA supports dosing guidelines that align with this age group.

The Advisory Committee also suggested a recommendation to provide prefilled syringes for all weight-based doses for the product. DMEPA notes that the current packaging configuration of the product provides for three different single-use prefilled syringe sizes including 7.5 mL, 10 mL and 15 mL. The packaging configuration also includes single-use vials in the same 7.5 mL, 10 mL and 15 mL sizes. DMEPA believes that since the vials are available, the smaller doses can be achieved using this packaging configuration. Providing prefilled syringes or vials for all weight-based doses may offer convenience for practitioners who are dosing and administering the product. However, this packaging configuration would require syringes in 18 different volumes of prefilled syringes and is

² 2000 CDC Growth Charts for the United States: Methods and Development

impractical. Additionally, supplying this many options may not reduce the risk of not identifying the concentration differences and may introduce added risks of errors in product selection and dosing.

The Applicant proposes differentiating the labels and labeling features for (b) (4) using a large red box on the principal display panel that contained “(b) (4) Dose 0.1 mL/kg.” DMEPA supports efforts to warn practitioners about the higher concentration dose of this product compared to other GBCAs. However, we are concerned that this term is relative. In the event that other ‘higher’ concentration products are introduced to the market in the future, this warning becomes inaccurate. Therefore, we would recommend alternate language to convey the safety that would not become obsolete if other more concentrated formulations of GBCAs are introduced. We have outlined these and other recommendations for revisions to (b) (4) labels and labeling in Section 5.

Therefore, due to the difference in this product compared to other GBCA products for CNS indications, education and awareness about the unique features of this GBCA product is essential at the time of launch to inform practitioners who commonly work with contract imaging agents about the unique nature of this GBCA. In the Applicant’s original submission, they provided a Risk Management Minimization Plan, currently being reviewed by the Division of Risk Management (DRISK). The plan includes the history of Gadobutrol postmarketing experience in Europe, the safety risks associated with NSF commonly seen in GBCA products, and targeted pharmacovigilance and risk management activities. The plan includes reference to communicate via public safety alerts/advisories, publications, ‘Dear Healthcare Professional Letters’, outreach and education efforts, ongoing preclinical and website activities, and quarterly NSF reports. However, no specific plan was provided to communicate and educate providers about the varying concentration of this unique GBCA product in order to help minimize the risk of wrong dose medication errors. DMEPA discussed the characteristics of this product with a practicing radiology technician who works with GBCA products, who stated that if a new product was introduced to the market that varied in milliliter per kilogram dosing compared to currently marketed products, education and communication efforts would be imperative to communicate the dosing variation for this product. Therefore, practitioners who currently use imaging agents as a part of their practice will need to be informed and educated about this new product because it differs from all other similar products that are currently on the market. Education and communication efforts will help minimize wrong dose errors when the proposed product is introduced on the market.

5 CONCLUSION AND RECOMMENDATIONS

Our evaluation identified areas of needed improvement in order to minimize the potential for wrong dose medication errors with this product. We provided our recommendations for a communication plan in Section 5.1 Comments to the Division for discussion during the labeling meetings. Section 5.2 Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions

or need clarifications on this review, please contact the OSE Regulatory Project Manager, Sandra Griffith at 301-796-2445.

5.1. COMMENTS TO THE DIVISION

A. Education and Awareness for Healthcare Providers

We are concerned that dosing errors will occur with [REDACTED] (b) (4) since the dose for this product requires one half of the volume compared to all other Gadolinium-based contrast agents for central nervous system indications that are currently on the market. During the January 21, 2011 Advisory Committee meeting for this product, the Committee also expressed concerns about the potential for confusion that may occur with the product that may lead to overdoses provided recommendations that support efforts to education providers about the concentration of this product.

At the time of product launch for this product and for the lifetime of marketing for this product or for at least five years from the date the product is marketed, DMEPA recommends that the Applicant educate health care practitioners about the unique higher concentration dose for this product compared to other GBCA products. We believe that these efforts should provide awareness through Dear Healthcare Professional letters, articles in medical journals, and other oral and written media geared towards health practitioners who work in the radiology field. Additionally, the Applicant should develop and include a dosing charts (formatted similar to the chart provided in Section 2.1 of the insert labeling) for distribution to healthcare facilities where the product will be distributed. DMEPA believes these efforts may educate providers and technicians who work with GBCA products at the time of product launch and help minimize confusion that may lead to wrong dose (wrong volume) medication errors. We note that part of the CDER standard letter template approval letters provide directives for the Applicant's submission of promotional materials and Dear Healthcare Professionals letters.

B. Dosing Chart

The dosing chart currently provided in Section 2.1 of the insert labeling does not provide dosing for patients in excess of 300 pounds (dosing currently provided up to 298 pounds/140 kg). The Advisory Committee provided a recommendation to include dosing for morbidly obese patients. DMEPA agrees and believes that the Division should consider recommending that the Applicant revise the dosing chart to include patient weights that exceed 298 pounds, since MRI procedures are performed for patients in excess of 300 pounds. Although the Committee also recommended that the dosing chart should include dosing for infants weighing less than 22 pounds, the patient population for [REDACTED] (b) (4) is currently labeled for 'adults and children two years and older'. Thus, DMEPA does not agree with this recommendation. The dosing chart should provide doses for the approved population and include a statement that this product has not been studied for children less than two years old. However, there should be language added that provides directives for dosing outside of the weight ranges, including the information regarding maximum doses, if applicable. The dosage and administration section of the insert labeling does not specify whether there is a maximum dose for this product.

C. Proprietary Name

DMEPA's recommendations for revisions to labels and labeling are outlined below in Section 5.2 Comments to the Applicant. Prior the completion of this label and labeling review, DMEPA found the proposed name, (b) (4) unacceptable. The Applicant withdrew their request for review of the proposed name, (b) (4) on February 11, 2011 and submitted a request for review of the proposed name, Gadavist, on February 18, 2011, which DMEPA found acceptable in OSE Review #2011-406 dated February 28, 2011. Because the labels and labeling evaluated in this review incorporate the name, (b) (4) DMEPA will need to review revised labels that incorporate the new name, Gadavist, prior to approval.

5.2. COMMENTS TO THE APPLICANT

- A. Replace the unit of measure displayed as (b) (4) on container labels and carton labeling with '1 mmol/mL' to align with the unit of measure used in the package insert labeling.
- B. The proposed prefilled syringe does not provide graduations that support the dosing for this product. Revise the presentation of the graduation marks used on the prefilled syringe container labels to include half-milliliter measurements and the total volume measurement (i.e. 7.5 mL). (b) (4) is dosed in half-milliliter increments depending on the patient's weight, however, the current presentation does not include (b) (4) markings. Additionally the graduation markings are not labeled to include the total volume (i.e. the 7.5 mL syringe is marked with the number (b) (4) but does not include the total volume measurement '7.5'.
- C. Add 'mL' to the graduated marks that appear on the container labels so that the intended unit of measure is clear to the provider during dosing and administration of the product. The current presentation includes only the numbers but does not display the unit of measure (mL).
- D. Delete the words (b) (4), that are currently displayed in the red box of all container labels and carton labeling for the product. DMEPA supports efforts to warn practitioners about the higher concentration dose of this product compared to other GBCAs, as we believe this is important product information that needs to be communication to healthcare providers. However, we are concerned that (b) (4) is a relative term. In the event that other 'higher' concentration products are introduced to the market in the future, this warning becomes inaccurate. Therefore, we would recommend alternate language to convey the safety that would not become obsolete if other more concentrated formulations of GBCAs are introduced. In conjunction with this revision, the warning statement currently displayed on the side panel should be relocated to the principal display panel of the container label and carton labeling. This information should be displayed on the principal display panel of labels and labeling to bring prominence to the statement so that it alerts health care practitioners and technicians during drug dose calculation, preparation and administration.

- E. [REDACTED] (b) (4) [REDACTED] distracts from other important product information and removing it provides space needed to display the warning statement to be displayed per 21 CFR 201.15(a)(4).
- F. Relocate the 'Rx Only' statement that appears on the principal display to another location. Relocating this information will allow more space for other important product information on the principal display panel.
- G. Decrease the prominence of the total volume (7.5 mL, 10 mL and 15 mL) displayed on principal display panel of the container labels and carton labeling. The current presentation detracts away from the prominence of the strength and concentration information provided on the label. If the strength and concentration information is overlooked by healthcare providers, this could lead to medication errors. The prominence of the volume can be decreased by decreasing the font size and removing the box and the color currently used to encase the volume. This will also provide space to display other important product information including the warning statement alerting about the 0.1 mL/kg concentration.
- H. Revise (b) (4) to read 'intravenous' where it appears on the container label and carton labeling. [REDACTED] (b) (4) [REDACTED] Thus, we request that you revise the language accordingly.
- I. [REDACTED] (b) (4) [REDACTED]
- J. Create a dosing chart for this product that can be distributed to healthcare facilities where the product will be used for display in radiology departments. We recommend that the chart be formatted similar to the dosing chart provided in Section 2.1 of package insert labeling. We also recommend that the chart be large enough to be easily visible by practicing healthcare practitioners and radiology technicians who will be referring to the information for dosing, preparation and administration of the product.

6 REFERENCES

OSE Reviews

Miller, C.A. OSE Review #2011-406 Gadavist (Gadabutrol) Proprietary Name Review dated February 28, 2011.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CATHY A MILLER
03/03/2011

ZACHARY A OLESZCZUK
03/03/2011

KELLIE A TAYLOR
03/03/2011

CAROL A HOLQUIST
03/03/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging Products

Application Number: NDA 201-277

Name of Drug: Gadovist (Gadobutrol) Injection 1.0M

Applicant: GE Healthcare

Date: February 21, 2011

Material Reviewed:

Submission Date: May 13, 2010, October 22, 2010

Receipt Date: May 14, 2010, October 25, 2010

Submission Date of Structure Product Labeling (SPL): May 13, 2010, October 22, 2010

Type of Labeling Reviewed: Word/SPL

Background and Summary

Labeling was received from Bayer Healthcare in their submission of May 13, 2010. The 74 day letter which issued on July 30, 2010 cited a need to change the product name to remove the (b) (4) from the product name. On August 12, 2010, DMEPA completed their initial review of the product name and stated that the name was not acceptable. The company then resubmitted on October 22, 2010 another product name (b) (4). DMEPA reviewed the name and found it acceptable, but the Division found the name unacceptable. The Division and DMEPA met via telephone conference with Bayer Health Care and after discussion Bayer stated that they would propose several names informally and ask for DMEPA's input prior to submitting another product name for approval.

Changes were made to the package insert in the submission of October 22, 2010 to address both the request for a change in the Proprietary name of the product and the changes requested in the letter to Bayer on September 8, 2010 to incorporate certain language regarding Nephrogenic System Fibrosis (NSF).

Review

The package insert from the May 13, 2010 submission was reviewed. In the 74 day letter it was suggested to Bayer that [REDACTED] (b) (4)

[REDACTED] The October 22, 2010 labeling contained language from FDA requested in their letter of September 8, 2010 where FDA requested revised labeling to include updated language regarding Nephrogenic Systemic Fibrosis.

In that submission Bayer [REDACTED] (b) (4)

The drug name [REDACTED] (b) (4) was submitted as a second tradename in the October 22, 2010 submission.

Bayer should remove the [REDACTED] (b) (4) in the package insert when a draft label is sent to them by the Division and add the package type (vial, syringe) to their revised label.

The format of the package inserts and the carton and container label were acceptable.

Recommendations

If Bayer accepts the changes to the package insert recommended by FDA after the final FDA review, I recommend that FDA issue an approval letter for this Gadobutrol application.

James Moore, PharmD., M.A.
Regulatory Project Manager, DMIP

Supervisory Concurrence

Kyong Kang, PharmD.
Chief, Project Management Staff
February 21, 2011

CSO LABELING REVIEW

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/s/

JAMES W MOORE
03/30/2011

KYONG A KANG
03/30/2011



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Maternal Health Team Labeling Review

Date: February 3, 2011 **Date Consulted:** August 2, 2010

From: Leyla Sahin, MD
Medical Officer, Maternal Health Team

Through: Karen Feibus, MD
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: The Division of Medical Imaging Products (DMIP)

Drug: Gadovist 1.0 (gadobutrol) injection; NDA 201-277

Subject: Labeling Review

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Gadovist labeling.

Consult Question: Please review the sponsor's proposed labeling related to pregnancy and lactation.

INTRODUCTION

On May 14, 2010, Bayer Healthcare Pharmaceuticals submitted a new drug application (NDA 201-277) for Gadovist 1.0 (gadobutrol) injection. Gadovist is a new gadolinium-based contrast agent. The sponsor's proposed indication for Gadovist is intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (two years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. The Division of Medical Imaging Products (DMIP) consulted the Maternal Health Team (MHT) to review the Pregnancy and Nursing Mothers subsections of the sponsor's proposed labeling.

BACKGROUND

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy subsection, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label.

This review provides suggested revisions to the sponsor's proposed Gadovist labeling related to pregnancy and lactation.

SUBMITTED MATERIAL

Sponsor's Proposed Labeling Related to Pregnancy and Nursing Mothers

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Gadovist 1.0 in pregnant women. While it is unknown if Gadovist 1.0 crosses the human placenta, other gadolinium based (b) (4) do cross the placenta in humans and result in fetal exposure. Limited published human data on exposure to other (b) (4) during pregnancy did not show adverse effects in exposed neonates. Retardation of embryonal development and embryoletality occurred in pregnant rats receiving maternally toxic doses of Gadovist 1.0 (≥ 7.5 mmol/kg body weight) that were 12 (b) (4) times the human equivalent dose and in pregnant rabbits receiving doses (≥ 2.5 mmol/kg body weight) that were 8 times the recommended human dose (based on body surface area). In (b) (4) rabbits, this occurred without evidence of maternal toxicity (b) (4).

(b) (4)

Gadovist 1.0 was not teratogenic when given intravenously during organogenesis at doses up to (b) (4) & (b) (4) times (b) (4) the recommended single human dose (based on body surface area). Because pregnant animals received repeated daily doses of Gadovist 1.0, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans.

8.3 Nursing Mothers

It is not known whether gadobutrol is excreted in human milk. (b) (4)

12.3 Pharmacokinetics

Distribution

After intravenous administration, gadobutrol is rapidly distributed in the extracellular space.

After a gadobutrol dose of 0.1 mmol /kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the injection. (b) (4)

REVIEW OF LITERATURE AND PRACTICE GUIDELINES

Gadolinium exposure during pregnancy

MHT performed a PubMed search with the following terms: pregnancy and gadolinium, pregnancy and gadobutrol, pregnancy and contrast agents. MHT's review of the literature showed a limited number of human exposures to gadolinium contrast agents during pregnancy. A prospective cohort study of 26 women who were exposed to gadopentetate dimeglumine [a gadolinium derivative approved for use as a contrast agent with MRI to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues] in the first trimester reported 23 full term births without any malformations, two miscarriages, and one elective termination¹. One case report described a successful pregnancy in a patient with multiple sclerosis who was inadvertently injected intravenously with gadopentetate dimeglumine during very early pregnancy². No adverse effects were detected at birth in eleven newborns exposed to gadopentetate dimeglumine prenatally during the second and third trimesters as part of a

¹ De Santis M, Straface G, Cavaliere AF, Carducci B, Caruso A: Gadolinium periconceptional exposure: pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2007;86:99- 101.

² Barkhof F, Heijboer RJ, Algra PR: Inadvertent i.v. administration of gadopentetate dimeglumine during early pregnancy [letter]. Am J Roentgenol 158: 1171, 1992.

placental imaging study³. A case series reported normal pregnancy outcomes for a woman who was three months pregnant and a woman who was five months pregnant who received gadopentetate dimeglumine to establish a diagnosis of Crohn's disease⁴. There were no adverse outcomes in the newborns of 15 pregnant women who were exposed to gadolinium-enhanced MRI to diagnose placenta accrete and placenta percreta⁵.

Practice guidelines from professional radiology organizations in the United States and Europe address the use of gadolinium containing drug products during pregnancy. The American College of Radiology Manual on Contrast Media from 2010 states that:

- The potential risks with administration of gadolinium-based contrast agents, including the risk of nephrogenic systemic fibrosis in the neonate, and the long-term risks to the developing fetus, remain unknown and may be harmful
- Gadolinium chelates should not be routinely provided to pregnant patients
- Pregnant patients can be administered gadolinium agents if the risk-benefit ratio warrants the study to be performed

Based on a review of the literature, which has been discussed above, in 2005 The European Society of Urogenital Radiology issued Guidelines⁶ which state that when MRI is necessary, gadolinium media may be given to the pregnant woman.

Gadolinium exposure and lactation

MHT conducted a PubMed search with the following terms: gadolinium and lactation/breastfeeding, contrast agents and lactation/breastfeeding, gadolinium and lactation/breastfeeding. MHT's review of the literature identified two case reports of lactating women who were exposed to gadopentetate dimeglumine. Milk levels of gadolinium were 0.01⁷ – 0.023% of the maternal dose.⁸ Data from 19 lactating women who received an intravenous dose of gadopentetate dimeglumine suggested that a mean of 0.009% (range 0.001% - 0.04%) of the maternal dose was excreted in milk over the following 24 hours⁹. The authors of this study commented that this dose is less than 1/100th of the therapeutic dose for a neonate (200 µmol per kilogram of body weight), and study data suggest that very little orally administered

³ Marcos HB, Semelka RC, Worawattanakul S: Normal placenta: gadolinium-enhanced dynamic MR imaging. *Radiology* 1997; 205:493-6.

⁴ Shoenut JP, et al. MRI in the diagnosis of Crohn's Disease in two pregnant women. *J Clin Gastroenterology* 1993; 17(3):244-7.

⁵ Jaraquemada JM, Bruno C: Gadolinium-enhanced MR imaging in the differential diagnosis of placenta accreta and placenta percreta. *Radiology* 2000; 216:610-611.

⁶ Webb JA, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol.* 2005;15:1234-40.

⁷ Schmiedl U, Maravilla KR, Gerlach R, Dowling CA. Excretion of gadopentetate dimeglumine in human breast milk. *AJR.* 1990;154:1305-6.

⁸ Rofsky NM, Weinreb JC, Litt AW. Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. *J Magn Reson Imaging.* 1993;3:131-2.

⁹ Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, Seifert B, Puchert E, Wittek S, Debatin JF: Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology* 2000;216:555-8.

gadopentetate dimeglumine is systemically absorbed¹⁰. For these reasons, they and other commentators¹¹ question older recommendations that breastfeeding be delayed for 24 hours after maternal exposure to this agent.

Both the American College of Radiology¹² and the European Society of Urogenital Radiology⁶ have policies that do not recommend disrupting nursing after a mother receives a gadolinium contrast agent. Both organizations conclude that based on the above mentioned studies, the amount of gadolinium in breast milk is very small, and its oral absorption is minimal. The extremely low risk to the neonate from the contrast agent is not considered sufficient to warrant disruption to breastfeeding.

Reviewer comment

The above recommendations are based on studies involving gadolinium products with half lives of approximately two hours. Gadovist has a half life of approximately 1.8 hours, and although interruption of breastfeeding is not indicated, women who feel uncomfortable breastfeeding following exposure to Gadovist can temporarily interrupt nursing (pump and discard milk) for five half lives, or about 10 hours to allow near-complete clearance of the drug.

DISCUSSION/CONCLUSIONS

The MHT recognizes that due to the limited number of exposed pregnant or lactating women, and the fact that other gadolinium agents, not Gadovist, were the drug of exposure, these post-marketing data do not reliably estimate the frequency or absence of drug-associated adverse outcomes due to Gadovist. The MHT also recognizes that long term risks of fetal exposure to Gadovist are unknown. However, the MHT is of the opinion that it is useful to include available human data regarding pregnancy or lactation, even if limited. While gadolinium products should be avoided in pregnancy, there are potential clinical situations when using a gadolinium product may be necessary to optimize the care of the mother and fetus. Due to minimal excretion in breast milk, and limited gastrointestinal absorption, gadolinium-based contrast agents appear to be safe for the neonate. The MHT's goal is to make the Pregnancy and Nursing Mothers sections of labeling a more effective communication tool for clinicians, and therefore our recommendation is to include the available human data in the label in a way that is consistent with other approved gadolinium products.

RECOMMENDATIONS

¹⁰ Laniado M, et al. MR imaging of the gastrointestinal tract: value of Gd-DTPA. Am J Roentgenology 1988;150; 817-821.

¹¹ Chen MM, et al. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstetrics and Gynecology 2008;112; 333-340.

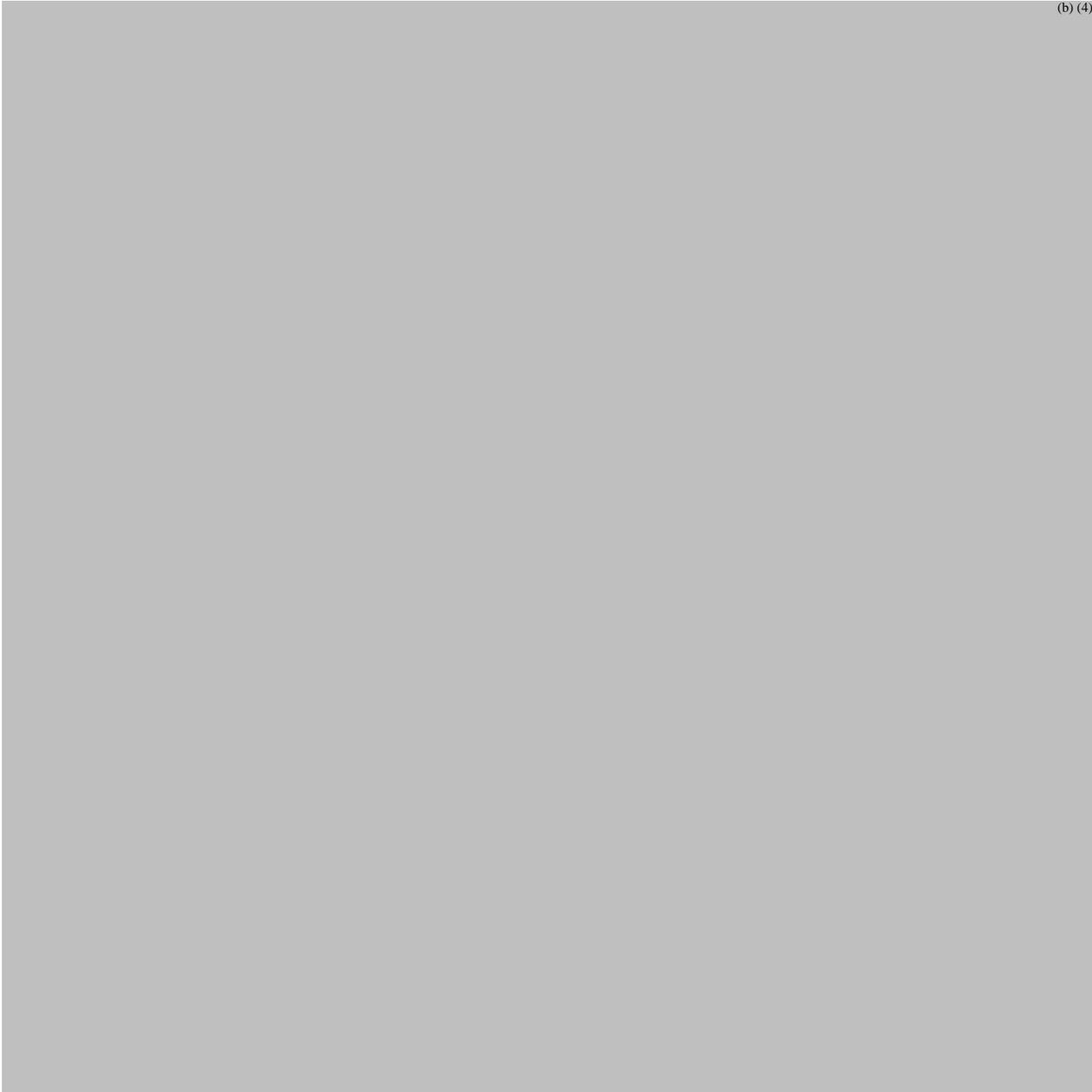
¹² American College of Radiology Committee on Drugs and Contrast medium Manual on Contrast Media; Version 7, 2010.

Provided below are the MHT's recommended revisions to the sponsor's proposed labeling. This version of the labeling includes recommendations made by the Toxicology Reviewer, Dr. Olayinka Dina.

Highlights of Prescribing Information:

-----**USE IN SPECIFIC POPULATIONS**-----

Pregnancy: Based on animal data may cause fetal harm (8.1).



(b) (4)

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/s/

LEYLA SAHIN
02/03/2011

Karen B FEIBUS
02/03/2011
I concur with the labeling recommendations presented in this review.

LISA L MATHIS
02/03/2011

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: January 19, 2011

TO: James Moore, Regulatory Project Manager
Barbara Stinson, D.O., Medical Officer
Division of Medical Imaging Products

FROM: Susan D. Thompson, M.D., Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 201-277

APPLICANT: Bayer HealthCare Pharmaceuticals

DRUG: Gadovist (gadobutrol)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Gadolinium based contrast agent for magnetic resonance imaging (MRI) of the Central Nervous System (CNS)

CONSULTATION REQUEST DATE: August 16, 2010

DIVISION ACTION GOAL DATE: March 10, 2011

PDUFA DATE: March 14, 2011

I. BACKGROUND:

Bayer HealthCare Pharmaceuticals submitted this New Drug Application for the use of gadobutrol (Gadovist) as a gadolinium based contrast agent for magnetic resonance imaging (MRI) of the Central Nervous System (CNS).

Magnetic resonance imaging (MRI) provides reliable imaging information in patients with neurological disorders, vessel abnormalities, and parenchymal organ disorders. Unenhanced MRI is used to display/demarcate focal pathologies of the central nervous system (CNS), vascular system, and other body regions. Contrast agents are routinely used to improve the detection and visualization of the specific features of such pathologies. Currently, contrast-enhanced MRI is the clinical “gold standard” for detection, localization, and depiction of the intrinsic properties of a CNS lesion.

Gadobutrol (Gadovist) is an extracellular MRI contrast agent. The active ingredient is gadobutrol. In common with other MRI contrast agents, gadobutrol contains gadolinium, which causes shortening of relaxation times (T1 and T2), yielding contrast enhancement in MRI scans. Gadobutrol was first approved in Switzerland in 1998, and has since been approved in many countries, including most of the European Union countries. The sponsor claims that gadobutrol has demonstrated an excellent safety profile in more than 2,900 adults enrolled in phase 1 to 3 trials and in more than (b)(4) patients in countries where it is approved. Gadobutrol 1.0 molar is now being developed in the United States for the indication “CNS imaging.”

The purpose of these studies was to demonstrate the safety and efficacy of gadobutrol 1.0 molar in patients for CNS imaging. The sponsor anticipated that the higher relaxivity of gadobutrol may provide improved visualization of lesions compared with other approved gadolinium agents.

Brief synopses of the protocols for which the division has requested clinical investigator inspections are given below.

Protocol 310123: A multicenter, randomized, double-blind, crossover, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist[®]) in patients referred for contrast-enhanced MRI of the central Nervous system (CNS)

This multicenter, randomized, double-blind, crossover, Phase 3 study was conducted at 13 United States sites and 38 foreign sites between June, 2008 and April, 2009. The primary objectives of the study were:

- The superiority of combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI based on the evaluation of the following:
 - Degree of contrast enhancement
 - Assessment of border delineation
 - Internal morphology of lesions

AND

- Noninferiority of combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI based on the evaluation of the total number of lesions detected.

Subjects included were male and female subjects at least 18 years of age referred for contrast-enhanced MRI of the CNS based on current clinical symptoms or on a previous imaging procedure. The test product was gadobutrol 1.0 molar in a dose of 0.1 mmol/kg body weight IV in a single dose. The reference therapy was ProHance[®] (gadoteridol) 0.5 molar in a dose of 0.1 mmol/kg of body weight IV in a single dose. During Study period 1, the subject was randomized to receive either gadobutrol or gadoteridol prior to MRI; the subject received the other contrast agent prior to MRI during Study period 2, which was to take place at least 24 hours later, but not more than 15 days later. Efficacy evaluations included the evaluation of the unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and gadoteridol-enhanced MRI by the clinical study investigators and 3 independent blinded readers. A final clinical diagnosis was determined by an independent truth committee following evaluation of findings from referral through a 3-month follow-up period, not including the study-specific MR image sets (both enhanced and unenhanced). Safety evaluations included vital signs, physical examinations, clinical laboratory parameters (blood and urine), and monitoring of adverse events (AEs) up to 72 hours following study period 2.

Brief Summary of Results

A total of 419 subjects were screened for inclusion in the study; 17 prematurely discontinued before receiving study drug. A total of 402 subjects received study drug and were analyzed for safety, and 336 subjects were analyzed for efficacy (316 in the per protocol analysis). Most of the subjects were <65 years of age (76.6%), with a mean age of 50.8 years. Approximately one-third of all subjects were enrolled at study centers in the United States. The most commonly reported referral lesions types were “other” (36.3% of subjects), multiple sclerosis (15.9% of subjects), metastasis (14.9% of subjects), and meningioma (10.9% of subjects). For three of the four primary efficacy variables (contrast enhancement, border delineation, and internal morphology), the improvement in scores from unenhanced to combined unenhanced/gadobutrol-enhanced was statistically significant for the average reader, as well as for the 3 individual readers. For the number of lesions, there was a high level of variability across the 3 readers resulting in a failure to demonstrate noninferiority. The results were identical for the comparison between gadobutrol and gadoteridol. Conclusions were identical when analyses were performed on the intent to treat and per protocol populations.

Of the 402 subject who received gadobutrol, 100 (25.1%) subjects reported at least 1 AE during the study. Of the 393 subject who received gadoteridol, 96 (24.4%) subjects reported at least 1 AE during the study. The proportion of subjects with at least 1 drug-related AE in both treatment groups were similar: 40 (10%) subjects in the gadobutrol group and 38 (9.7%) in the gadoteridol group. The most common drug-related AE in both the gadobutrol and gadoteridol treatment groups was nausea (6 [1.5%] and 10 [2.5%] subjects, respectively). Two subject each experienced 1 SAE during the gadobutrol period (100180001 – brain metastases and 200030019 – aggravation of hydrocephalus). One subject experienced 2 SAEs (100080002 – worsening of his general condition and somnolence) during the gadoteridol period. None of the SAEs were considered to be related to the study drug. No deaths were reported during the study. Clinical laboratory evaluations performed at baseline, at 24 ± 4 hours postinjection for

study periods 1 and 2 did not demonstrate clinically relevant changes from baseline, nor did serum creatinine additionally collected at 72 ± 4 hours postinjection during study period 2.

Protocol 310124: A multicenter, open-label, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist[®]) in patients referred for contrast-enhanced MRI of the central nervous system (CNS)

This multicenter, open-label, Phase 3 study was conducted at 7 United States sites and 15 foreign sites between December, 2007 and December, 2008. The primary objectives of the study were to demonstrate:

- The superiority of combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI based on the evaluation of the following:
 - Degree of contrast enhancement
 - Assessment of border delineation
 - Internal morphology of lesions

AND

- Noninferiority of combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI based on the evaluation of the total number of lesions detected.

Subjects included were male and female subjects at least 18 years of age referred for contrast-enhanced MRI of the CNS based on current clinical symptoms or on a previous imaging procedure. The test product was gadobutrol 1.0 molar in a dose of 0.1 mmol/kg body weight IV in a single dose. Efficacy evaluations included the evaluation of the unenhanced MRI and the combined unenhanced and gadobutrol-enhanced MRI by the clinical study investigators and 3 independent blinded readers. A final clinical diagnosis was determined by an independent truth committee following evaluation of findings from referral through a 3-month follow-up period, not including the study-specific MR image sets (both enhanced and unenhanced). Safety evaluations included vital signs, physical examinations, clinical laboratory parameters (blood and urine), and monitoring of adverse events (AEs) up to 72 hours.

Brief Summary of Results

A total of 347 subjects were screened for inclusion in the study; 4 subjects failed screening because they did not meet the inclusion criteria. A total of 343 subjects received study drug and were analyzed for safety, and 321 subjects were analyzed for efficacy (314 in the per protocol analysis). Most of the subjects were <65 years of age (85.7%), with a mean age of 47.7 years. The majority of subjects were enrolled at study centers outside the United States. The most commonly reported referral lesions types were “other” (33.8% of subjects), meningioma (14.0% of subjects), and metastasis (6.1% of subjects).

For three of the four primary efficacy variables (contrast enhancement, border delineation, and internal morphology), the improvement in scores from unenhanced to combined unenhanced/gadobutrol-enhanced were statistically significant for the average reader, as well as for the 3 individual readers. For the number of lesions, noninferiority was demonstrated between unenhanced and combined unenhanced/gadobutrol-enhanced. Conclusions were identical when analyses were performed on the intent to treat and per protocol populations.

Of the 343 subject who received gadobutrol, 67 (19.5%) subjects reported at least 1 AE during the study. The most commonly reported AEs were headache (3.5%), nausea (2.3%), fatigue (1.5%), white blood cells present in the urine (1.5%), and red blood cells present in the urine (1.2%). Fourteen (4.1%) of subjects experienced at least 1 drug-related AE. The most common drug-related AE was nausea in 6 (1.7%) subjects. There were no deaths and no subject prematurely discontinued the study drug due to an AE. One subject experienced a SAE (transient ischemic attack), which the investigator did not consider drug-related. Clinical laboratory evaluations were performed at baseline, and at 24 and 72 hours postinjection. Two subjects had a postinjection hematology value which was considered an AE (decrease in WBC), seven subjects had postinjection chemistry values and seven subjects had postinjection urinalysis values that were reported as AEs. None of the laboratory AEs were considered by the investigators to be related to study drug.

Blinded Image Evaluation (BIE) for Studies 310123 and 310124

Similar BIE procedures were followed for Studies 310123 and 310124; relevant differences will be mentioned below. The blinded readers were independent radiologists who were not involved in the clinical study. They were blinded to all patient history and did not have information about the study center, detailed information about the sequence parameters, the application of the contrast agent, or the study protocol. All image sets were sent electronically to the image core laboratory (b)(4). Received images were reviewed by the core laboratory for quality control, and patient, center, and sequence information was masked in the MR images. An audit trail was maintained.

During the BIE, an eCRF was used. The blinded reading consisted of the following parts (Study 310123):

Part I Lesion visualization parameters, normal structure visualization parameters and diagnosis (3 sessions separated by at least 2 weeks)

- Total number of lesions detected
- Border delineation
- Degree of contrast enhancement
- Internal morphology
- Diagnosis
- Confidence in Diagnosis

Part II Normal/abnormal diagnosis by patient

Part III Image quality

Part IV Signal intensity (SI) measurement

Part V

- Number of contrast enhanced lesions
- Adjudication

Training was provided for the readers before the BIE in the completion of the eCRF, operation of the imaging work station, and specific protocol language. All MRI images were provided to

the blinded readers in randomized order. Representatives from the sponsor could be present; they were blinded and their presence recorded. All evaluations were stored in the sponsor's central study destination database for analysis. Please see the protocols for details of the reading sessions and randomization of image material.

Rationale for Site Selection

Gadovist has not been previously approved in the United States and is considered to be an NME. Four clinical investigator sites, a CRO and the sponsor were inspected in support of this application. Dr. Melhem's and Dr. Booth's sites were chosen for inspection based on relatively high enrollment and a relatively high number of treatment emergent adverse events. Dr. Von Kummer's site was chosen for inspection based on relatively high enrollment and a relatively high number of protocol violations reported. The CRO (b)(4) was responsible for provision of the independent interpretation of study primary efficacy data necessary for the evaluation of clinical efficacy. Bayer was inspected as the sponsor of the NDA for an NME.

II. RESULTS (by Site):

| Name of CI, IRB, or Sponsor & Location | Protocol # and # of Subjects | Inspection Date | Preliminary Classification | Final Classification |
|---|--|------------------------|----------------------------|----------------------|
| Dr. Elias Melhem University of Pennsylvania Health System 3400 Spruce Street 2 nd floor Dulles Building Philadelphia, PA 19104 | Protocol 310123 Site #14002 19 Subjects | 11/16/10 – 11/19/10 | NAI | Pending |
| Dr. Robert Booth UF College of Medicine – C90 655 West Eighth Street Jacksonville, FL 32209 | Protocol B: #310124 Site 14001 19 Subjects | 10/12/10 – 10/14/10 | NAI | NAI |
| Dr. Jae K. Kim 677 N. Willmot Road Tuscon, AZ 85711 | Protocol 310124 Site 14004 15 Subjects | Pending | NAI | Pending |
| Hr. Prof. Dr. Rudiger Von Kummer Universitasklinikum Carl Gustav Carus Abteilung Neuroradiologie (Haus 59) Fetscherstrasse 74 01307 Dresden, Germany | Protocol 310123 Site 14006 27 Subjects | 11/8/10 – 11/10/10 | NAI | Pending |
| Bayer HealthCare Pharmaceuticals Global Regulatory Affairs 340 Changebridge Road Montville, NJ 07045 | Protocol 310123 Protocol 310124 | 10/18/10 – 11/8/10 | VAI | Pending |
| (b)(4) | Protocol 310123 Protocol 310124 | Pending | NAI | Pending |

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.1. **Dr. Elias Melhem****University of Pennsylvania Health System****3400 Spruce Street****2nd floor Dulles Building****Philadelphia, PA 19104**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 22 subjects screened, 19 subjects enrolled, and all 19 subjects completed the study. Review of 100% of informed consent documents was performed. Source documents were compared to electronic case report forms and data listings for all subjects. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** The study appeared to have been conducted adequately at this site. There were no discrepancies between subject source documents, the electronic case report forms, and the data listings. No discrepancies were observed in the informed consent forms. No evidence of underreporting of adverse events was noted. No Form FDA 483 was issued to the investigator.
- c. **Assessment of data integrity:** The data from Dr. Melhem's site appear acceptable for use in support of the NDA.

2. **Dr. Robert Booth****UF College of Medicine – C90****655 West Eighth Street****Jacksonville, FL 32209**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 19 subjects screened and enrolled, and all subjects completed the study. Review of 100% of informed consent documents was performed. The following records and source data were reviewed: adequacy of documentation; laboratory reports; key personnel responsibility log; inclusion and exclusion criteria; review and reporting of adverse events; test article accountability; IRB and sponsor correspondence; receiving and dispensing of study test article; drug accountability records; and protocol deviations. Source documents were compared with electronic CRFs,

and the data listings. The observations noted are based on the EIR. There were no limitations to the inspection.

- b. **General observations/commentary:** The study appeared to have been conducted adequately. No issues were noted with the Informed Consent Documents, study drug accountability, adverse event reporting, or general conduct of the study. Comparison of the source documents to the electronic CRFs and the data listing revealed no discrepancies. No Form FDA 483 was issued to the investigator.
- c. **Assessment of data integrity:** The data from Dr. Booth's site appear acceptable for use in support of the NDA.

3. **Dr. Jae K. Kim**
677 N. Wilmot Road
Tucson, AZ 85711

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 19 subjects screened and 15 subjects were enrolled and completed the study. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** This inspection has been completed, and no Form FDA 483 was issued. No under reporting of adverse events was identified. The primary efficacy endpoints were verifiable based on the data at the site. The primary efficacy endpoint data matched what was sent to FDA for all subject files reviewed. As a Form FDA 483 was not issued at this site, it is unlikely that significant violations affecting data integrity occurred at this site.
- c. **Assessment of data integrity:** At this time, the data from this site appear acceptable for use in the NDA. If conclusions change when the EIR is reviewed, a CIS addendum will be generated and the review division notified.

4. **Hr. Prof. Dr. Rudiger von Kummer**
Universitasklinikum Carl Gustav Carus
Abteilung Neuroradiologie (Haus 59)
Festscherstrasse 74
01307 Dresden, Germany

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 738.811. There were 27 subject screened and enrolled and 26 subjects who completed the study. One subject discontinued the study

when the MRI device malfunctioned between the enhanced and unenhanced procedures, and she elected to discontinue from the study. A comprehensive audit of 12 subjects' records in their entirety was conducted. Included in the audit were the primary efficacy endpoint, informed consent, subject eligibility, test article accountability, randomization procedures, and protocol adherence. Informed consent, primary efficacy endpoint, and adverse events were covered for all 27 subjects. There were no limitations to the inspection. The observations noted were based on the EIR and communications with the FDA inspector.

- b. **General observations/commentary:** The study appeared to have been conducted adequately at this site. Study records were complete. All protocol deviations identified were listed in the final study report. All subjects met inclusion criteria. No under-reporting of adverse events was revealed. Test article accountability and disposition were adequately documented. Protocol – specified blinding and randomization procedures were followed. Source documents and case report forms were consistent with data listings provided by the sponsor to CDER. No Form FDA 483 was issued to the investigator.
- c. **Assessment of data integrity:** The data from Dr. von Kummer's site appear acceptable for use in support of the NDA.

5. **Bayer HealthCare Pharmaceuticals**
Global Regulatory Affairs
340 Changebridge Road
Montville, NJ 07045

- a. **What was inspected:** During this inspection, the following were reviewed: sponsor training of clinical investigators, CVs and financial disclosure statements of the clinical investigators, clinical monitoring plans, serious adverse events and adverse events reporting, IRBs utilized for the studies, and drug accountability logs for 25 clinical investigator sites including the 4 clinical investigator sites inspected. The observations noted are based on communications with the FDA field investigator, the Form FDA 483, and Bayer Healthcare's written response to the Form FDA 483 of November 29, 2010.
- b. **General observations/commentary:** One deviation from FDA regulations was noted, and a Form FDA 483 was issued for this observation. The investigation documented that the sponsor did not ensure adequate monitoring of a clinical investigation, in violation of 21 CFR 312.56. A written response to the Form FDA 483 dated November 29, 2010 was received from Bayer Healthcare.

Monitoring violations [21 CFR 312.56]

For Study 310123, Site #58005, the clinical investigator Dr. Lovblad enrolled (b) (6) into the clinical trial. Although there was no exclusion criterion (b) (4)

(b) (6)

The sponsor acknowledges this sequence of events in their November 29, 2010 written response. (b) (6)

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- c. **Assessment of data integrity:** Although there were monitoring deficiencies by the sponsor at a single clinical investigator site, this deficiency was not widespread and should not significantly impact the efficacy or safety outcomes of the study. The data from the sponsor appear acceptable for use in support of the NDA.

6. (b) (4)



IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites, a CRO and the sponsor were inspected in support of this application. In general, inspection at the sites of Drs. Melhem, Booth, Kim and von Kummer revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication. The inspection of the CRO [REDACTED]^{(b) (4)} also revealed no regulatory violations, and there were no adverse findings described regarding the Blinded Image Evaluations. The inspection of Bayer Healthcare documented isolated regulatory violations with respect to monitoring. There was no evidence that the monitoring deficiencies were widespread, and these deficiencies should not significantly impact the efficacy or safety outcomes of the study. The data appear acceptable for use in support of the NDA.

Follow-Up Actions: The observations for Drs. Melhem and Kim as well as for Bayer Healthcare and [REDACTED]^{(b) (4)} are based on preliminary communications with the FDA Field investigators. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN D THOMPSON
01/19/2011

TEJASHRI S PUROHIT-SHETH
01/20/2011

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

| | |
|------------------------------------|--|
| IND or NDA | NDA 201277 |
| Brand Name | Gadovist |
| Generic Name | Gadobutrol |
| Sponsor | Bayer HealthCare Pharmaceuticals |
| Indication | Intravenous use in diagnostic MRI in adults and children (> 2 y.o.) to detect and visualize with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system |
| Dosage Form | Gadovist 1.0 injection contains 1 mmol gadobutrol/mL |
| Drug Class | Gadolinium-based contrast agent |
| Therapeutic Dosing Regimen | 0.1 mL/kg body weight (0.1 mmol/kg), administered as an intravenous bolus injection at a flow rate of approximately 2 mL/second |
| Duration of Therapeutic Use | Single dose |
| Maximum Tolerated Dose | 1.5 mmol/kg |
| Submission Number and Date | SDN 001 |
| Review Division | DHP / HFD 160 |

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The largest upper bounds of the 2-sided 90% CI for the mean difference between gadobutrol (0.1 mmol/kg, 0.3 mmol/kg and 0.5 mmol/kg) and placebo were 6.6 ms, 11.0 ms and 11.9 ms, respectively. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in

Figure 3, indicating that assay sensitivity was established.

In this randomized, placebo-controlled, 5-period crossover study, 57 healthy subjects received gadobutrol 0.1 mmol/kg, 0.3 mmol/kg, 0.5 mmol/kg, placebo, and a single i.v. dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Gadobutrol (0.1 mmol/kg, 0.3 mmol/kg and 0.5 mmol/kg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

| Treatment | Time (hour) | $\Delta\Delta QTcF$ (ms) | 90% CI (ms) |
|------------------------|----------------|--------------------------|--------------|
| Gadobutrol 0.1 mmol/kg | 3 | 2.6 | (-1.4, 6.6) |
| Gadobutrol 0.3 mmol/kg | 0.033 (2 min) | 7.4 | (3.9, 11.0) |
| Gadobutrol 0.5 mmol/kg | 0.017 (1 min) | 8.4 | (4.8, 11.9) |
| Moxifloxacin 400 mg* | 1 | 15.1 | (11.7, 18.6) |

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 10.7 ms.

Gadovist, the aqueous solution of gadobutrol, is administered as an intravenous bolus single-dose injection of dose 0.1 mL/kg. The drug PK is dose-proportional in the studied range 0.04 to 0.4 mmol/mL after single intravenous administration. Gadobutrol is primarily distributed into the extracellular space. Plasma protein binding in humans is negligible. Gadobutrol is not metabolized and is therefore renally excreted as unchanged drug. The worst case of clinical exposure scenario is in patients with renal impairment. Significant increases in the AUC and terminal elimination half-life were observed that correlated with the degree of renal impairment (an about 10-fold increase for subjects with $CL_{Cr} < 30$ ml/min compared to subjects with normal renal function). However, volume of distribution (V_d) of gadobutrol is not affected by renal impairment. The maximal exposure of single-dose i.v. administration (C_{max}) is similar between subject with renal impairment and subjects with normal renal function. Therefore, the studied suprathereapeutic dose (0.5 mmol/kg) provided 5-fold higher of the C_{max} than that of the therapeutic dose (0.1 mmol/kg) and should cover the predicted worst case of clinical exposure scenario regarding C_{max} .

2 PROPOSED LABEL

2.1

The sponsor did not propose any label language.

2.2 QT-IRT RECOMMENDATION

12.2- Pharmacodynamics

The effect of intravenous gadobutrol 0.1, 0.3, 0.5 mmol/kg on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) crossover thorough QTc study in 57 healthy subjects. In the study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline corrected QTc based on Fridericia's correction method (QTcF) was 11.9 ms (at 1 min post-dose) following a 0.5-mmol/kg dose, respectively. A 0.5-mmol/kg dose is adequate to represent the high clinical exposure scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Gadovist is an extracellular MRI contrast agent. Like gadopentetate dimeglumine (Magnevist®) and other extracellular MRI contrast agents, Gadovist contains gadolinium (Gd^{3+}). Gadolinium is a rare earth element which causes contrast enhancement in MRI scans. The active ingredient in Gadovist is gadobutrol, a macrocyclic, low osmolar and electrically neutral compound.

Development of gadobutrol in the US ([REDACTED] ^{(b) (4)} imaging) was discontinued in 1999. The IND was inactivated by the sponsor [REDACTED] ^{(b) (4)}

[REDACTED]

[REDACTED] ^{(b) (4)}

3.2 MARKET APPROVAL STATUS

Gadovist® 1.0 M (gadobutrol injection) has been marketed in various countries outside the United States since 2000 for the approved indication, contrast-enhanced magnetic resonance imaging of the central nervous system (CNS) at doses up to 0.3 mmol/kg as an i.v. bolus injection. Worldwide, more than [REDACTED] ^{(b) (4)} doses of gadobutrol injection have been administered for approved indications.

The first marketing authorization for gadobutrol 1.0 M (Gadovist) was granted in Switzerland in 1998, and the first launch was in Switzerland in 1999. Gadovist 1.0 M is currently authorized to be marketed in 55 countries and is marketed in 38 countries.

The first marketing authorization for gadobutrol 0.5 M was granted in Switzerland in 1998. Gadobutrol 0.5 M was never marketed. The marketing authorizations were withdrawn voluntarily by the company. Currently, gadobutrol 0.5 M is not authorized to be marketed.

Gadovist 1.0 M is approved for the following indications:

The indication ‘Contrast Enhancement in Cranial and Spinal MRI’ is approved in 49 countries worldwide, including all countries of the old European Union (Mutual recognition [MR] approval in June 2000) and 8 new EU countries, Switzerland, Australia, New Zealand, Canada, Turkey, South Africa and Mexico, as well as countries in Eastern Europe and Asia.

The indication ‘Contrast enhancement in Magnetic Resonance Angiography’ (CE-MRA) is approved in 35 countries worldwide, including all countries of the European Union (MR approval in November 2003) and 4 new EU countries.

The indication ‘Contrast enhanced MRI of liver and kidneys’ was mutually approved in the EU in 2006. This indication is presently, nationally approved in 27 EU countries and 5 non-EU countries.

3.3 PRECLINICAL INFORMATION

From the IB (March 2009, Version 7.0)

“The impact on the rapidly activating delayed rectifier current was studied in vitro using transfected cells expressing hERG mediated potassium channels, as inhibition of this current is known to be associated with Torsade de pointes. In this model, the addition of gadobutrol resulted in a concentration-dependent inhibition of hERG mediated current amplitude, but even at the highest concentration of 100 mmol Gd/L, the half maximum inhibition concentration (IC₅₀) was not reached. The effects caused by gadobutrol were comparable to those of the other tested contrast agents gadodiamide (Omniscan™), gadoteridol (Prohance®), iomeprol (Imeron®). The observed effect of gadobutrol on this isolated ion channel is not expected to have a relevant impact on the course of the action potential, which was confirmed in an in vitro model using intact cardiac cells. Action potential was not significantly altered in the isolated guinea pig papillary muscle at concentrations up to 50 mmol Gd/L, whereas the reference compound Imeron resulted in a marked prolongation of action potential duration at 30% repolarization (APD₃₀) and in hyperpolarization. When considering that the human peak serum concentration is expected to be lower than 5 mmol Gd/L, concentrations of gadobutrol exceeding the maximum expected exposure of coronary cells by a factor of 10 to 20 did not induce any relevant changes indicative for a risk of QT prolongation.

“In vivo, cardiovascular effects of intravenous administration of gadobutrol were investigated in anesthetized rabbits at dose levels of 0.15, 0.5 and 1.5 mmol Gd/kg, in anesthetized dogs at dose levels of 0.25 and 1.25 mmol Gd/kg, and in conscious dogs at dose levels of 0.1, 0.5 and 2.5 mmol Gd/kg. Rabbits showed a transient decrease in heart rate and P-wave amplitude and a transient increase in blood flow and QRS amplitude in the first minutes after administration at the dose of 0.5 mmol Gd/kg and higher, whereas anesthetized dogs exhibited a minor increase in blood pressure with a concomitant rise in myocardial contractility in the first 15 min after administration.

“In the safety pharmacology study in conscious, telemetered dogs, the intravenous administration of gadobutrol did not affect arterial blood pressure, PR interval, QRS duration or gross morphology and rhythm of the ECG. However, it caused a transient slight to moderate increase in heart rate in the first 2.5 to 20 min after administration at the low dose and higher. In addition, transient small prolongation of QT and QTc intervals (using individual linear regression to correct for changes in heart rate) were found within the first 0.5 to 2.5 min after administration at the high dose of 2.5 mmol Gd/kg, which also provoked retching and emesis. The slight transient alterations in hemodynamic parameters observed in anesthetized animals were not consistent in the different species and are considered to be of minor relevance. The observed transient increase in heart rate and the QT prolongation found in conscious dogs at a dose representing a HEDacute of about 3.7 times the maximum clinical dose (MCD, 0.5 mmol/kg) (5 times the MCD in terms of body weight) were slight and limited to the first minutes after administration. Thus, injection of gadobutrol is not expected to cause serious or prolonged cardiac side effects, although slight transient effects in the first minutes after injection including a slight prolongation of QT interval may occur in the clinical dosing scheme.”

Reviewer's comments: Based on data obtained in vivo there is a potential for gadobutrol to prolong QT and increase HR in the first minutes after injection with exposures equivalent to a clinical dose of 0.5 mmol/kg.

3.4 PREVIOUS CLINICAL EXPERIENCE

From the IB (March 2009, Version 7.0), Integrated Review of Safety eCTD 5.3.5.3 and Study Report 307362

ECG data in healthy subjects

“Study 98216. In this ECG re-evaluation study, ECGs from studies 9746 and 9748 were manually re-evaluated by a certified cardiologist who was blinded to time point and dose. QTcB changes >60 ms were observed at early post-injection time points (2, 5, 15, 30, 60 min after injection) in three subjects (placebo: 1, study drug: 2). All respective QTcB values were below 460 ms.

“The QTcB changes are likely to be caused by the change in heart rate and the respective Bazett over-correction of the post-injection value. This is supported by the similar observation in the placebo group.

“Study 97113 [Report B113] Study 97113 tested a possible effect of different doses by far exceeding the recommended dose range to allow a better risk assessment in case of serious overdosing. A 12-lead ECG was recorded before, during and up to 30 s after bolus injection of 0.3, 0.5, 0.75, 1.0, 1.25, and 1.5 mmol/kg bw. Further recordings were obtained at 1, 2, 4, 6, 12, and 24 h after administration.

“Overall, 9 subjects had at least one QTcB value with an increase >60 ms: the heart rate was simultaneously increased by 9-35 bpm compared to baseline. In most cases the heart rate as well as the QTcB were already increased at the first post-injection measurement (5-10 sec after injection), a time at which it can be assumed that the contrast agent had not yet reached the heart. The increased QTcB values are thus very likely caused by the correction method. Two subjects (both 1.25 mmol/kg bw) had at least one QTcB value >500 ms at some time during the course of the recording. Both values were explained by an increase in heart rate. In the low-dose groups (up to 0.5 mmol/kg bw), no Gadovist-related effects on the QT-interval were observed. No subject examined in the 0.3 mmol/kg bw group showed a relevant QTcB prolongation. In the 0.5 mmol/kg bw group, a rise in QTcB over 60 ms at any time during the recording as compared to the early baseline value was seen in 1 subject (no. 11).

“The number of subjects with potential risk factors, ie, (1) QTcF \leq 460 msec as mean of baseline and pre-contrast and > 460 msec in any post-contrast period, and (2) QTcF increases 30 to 60 msec from mean of baseline and pre-contrast or increases more than 60 msec compared to mean of baseline and pre-contrast) was evaluated in the Phase I studies. The evaluation was based on Study 307362, where the QTcF values were explicitly documented. There were 38 subjects injected with gadobutrol and 13 subjects with placebo (saline). Only one subject in the gadobutrol group showed an increase in QTcF > 460 msec from baseline > 15 to 30 min after injection. The subject (Subject 1096, a Black female) with a predose QTcF value of 424 msec had an increase in value to 461 msec (mean change of 37 msec from baseline) (Tables 230, 238 and Listing 33, Appendix 4). A total of 4 subjects (3 gadobutrol, 1 placebo, all Blacks in ethnicity)

showed increases in QTcF values 30 to 60 msec from mean of baseline and pre-contrast after injection (Table 232 and Listing 35, Appendix 4).

- Subject 1041, a male with baseline QTcF value of 379 msec, had an increase in value to 410 msec > 1 to 2 h after injection of gadobutrol.
- Subject 1084, a male with a baseline QTcF value of 400 msec, had an increase in value to 432 msec > 2 to 4 h after injection of gadobutrol.
- Subject 1096, a female with a baseline QTcF value of 424 msec, had an increase in value to 461 msec > 15 to 30 min after injection of gadobutrol.
- Subject 1015, a male from the placebo group, with a baseline QTcF value of 395 msec, had an increase in value to 425 msec > 1 to 2 h after injection of placebo (saline).”

ECG data in patients

“The 12-lead ECG data of 93 patients included in three phase 3 CE-MRA studies with Gadovist 1.0 M are available for the evaluation of cardiac safety. 86% of these patients (80/93 patients) had cardiovascular disease, including 39/93 patients (42%) with severe cardiac disease. The 12-lead ECGs were recorded over a period of 30 seconds before the MRI, directly after the end of the MRI examination, and 2-4 and 24 hours after the injection of Gadovist 1.0 M. For heart rate-correction, the Bazett method was used. No indication of a Gadovist-induced change (prolongation) of the QT interval was observed at any time point.

“After injection, more patients had lower QTcB compared with baseline than higher. In one patient (30002 from study 97099), a maximum increase of 62 ms in QTcB was seen at 2-4 h after injection. However, in the remaining 92 of the 93 patients, the QTcB increases were less than 60 ms. The maximum increase in the remainder of the group was 43 ms, from 436 ms at baseline to 479 ms after injection, with a simultaneous heart rate increase of 18 bpm from 68 to 86 bpm.

“In 4 cases, the baseline QTcB was ≥ 500 ms, probably indicating a long QT syndrome. In three of these four patients, the post-injection QTcB was lower than the baseline value; in one case it was further increased by 37 ms. In the context of the above discussion, this does not raise a concern regarding a Gadovist-related effect. In another three cases, the post-injection QTcB was ≥ 500 ms while the baseline value was below 500 ms.

“As discussed above, such high QTcB values are likely to result from the Bazett correction which uses the square root for correction. This leads to artificially long QTcB values for higher heart rates (e.g. measured QT < 400 ms).

“The mean values of QT interval and QTcF interval including differences from mean values at baseline are shown in the following table (bottom part) for the integrated analysis pool, S2.

Table 2: ECG Data (QTcF) by timepoint-Including Differences from Mean of baseline and Pre-contrast-Phase II-IV Studies.

| Treatment | Time Interval | Value at Visit | | | | | | Change from Baseline | | | | | |
|----------------|---------------|----------------|-------|------|-----|--------|-----|----------------------|------|------|-----|--------|-----|
| | | n | Mean | SD | Min | Median | Max | n | Mean | SD | Min | Median | Max |
| Gadobutrol | Predose | 447 | 408.9 | 24.7 | 339 | 408.0 | 554 | | | | | | |
| | >0-15min | 223 | 412.8 | 26.8 | 342 | 413.0 | 509 | 222 | 3.4 | 16.3 | -46 | 4.5 | 41 |
| | >30-60min | 223 | 412.2 | 22.8 | 350 | 411.0 | 548 | 222 | 3.6 | 13.1 | -43 | 3.0 | 46 |
| | >2-4h | 221 | 409.5 | 22.3 | 368 | 408.0 | 553 | 220 | 1.1 | 13.3 | -35 | 0.0 | 63 |
| | 1 day | 221 | 408.0 | 21.0 | 364 | 406.0 | 501 | 220 | -0.7 | 14.9 | -53 | -1.0 | 47 |
| | 3 days | 214 | 408.0 | 20.9 | 357 | 407.0 | 499 | 213 | -1.0 | 16.3 | -68 | -1.0 | 61 |
| Gadoversetamid | Predose | 220 | 407.9 | 24.7 | 344 | 408.0 | 529 | | | | | | |
| | >30-60min | 223 | 410.7 | 23.2 | 363 | 410.0 | 533 | 220 | 3.0 | 15.7 | -86 | 5.0 | 38 |
| | >2-4h | 222 | 408.0 | 22.1 | 355 | 407.0 | 531 | 219 | 0.3 | 14.0 | -38 | 1.0 | 44 |
| | 1 day | 219 | 406.3 | 22.4 | 361 | 403.0 | 531 | 215 | -1.7 | 15.1 | -52 | -2.0 | 39 |
| Total | Predose | 667 | 408.5 | 24.7 | 339 | 408.0 | 554 | | | | | | |
| | >0-15min | 223 | 412.8 | 26.8 | 342 | 413.0 | 509 | 222 | 3.4 | 16.3 | -46 | 4.5 | 41 |
| | >30-60min | 446 | 411.5 | 23.0 | 350 | 410.0 | 548 | 442 | 3.3 | 14.4 | -86 | 4.0 | 46 |
| | >2-4h | 443 | 408.7 | 22.2 | 355 | 408.0 | 553 | 439 | 0.7 | 13.6 | -38 | 1.0 | 63 |
| | 1 day | 440 | 407.1 | 21.7 | 361 | 404.5 | 531 | 435 | -1.2 | 15.0 | -53 | -2.0 | 47 |
| | 3 days | 214 | 408.0 | 20.9 | 357 | 407.0 | 499 | 213 | -1.0 | 16.3 | -68 | -1.0 | 61 |

Source: Table 412, Biometrical Report, page 1011

“A total of 57 (7.2%) subjects in the gadobutrol group had clinically significant changes in ECG from baseline, 25 (12.1%) subjects at < 0.09 mmol/kg bw dose, 20 (6.2%) subjects at > 0.09 to 0.11 mmol/kg bw dose, and 12 (13.0%) subjects at > 0.11 to 0.21 mmol/kg.

“In clinical trials in Europe, gadobutrol has been administered in doses up to 1.5 mmol/kg body weight (BW) overall and at doses up to 0.3 mmol/kg BW at injection rates up to 5 mL/sec. No clinical safety issues were evident in those studies. Adverse events (AEs) related to the cardiovascular system were infrequent. No related events with severe intensity and no related serious adverse events were observed. In clinical studies with Gadovist used for contrastenhanced magnetic resonance angiography in doses of 0.1 to 0.3 mmol/kg, ECG was recorded in 93 of 415 patients before, immediately after, and 2 to 4 hours and 24 hours after administration of the contrast agent to assess the potential effect of gadobutrol on ventricular repolarization. The incidence of QTc prolongation by 30 to 60 msec was 6% immediately after, 9% at 2 to 4 hours and 11% at 24 hours after Gadovist injection. Prolongation of QTc by >60 msec was observed 1 patient. QTc decreases by the same range were observed in a similar percentage of patients 2 to 4 hours and 24 hours after injection. The clinical relevance of these changes is not known. There were no significant cardiovascular adverse events related to QTc prolongation in patients with known cardiovascular diseases.

Adverse events

“In Phase I studies, the AEs of allergic reactions were reported in 2 (1.0%) subjects within 24 hours after injection of gadobutrol, one subject at ≤ 0.11 mmol/kg bw (Subject 410 / Study 310865) and 1 subject at > 0.11 to 0.21 mmol/kg bw dose (Subject 209 / Study 310865).

“In the phase 2-4 studies, all adverse events were coded according to MedDRA. In the S2 integrated analysis pool (4549 subjects), 6 (0.1%) subjects (5 subjects at > 0.09 to 0.11 and 1 subject at > 0.21 to 0.31 mmol/kg bw dose) reported allergic reactions within 24

hours after injection of gadobutrol. No AEs were reported in subjects with a history of allergies to contrast media (Tables 65, 66, 71, and 72, Appendix 5).

“Of the 6 subjects with AEs identified by the sponsor as SMQ “Immediate Type Hypersensitivity Reactions”, 3 subjects reported AEs in the skin and subcutaneous tissue disorders SOC (for erythema, pruritus, rash, and urticaria PT), 2 subjects in the immune system disorders SOC (hypersensitivity PT), 1 subject in the respiratory, thoracic, mediastinal disorders SOC (respiratory arrest PT), and 1 subject in the vascular disorders SOC (hypotension PT).”

Table 3: Drug Related Adverse events with $\geq 5\%$ incidence (gadobutrol)-Integrated Analysis Pool, S2

| Primary System Organ Class and Preferred Term | Gadobutrol |
|---|--------------------|
| Number of subjects | 4549 (100%) |
| Total number of events | 716 (100.0%) |
| No. of subjects with any drug related event | 182 (4.0%) |
| Number of drug related events | 240 (33.5%) |
| Gastrointestinal disorders | |
| Nausea | 35 (0.8%) |
| General disorders and administration site conditions | |
| Feeling hot | 22 (0.5%) |
| Nervous system disorders | |
| Dysgeusia | 22 (0.5%) |

Source: Tables 52, 55, and 101 of the ISS Biometrical Report (pool S2)
 AEs coded by MedDRA, Version 12.1

Source: Table 8, eCTD 2.7.4, page 42

Deaths

No deaths were reported in Phase 1 and there was only one death reported in the gadobutrol group (of the total 4549 subjects) that was not linked to study drug.

Reviewer’s Comments: Although mean effects on QT duration were not found during Phase II-IV gadobutrol clinical program, some subjects had clinically relevant QT changes over baseline. Similar findings on QT interval were reported in EU. However, no syncope, seizure, sudden death or ventricular arrhythmia was reported in these trials.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of gadobutrol’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study.) The sponsor submitted the study report A21381 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Cardiovascular safety study of 0.1, 0.3 and 0.5 mmol/kg gadobutrol (Gadovist®) bolus injection in normal subjects following a randomized, cross-over design using placebo and a concurrent positive control.

4.2.2 Protocol Number

307362

4.2.3 Study Dates

02 March 2004 -- 02 June 2004

4.2.4 Objectives

The objective of this study was to evaluate the electrocardiographic effects, especially a potential influence on cardiac repolarization, of gadobutrol. Gadobutrol was administered in normal subjects as a bolus (2 mL/sec) at doses of 0.1 mmol/kg (0.1 mL/kg), 0.3 mmol/kg (0.3 mL/kg), and 0.5 mmol/kg (0.5 mL/kg) using a power injector. QT measurements were compared with placebo (0.9% saline solution) as a negative control and to moxifloxacin 400 mg as a positive control.

4.2.5 Study Description

4.2.5.1 Design

This was a single-center, randomized, placebo-controlled, 5-period crossover, dose comparison study with a concurrent positive control.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The design was double-blind for gadobutrol and placebo. The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

“There were 5 treatments for each subject. Upon successful completion of the screening examinations, subjects were assigned to a 5-treatment sequence following a Williams design. Subjects were assigned randomization numbers sequentially in the order they entered the study from a randomization list provided by the sponsor. Study treatments and treatment assignment during the 5 crossover periods are summarized in following tables.”

Table 4: Study Design

| Number | Treatment |
|--------|--|
| 1 | Saline (0.9%) solution (placebo) (0.5 mL/kg) at 2 mL/sec |
| 2 | Gadobutrol 0.1 mmol/kg (0.1 mL/kg) at 2 mL/sec |
| 3 | Gadobutrol 0.3 mmol/kg (0.3 mL/kg) at 2 mL/sec |
| 4 | Gadobutrol 0.5 mmol/kg (0.5 mL/kg) at 2 mL/sec |
| 5 | Moxifloxacin 400 mg (positive control) at 0.07 mL/sec |

| | Period 1 | Period 2 | Period 3 | Period 4 | Period 5 |
|-------------|----------|----------|----------|----------|----------|
| Sequence 1 | 1 | 2 | 5 | 3 | 4 |
| Sequence 2 | 2 | 3 | 1 | 4 | 5 |
| Sequence 3 | 3 | 4 | 2 | 5 | 1 |
| Sequence 4 | 4 | 5 | 3 | 1 | 2 |
| Sequence 5 | 5 | 1 | 4 | 2 | 3 |
| Sequence 6 | 4 | 3 | 5 | 2 | 1 |
| Sequence 7 | 5 | 4 | 1 | 3 | 2 |
| Sequence 8 | 1 | 5 | 2 | 4 | 3 |
| Sequence 9 | 2 | 1 | 3 | 5 | 4 |
| Sequence 10 | 3 | 2 | 4 | 1 | 5 |

Source: sponsor's clinical report Text Table 1 and Table 2

4.2.6.2 Sponsor's Justification for Doses

“The dose range for gadobutrol was selected to include both the anticipated clinical dose for CNS magnetic resonance imaging (0.1 mmol/kg) and a 5-fold higher dose (0.5 mmol/kg BW) to resemble overdosing. The 0.5 mmol/kg dose is consistent with the highest dose for which there are systematic safety data currently available.”

Reviewer's Comment: The sponsor's dose justification is acceptable. Gadovist, the aqueous solution of gadobutrol, is administered as an intravenous bolus single-dose injection of dose 0.1 mL/kg. The drug exposure is dose-proportional in the studied range 0.04 to 0.4 mmol/mL after single intravenous administration. Gadobutrol is primarily distributed into the extracellular space. Plasma protein binding in humans is negligible. Gadobutrol is not metabolized and is therefore renally excreted as unchanged drug. The worst case of clinical exposure scenario is in patients with renal impairment. Significant increases in the AUC and terminal elimination half-life were observed that correlated with the degree of renal impairment (an about 10-fold increase for subjects with CL_{Cr} < 30 ml/min compared to subjects with normal renal function). However, volume of distribution (V_d) of gadobutrol is not affected by renal impairment. The maximal exposure of single-dose i.v. administration (C_{max}) is similar between subject with renal impairment and subjects with normal renal function. Therefore, the studied supratherapeutic dose (0.5 mmol/kg) provided 5-fold higher of the C_{max} than that of the

therapeutic dose (0.1 mmol/kg) and should cover the predicted worst case of clinical exposure scenario regarding C_{max} .

4.2.6.3 Instructions with Regard to Meals

“The administration of treatment plus saline flush during study periods 1 – 5 for each subject was completed at the same time of the day (e.g., 10:00 AM) to minimize diurnal effects on QT interval. Subjects fasted before entering the baseline period. Fasting started at midnight before the respective baseline period. A small snack was provided 2 hours after the end of the study drug administration and a standardized light meal was provided 4 hours post-end of injection. Dinner was provided after completion of all safety measurements at the 8-hour post-end of injection/infusion time point. Breakfast was served the next morning after completion of all 24-hour safety measurements.”

Reviewer’s Comment: Acceptable. Gadobutrol is administered intravenously.

4.2.6.4 ECG and PK Assessments

“QT interval assessment (used for calculation of the baseline mean) and all other ECG parameters were derived at the following time points:

- Prior to injection of the study drug at baseline -90, -70, -65 and -60 minutes
- After injection of the study drug at 0, 1, 2, 4, 6, 8, 10, 12, 15, 30, 60 minutes and 2, 3, 4, 6, 8 and 22 hours.

“A total of 14 blood samples were collected during each study period for PK analysis: 1 pre-dose sample prior to study drug administration and 13 samples during the first 24 hours after the end of the saline flush at time 2, 4, 6, 15, 30, 45 and 60 minutes and at 2, 3, 4, 6, 8 and 24 hours.”

Reviewer’s Comment: The timings of the ECGs and the PK are acceptable. The drug is administered intravenously. Gadobutrol is not metabolized and the terminal half-life is about 2 hours. The sampling schedule is adequate to cover the entire PK profile (5 half-life) and the potential delayed effect up to 22 hours.

4.2.6.5 Baseline

Baseline ECG was collected on the same day before each dosing (120 to 91 minutes prior to the administration of study drug).

4.2.7 ECG Collection

“The H-12™ 12-Lead Digital Holter Recorder (Mortara Instrument, Inc.; Milwaukee, WI) was used for continuous 12-lead ECG recording. Evaluation of the ECGs was performed at a dedicated core laboratory. Manual analysis was to be done for each subject by the same cardiologist who was blinded to the dose group (including placebo and positive control) and the origin of the ECG (subject). If this was not possible due to unforeseeable circumstances, at least all ECGs from one subject were to be read by a single cardiologist with the number of readers kept to a minimum.

“Because the QT interval adapts slowly to heart-rate changes, subjects were to have a stable heart rate (i.e., fluctuation ≤ 5 bpm) over a period of ≥ 2 minutes before the selected time point, whenever possible.

“ECG lead II was to be used as the standard lead for QT measurements. If the quality of lead II was not appropriate for the measurement, then another lead (lead V5, then V2 or V3) was to be used according to standard procedures at the ECG core laboratory. The lead used for interval measurements was identified in the electronic database transfer for each time point. Baseline interval measurements from this defined lead were also used for calculating the individual heart rate regression curve.

“Manual evaluation of the electronic data was performed on screen applying an automatic caliper. The intervals that were measured and the exact start and end of the interval were documented electronically. The ECG data with added measurements/evaluation were stored electronically and were made available for review upon request. The same hardware and software were used for all ECGs.

“At all time points, 3 consecutive RR and QT intervals were measured and the mean of these values was recorded. The QT interval was defined as the offset of the Q or R spike from the zero-line until the first contact with the zero-line at the end of the T wave.”

4.2.8 Sponsor’s Results

4.2.8.1 Study Subjects

Sixty-four subjects were randomized and 56 (87.5%) completed the study. Eight (12.5%) subjects discontinued the study prematurely. Three (4.7%) subjects discontinued the study due to adverse events.

Table 5: Disposition of Subjects

| Disposition/Reason | Total |
|---|------------|
| All-subjects analysis set | 64 (100%) |
| Completed study | 56 (87.5%) |
| Discontinued study ^a | 8 (12.5%) |
| Reasons for discontinuation | |
| Withdrawal of consent | 1 (1.6%) |
| Inclusion/exclusion criteria not met | 0 |
| Protocol deviation | 1 (1.6%) |
| Adverse event | 3 (4.7%) |
| Death | 0 |
| Subject lost to follow-up | 1 (1.6%) |
| Other ^b | 2 (3.1%) |
| ^a See Text Table 8 for list of subjects who prematurely discontinued the study. | |
| ^b Other reasons included no i.v. access (Subject No. 1069) and positive toxicology (Subject No. 1077). | |
| All-subjects analysis set = all randomized/enrolled subjects who received any amount of study drug. | |
| Reference: Table 2 | |

Source: CSR, table 7, page 67.

Table 6: Summary of Demographics: All Subjects

| Parameter | Total (N=64) |
|------------------------------------|-----------------|
| Age (years) | |
| Mean ± SD | 34.2 ± 9.38 |
| Range | 19 – 60 |
| Age group | |
| <45 | 54 (84.4%) |
| 45 – 64 | 10 (15.6%) |
| ≥65 | 0 |
| Sex | |
| Male | 35 (54.7%) |
| Female | 29 (45.3%) |
| Race | |
| Caucasian | 22 (34.4%) |
| Black | 35 (54.7%) |
| Hispanic | 2 (3.1%) |
| Asian | 4 (6.3%) |
| Other | 1 (1.6%) |
| Height (cm) | |
| Mean ± SD | 170.03 ± 9.734 |
| Range | 155.2 – 190.0 |
| Weight (kg) | |
| Mean ± SD | 79.05 ± 15.490 |
| Range | 49.5 – 115.0 |
| Reference: Table 5 | |

Source: CSR, Table 10, page 72.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary study variable was change from baseline in heart-rate corrected QT interval. Three correction methods were used: Fridericia, Bazett, and individual regression. The QTc changes assessed by Fridericia method were treated as the primary variable.

The difference between gadobutrol and placebo in Fridericia QTc maximum mean change from baseline was 0.8 ms (95% CI = -2.9 ms, 4.1 ms) for 0.1 mmol/kg, 1.8 ms (95% CI = -1.8 ms, 5.3 ms) for 0.3 mmol/kg, and 5.2 ms (95% CI = 1.8 ms, 8.8 ms) for 0.5 mmol/kg. Although the treatment contrast for the maximum mean change from baseline in Fridericia QTc for gadobutrol 0.5 mmol/kg exceeded 5 ms, the upper bound of the confidence interval for all 3 doses excluded 10 ms.

Table 7: Primary Treatment Contrasts for QTc – Maximum Value Postinjection (Sponsor’s Results)

| Correction Method Parameter | Gadobutrol 0.1 | Gadobutrol 0.3 | Gadobutrol 0.5 | Moxifloxacin |
|---|----------------|----------------|----------------|--------------|
| Fridericia | | | | |
| Test | 19.6 | 20.6 | 24.0 | 32.3 |
| Placebo | 18.8 | 18.8 | 18.8 | 18.8 |
| Difference | 0.8 | 1.8 | 5.2 | 13.5 |
| 95% confidence interval | -2.9, 4.1 | -1.8, 5.3 | 1.8, 8.8 | 9.9, 16.9 |
| Bazett | | | | |
| Test | 29.7 | 30.7 | 37.4 | 43.1 |
| Placebo | 27.4 | 27.4 | 27.4 | 27.4 |
| Difference | 2.3 | 3.3 | 9.9 | 15.6 |
| 95% confidence interval | -3.1, 7.3 | -2.1, 8.3 | 4.7, 15.1 | 10.2, 20.6 |
| Individual regression | | | | |
| Test | 21.8 | 22.3 | 26.9 | 33.2 |
| Placebo | 20.4 | 20.4 | 20.4 | 20.4 |
| Difference | 1.4 | 1.9 | 6.6 | 12.8 |
| 95% confidence interval | -2.4, 5.0 | -1.9, 5.4 | 2.9, 10.2 | 9.0, 16.4 |
| Test minus placebo: test = active drug (gadobutrol or moxifloxacin) | | | | |
| Mean change from baseline = mean of maximum QTc values up to 22 hours postinjection minus mean of QTc baseline values for each subject. | | | | |
| Difference is between the means (test minus placebo). Only 1 decimal place is reported; some rounding difference may occur. | | | | |
| 95% confidence interval for the difference was calculated using an analysis of variance (ANOVA) model with subject, treatment and period as the main effects. | | | | |

Source: Sponsor’s Clinical Study Report Text Table 14.

Reviewer’s Comments: Our independent analysis is presented in section 5.2.1.

4.2.8.2.2 Assay Sensitivity

For moxifloxacin, the difference from placebo in Fridericia QTc maximum mean post-injection change was 13.5 ms (95% CI = 9.9 ms, 16.9 ms). For Bazett and individual correction, the largest lower bound was 10.2 ms and 9.7 ms, respectively.

4.2.8.2.3 Categorical Analysis

“No subject experienced a ≥ 30 ms increase in Fridericia QTc following any gadobutrol dose. For moxifloxacin, 4 (7.4%) subjects experienced at least 1 Fridericia QTc interval increase from baseline of ≥ 30 ms. The rate difference between moxifloxacin and placebo was 7.4% (95% CI = 0.4, 14.4). One (1.9%) subject receiving gadobutrol 0.5 mmol/kg had a ≥ 30 ms QTc interval increase based on the Bazett and individual correction methods. The rate difference in QTc interval between gadobutrol 0.5 mmol/kg and placebo for both correction methods was 1.9% (95% CI = -1.7; 5.4). No subject experienced a ≥ 60 ms 15-minute average increase in QTc interval following any treatment regardless of correction method.”

“No subject experienced a >450 ms 15-minute average Fridericia QTc following any gadobutrol dose. For moxifloxacin, 3 (5.6%) subjects had 1 or more Fridericia QTc >450 ms. For the Bazett correction, 1 (1.9%) subject in the placebo group, 1 (1.9%) subject in the group of gadobutrol 0.3 mmol/kg, 3 (5.6%) subjects in the group of gadobutrol 0.5 mmol/kg, and 7 (13.0%) subjects in the moxifloxacin group had 1 or more QTc >450 ms. For the individual regression correction, 1 (1.9%) subject in the group of gadobutrol 0.3 mmol/kg, 1 (1.9%) subject in the group of gadobutrol 0.5 mmol/kg, and 3 (5.6%) subjects in the moxifloxacin group had 1 or more QTc >450 ms. No subject experienced a >480 ms 15-minute average QTc following any treatment using any correction method.”

4.2.8.3 Safety Analysis

“One subject prematurely discontinued due to AEs following administration of gadobutrol 0.3 mmol/kg. Subject 1022 discontinued the study due to chest discomfort and T-wave inversion. Both AEs were judged by the investigator as mild in intensity. The chest discomfort was considered probably related to study medication and the T-wave inversion was considered possibly related to study medication.

“Narrative (Page 167 CSR), Subject 1022. 45-year-old Black male, was enrolled in the study on 15 Mar 2004. Height and weight were 181 cm (71 inches) and 98 kg (216 lbs), respectively. There were no medical and surgical history findings. Relevant baseline findings included mild hypertension (149/87) (04 Mar 2004). The subject reported taking no medications within the previous 48 hours prior to the pre-baseline period. The subject was randomized to treatment sequence 10 and completed Period 1 only. The subject received the intended gadobutrol 0.3 mmol/kg injection on 17 Mar 2004, start time 10:00. At 10:03, the subject complained of chest tightness and pressure that was judged by the investigator as mild in intensity and probably related to study medication. The “slight tightness” persisted at 13:00 but was decreasing in intensity. The subject was given acetylsalicylic acid 500 mg p.o. at 13:58. The duration of chest discomfort was 4 hours. An unscheduled ECG at 13:09 showed changes from upward to downward on biphasic T waves in multiple leads. The T-wave changes persisted but improved at 13:22 and 13:43, and resolved after 22 hours. The T-wave changes were judged by the investigator to be mild in intensity and possibly related to study medication. The patient denied prior chest tightness with stress or exercise. QT/QTc remained within normal limits. There were no clinically significant changes in vital signs or laboratory results. The subject was prematurely discontinued from the study due to chest pressure and T-wave inversion on 18 Mar 2004. The subject’s serial ECGs were sent to an outside cardiologist (b) (6)

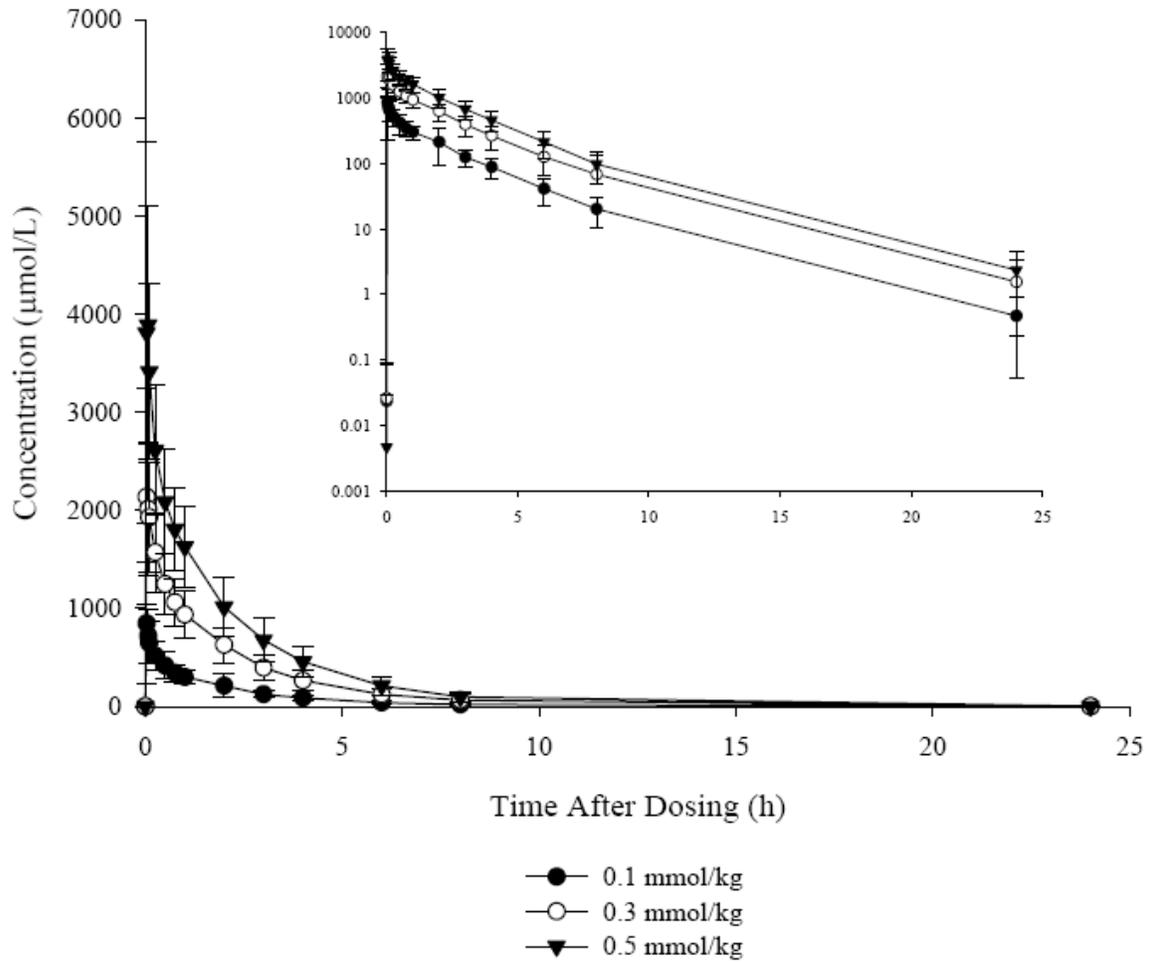
(b) (6) for independent interpretation. It was Dr. (b) (6) opinion that the T-wave changes appeared to be nonspecific and were not diagnostic of myocardial ischemia. A postprandial cause was suggested as the T-wave changes began after lunch. The subject was referred for a cardiology consultation with (b) (6) found no cardiomegaly. The 1st and 2nd heart sounds were of normal intensity, and there was no murmur, rub, or gallop heard. An ECG showed normal sinus rhythm with early repolarization changes. Dr. (b) (6) impression was labile hypertension. “

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of gadobutrol are presented in Figure 1 and Table 8: C_{max} and AUC values in the thorough QT study were about 5-fold higher following administration of 0.5 mmol/kg Supra compared to the intended clinical dose (0.1 mmol/kg).

Figure 1: Mean Concentration-Time Profiles of Gadobutrol



Source: Sponsor's Clinical Study Report, Figure 6 on Page 148

Table 8: Summary of Plasma Pharmacokinetic Parameters for Gadobutrol

| Gadobutrol | | C _{max} (µmol/L) | AUC(0-8) (µmol*h/L) | AUC(0-inf) (µmol*h/L) | t _{1/2} (h) | CL _t (mL/min/kg) | CL _t (mL/min) | V _{ss} (L/kg) | V _{ss} (L) | MRT (h) |
|-------------|----------------|------------------------------|------------------------|--------------------------|-------------------------|--------------------------------|-----------------------------|---------------------------|------------------------|------------|
| 0.1 mmol/kg | N | 56 | 56 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| | Mean | 936 | 1185 | 1244 | 1.84 | 1.43 | 113 | 0.201 | 15.9 | 2.36 |
| | Geometric Mean | 834 | 1150 | 1206 | 1.81 | 1.39 | 109 | 0.193 | 15.1 | 2.31 |
| | SD | 556 | 298 | 315 | 0.38 | 0.34 | 29 | 0.055 | 4.8 | 0.47 |
| | Min | 336 | 721 | 740 | 1.26 | 0.853 | 65.1 | 0.105 | 5.88 | 1.50 |
| | Median | 861 | 1121 | 1163 | 1.76 | 1.40 | 109 | 0.209 | 16.0 | 2.32 |
| | Max | 4110 | 1911 | 1992 | 3.04 | 2.12 | 184 | 0.323 | 27.2 | 3.87 |
| | CV% | 59 | 25 | 25 | 21 | 24 | 26 | 27 | 30 | 20 |
| 0.3 mmol/kg | N | 58 | 58 | 57 | 57 | 57 | 57 | 57 | 57 | 57 |
| | Mean | 2491 | 3587 | 3755 | 1.81 | 1.41 | 110 | 0.194 | 15.3 | 2.33 |
| | Geometric Mean | 2357 | 3485 | 3642 | 1.78 | 1.37 | 107 | 0.189 | 14.8 | 2.29 |
| | SD | 849 | 891 | 962 | 0.35 | 0.34 | 26 | 0.048 | 4.1 | 0.44 |
| | Min | 1061 | 2095 | 2163 | 1.23 | 0.817 | 68.4 | 0.116 | 8.42 | 1.64 |
| | Median | 2345 | 3466 | 3548 | 1.76 | 1.40 | 109 | 0.193 | 14.9 | 2.32 |
| | Max | 4997 | 5629 | 6037 | 2.96 | 2.26 | 181 | 0.302 | 24.7 | 3.64 |
| | CV% | 34 | 25 | 26 | 20 | 24 | 23 | 25 | 27 | 19 |
| 0.5 mmol/kg | N | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 58 |
| | Mean | 4437 | 6063 | 6357 | 1.83 | 1.40 | 109 | 0.194 | 15.2 | 2.34 |
| | Geometric Mean | 4014 | 5630 | 5901 | 1.79 | 1.42 | 106 | 0.196 | 14.6 | 2.30 |
| | SD | 1458 | 1479 | 1554 | 0.36 | 0.33 | 25 | 0.050 | 4.1 | 0.42 |
| | Min | 2075 | 3633 | 3987 | 1.26 | 0.815 | 65.9 | 0.117 | 7.58 | 1.69 |
| | Median | 4296 | 5801 | 6107 | 1.74 | 1.38 | 110 | 0.193 | 14.5 | 2.39 |
| | Max | 10240 | 9814 | 10270 | 2.86 | 2.14 | 174 | 0.386 | 26.6 | 4.01 |
| | CV% | 33 | 24 | 24 | 20 | 23 | 23 | 26 | 27 | 18 |

Source: Sponsor's Clinical Study Report, Table 48 on Page 149

Reviewer's Comments: The sampling schedule appears adequate to characterize the time course of gadobutrol.

4.2.8.4.2 Exposure-Response Analysis

Not performed.

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ vs. gadobutrol concentrations is presented in Figure 4.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI) provided by the sponsor.

We also evaluated the linear relationships between different correction methods (QTcF, QTcI) and RR. The mixed model shows a smaller slope of QTcF vs. RR than that of QTcI vs. RR, which indicates that QTcF is a better correction method than QTcI for this study. We also looked at the Mean Sum of Squared Slopes (MSSS). The smaller this value is, the better the correction. Again, QTcF produces the smallest MSSS. Therefore, the FDA reviewer used QTcF for the primary statistical analysis. Sponsor also used QTcF as the primary outcome. We evaluated both QTcF and QTcI methods and found out that the results based on both methods are similar.

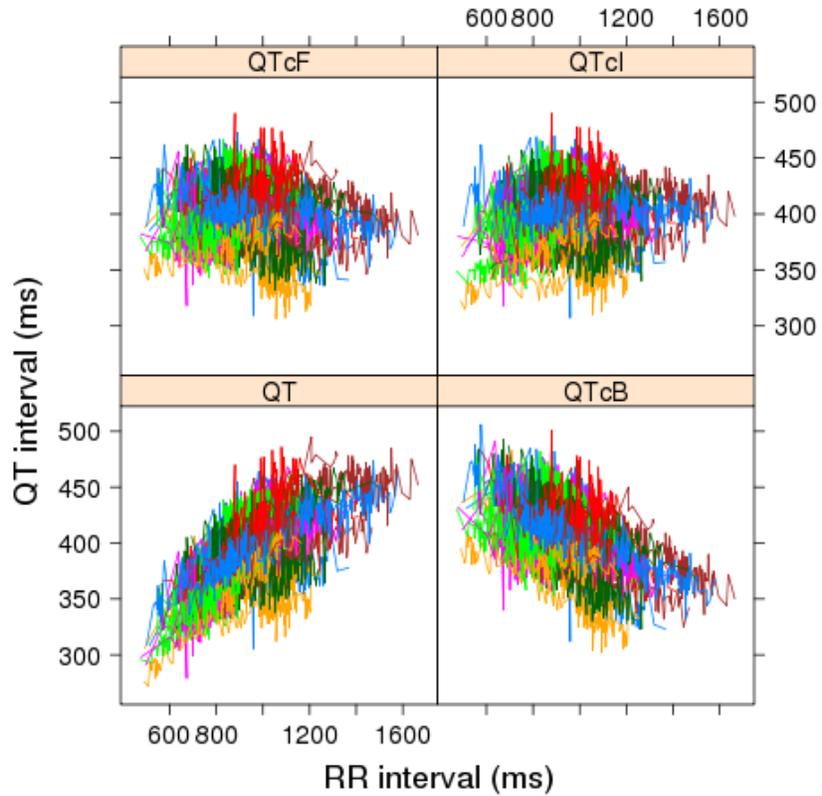
Table 9: Mixed Model Comparison of QTcF and QTcI

| Treatment Groups | Slope of QTcF | Slope of QTcI | diff_p_value |
|------------------|---------------|---------------|--------------|
| Gadobutrol 0.1 | -.02565 | -.05159 | 0.00000 |
| Gadobutrol 0.3 | -.03455 | -.05996 | 0.00000 |
| Gadobutrol 0.5 | -.03860 | -.06437 | 0.00000 |
| Moxifloxacin | -.02727 | -.05116 | 0.00000 |
| Overall | -.01645 | -.04229 | 0.00000 |
| Saline | -.02114 | -.04883 | 0.00000 |

Table 10: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

| Method | Treatment | | | | | | | | | | | |
|--------|----------------|--------|----------------|--------|----------------|--------|--------------|--------|---------|--------|-----|--------|
| | Gadobutrol 0.1 | | Gadobutrol 0.3 | | Gadobutrol 0.5 | | Moxifloxacin | | Placebo | | All | |
| | N | MSSS | N | MSSS | N | MSSS | N | MSSS | N | MSSS | N | MSSS |
| QTcF | 57 | 0.0030 | 57 | 0.0045 | 59 | 0.0054 | 59 | 0.0054 | 58 | 0.0035 | 64 | 0.0016 |
| QTcI | 57 | 0.0056 | 57 | 0.0062 | 59 | 0.0086 | 59 | 0.0063 | 58 | 0.0052 | 64 | 0.0039 |

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Gadobutrol

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes time point, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 11: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Gadobutrol 0.1

| | Gadobutrol 0.1 ΔQTcF | Placebo ΔQTcF | $\Delta\Delta$QTcF | |
|-----------------|---|--|--------------------------------------|--------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | 5.5 | 4.9 | 0.6 | (-2.9, 4.2) |
| 0.033 | 2.0 | 2.7 | -0.6 | (-4.1, 2.9) |
| 0.067 | 3.7 | 2.3 | 1.4 | (-2.0, 4.8) |
| 0.1 | 1.0 | 2.5 | -1.5 | (-4.8, 1.8) |
| 0.13 | 1.4 | 1.7 | -0.2 | (-3.6, 3.1) |
| 0.17 | 2.2 | 2.8 | -0.6 | (-4.0, 2.8) |
| 0.2 | 3.9 | 4.6 | -0.7 | (-4.4, 2.9) |
| 0.25 | 0.7 | 2.0 | -1.3 | (-5.1, 2.4) |
| 0.5 | 0.6 | -1.1 | 1.7 | (-1.8, 5.3) |
| 1 | -0.3 | -1.0 | 0.7 | (-2.8, 4.1) |
| 2 | -0.6 | -1.5 | 0.8 | (-3.3, 5.0) |
| 3 | -5.3 | -7.9 | 2.6 | (-1.4, 6.6) |
| 4 | -8.6 | -9.5 | 0.9 | (-2.6, 4.4) |
| 6 | -12.2 | -10.8 | -1.4 | (-5.1, 2.4) |
| 8 | -6.6 | -8.4 | 1.9 | (-1.9, 5.6) |
| 22 | -3.7 | -2.3 | -1.4 | (-5.7, 2.9) |

Table 12: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Gadobutrol 0.3

| | Gadobutrol 0.3 ΔQTcF | Placebo ΔQTcF | $\Delta\Delta$QTcF | |
|-----------------|---|--|--------------------------------------|--------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | 10.4 | 4.9 | 5.5 | (1.9, 9.2) |
| 0.033 | 10.1 | 2.7 | 7.4 | (3.9, 11.0) |
| 0.067 | 3.8 | 2.3 | 1.5 | (-2.0, 4.9) |
| 0.1 | 5.3 | 2.5 | 2.8 | (-0.5, 6.2) |
| 0.13 | 3.1 | 1.7 | 1.5 | (-2.0, 4.9) |
| 0.17 | 0.9 | 2.8 | -1.9 | (-5.3, 1.5) |
| 0.2 | 4.1 | 4.6 | -0.5 | (-4.3, 3.2) |
| 0.25 | 3.2 | 2.0 | 1.1 | (-2.7, 5.0) |
| 0.5 | 0.2 | -1.1 | 1.3 | (-2.3, 4.9) |
| 1 | -2.3 | -1.0 | -1.3 | (-4.8, 2.2) |
| 2 | 1.3 | -1.5 | 2.7 | (-1.4, 6.9) |
| 3 | -6.3 | -7.9 | 1.6 | (-2.5, 5.7) |
| 4 | -6.8 | -9.5 | 2.6 | (-0.9, 6.2) |
| 6 | -9.6 | -10.8 | 1.1 | (-2.7, 5.0) |
| 8 | -8.8 | -8.4 | -0.3 | (-4.1, 3.4) |
| 22 | -5.7 | -2.3 | -3.5 | (-7.7, 0.8) |

Table 13: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Gadobutrol 0.5

| | Gadobutrol 0.5 ΔQTcF | Placebo ΔQTcF | $\Delta\Delta$QTcF | |
|-----------------|---|--|--------------------------------------|--------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | 13.2 | 4.9 | 8.4 | (4.8, 11.9) |
| 0.033 | 10.8 | 2.7 | 8.2 | (4.6, 11.7) |
| 0.067 | 7.0 | 2.3 | 4.7 | (1.2, 8.1) |
| 0.1 | 6.1 | 2.5 | 3.6 | (0.3, 6.9) |
| 0.13 | 3.3 | 1.7 | 1.7 | (-1.7, 5.1) |
| 0.17 | 4.0 | 2.8 | 1.2 | (-2.2, 4.6) |
| 0.2 | 2.6 | 4.6 | -2.0 | (-5.6, 1.7) |
| 0.25 | 3.6 | 2.0 | 1.5 | (-2.2, 5.3) |
| 0.5 | 1.2 | -1.1 | 2.3 | (-1.3, 5.9) |
| 1 | 0.4 | -1.0 | 1.4 | (-2.0, 4.9) |
| 2 | -0.4 | -1.5 | 1.1 | (-3.0, 5.2) |
| 3 | -5.6 | -7.9 | 2.3 | (-1.7, 6.3) |
| 4 | -7.7 | -9.5 | 1.8 | (-1.7, 5.3) |
| 6 | -9.6 | -10.8 | 1.2 | (-2.7, 5.1) |
| 8 | -3.7 | -8.4 | 4.7 | (1.0, 8.4) |
| 22 | -3.7 | -2.3 | -1.4 | (-5.6, 2.8) |

The largest upper bounds of the 2-sided 90% CI for the mean difference between gadobutrol 0.1-mmol/kg, 0.3-mmol/kg, 0.5-mmol/kg groups and placebo were 6.6 ms, 11.0 ms and 11.9 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in following table. The largest unadjusted 90% lower confidence interval is 11.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 10.7 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 14: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Moxifloxacin

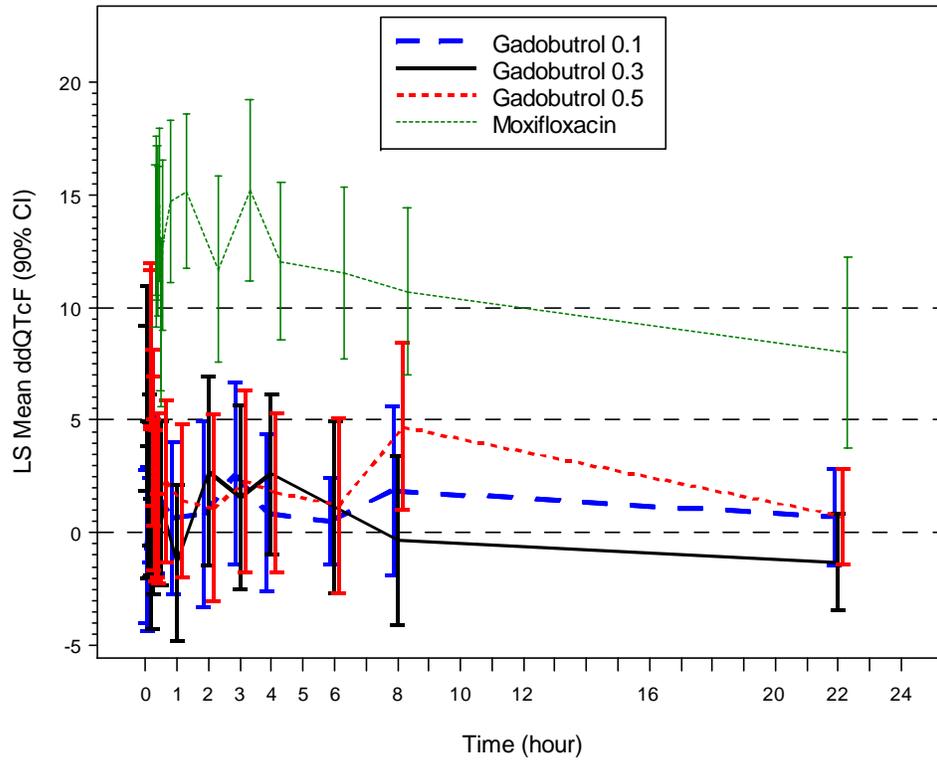
| | Moxifloxacin ΔQTcF | Placebo ΔQTcF | $\Delta\Delta$QTcF | |
|-----------------|---|--|--------------------------------------|---------------------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | Adjusted 90% CI (ms) |
| 0.017 | 17.6 | 4.9 | 12.8 | (8.1, 17.4) |
| 0.033 | 16.7 | 2.7 | 14.1 | (9.5, 18.6) |
| 0.067 | 16.0 | 2.3 | 13.7 | (9.3, 18.1) |
| 0.1 | 15.4 | 2.5 | 12.9 | (8.6, 17.2) |
| 0.13 | 16.2 | 1.7 | 14.6 | (10.2, 19.0) |
| 0.17 | 12.5 | 2.8 | 9.7 | (5.3, 14.1) |
| 0.2 | 13.8 | 4.6 | 9.3 | (4.5, 14.1) |
| 0.25 | 14.8 | 2.0 | 12.8 | (7.9, 17.7) |
| 0.5 | 13.6 | -1.1 | 14.7 | (10.1, 19.4) |
| 1 | 14.2 | -1.0 | 15.1 | (10.7, 19.6) |
| 2 | 10.2 | -1.5 | 11.7 | (6.4, 17.0) |
| 3 | 7.3 | -7.9 | 15.2 | (10.0, 20.4) |
| 4 | 2.6 | -9.5 | 12.0 | (7.5, 16.6) |
| 6 | 0.7 | -10.8 | 11.5 | (6.6, 16.5) |
| 8 | 2.3 | -8.4 | 10.7 | (5.9, 15.5) |
| 22 | 5.7 | -2.3 | 8.0 | (2.5, 13.5) |

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta\text{QTcF}$ Over Time

The following figure displays the time profile of $\Delta\Delta\text{QTcF}$ for all treatment groups.

Figure 3: Mean and 90% CI $\Delta\Delta\text{QTcF}$ Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 15 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. One subject's QTcF was above 480 ms under moxifloxacin treatment.

Table 15: Categorical Analysis for QTcF

| Treatment Group | Total | | Value≤450 ms | | 450 ms<Value≤480 ms | | 480 ms<Value≤500 ms | |
|-----------------|---------|--------|--------------|-------------|---------------------|-----------|---------------------|----------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| Baseline | 64 | 6808 | 64 (100%) | 6808 (100%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Gadobutrol 0.1 | 57 | 896 | 52 (91.2%) | 890 (99.3%) | 5 (8.8%) | 6 (0.7%) | 0 (0.0%) | 0 (0.0%) |
| Gadobutrol 0.3 | 56 | 851 | 54 (94.7%) | 846 (99.4%) | 3 (5.3%) | 5 (0.6%) | 0 (0.0%) | 0 (0.0%) |
| Gadobutrol 0.5 | 59 | 901 | 54 (91.5%) | 891 (98.9%) | 5 (8.5%) | 10 (1.1%) | 0 (0.0%) | 0 (0.0%) |
| Moxifloxacin | 59 | 897 | 49 (83.1%) | 854 (95.2%) | 9 (15.3%) | 42 (4.7%) | 1 (1.7%) | 1 (0.2%) |
| Placebo | 58 | 914 | 55 (94.8%) | 910 (99.6%) | 3 (5.2%) | 4 (0.4%) | 0 (0.0%) | 0 (0.0%) |

Table 16 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 16: Categorical Analysis of Δ QTcF

| Treatment Group | Total | | Value≤30 ms | | 30 ms<Value≤60 ms | |
|-----------------|---------|--------|-------------|-------------|-------------------|-----------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| Gadobutrol 0.1 | 57 | 896 | 49 (86.0%) | 885 (98.8%) | 8 (14.0%) | 11 (1.2%) |
| Gadobutrol 0.3 | 56 | 851 | 48 (84.2%) | 842 (98.9%) | 9 (15.8%) | 9 (1.1%) |
| Gadobutrol 0.5 | 59 | 901 | 49 (83.1%) | 886 (98.3%) | 10 (16.9%) | 15 (1.7%) |
| Moxifloxacin | 59 | 897 | 27 (45.8%) | 821 (91.5%) | 32 (54.2%) | 76 (8.5%) |
| Placebo | 58 | 914 | 51 (87.9%) | 906 (99.1%) | 7 (12.1%) | 8 (0.9%) |

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in the following tables. The largest upper bounds of the 2-sided 90% CI for the mean difference between gadobutrol 0.1-mmol/kg, 0.3-mmol/kg, 0.5-mmol/kg groups and placebo were 5.9 ms, 6.8 ms and 6.7 ms, respectively.

The outlier analysis results for PR are presented in Table 20. The percent of observations with PR>200 ms were 2.1%, 3.4% and 0.8% in gadobutrol 0.1-mmol/kg, 0.3-mmol/kg and 0.5-mmol/kg groups, respectively.

Table 17: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Gadobutrol 0.1

| | Gadobutrol 0.1 ΔPR | Placebo ΔPR | $\Delta\Delta$PR | |
|-----------------|---|--|--------------------------------------|--------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | -1.3 | 0.3 | -1.6 | (-4.3, 1.1) |
| 0.033 | -0.4 | 0.3 | -0.7 | (-3.3, 1.8) |
| 0.067 | 0.4 | -1.2 | 1.6 | (-0.8, 4.1) |
| 0.1 | 0.0 | 1.1 | -1.1 | (-3.8, 1.6) |
| 0.13 | -1.7 | 1.2 | -2.9 | (-5.3, -0.4) |
| 0.17 | 0.2 | 0.6 | -0.5 | (-2.9, 2.0) |
| 0.2 | -0.1 | -2.6 | 2.5 | (-0.2, 5.2) |
| 0.25 | -1.3 | -2.5 | 1.2 | (-1.4, 3.9) |
| 0.5 | -0.4 | -0.1 | -0.3 | (-2.9, 2.3) |
| 1 | 0.5 | 1.2 | -0.7 | (-3.6, 2.2) |
| 2 | 0.9 | -1.6 | 2.5 | (-0.3, 5.3) |
| 3 | -4.6 | -3.8 | -0.9 | (-4.1, 2.3) |
| 4 | -3.8 | -4.1 | 0.3 | (-2.5, 3.2) |
| 6 | -8.5 | -8.1 | -0.3 | (-3.5, 2.8) |
| 8 | -5.7 | -6.9 | 1.2 | (-1.5, 3.8) |
| 22 | -5.8 | -8.1 | 2.3 | (-1.3, 5.9) |

Table 18: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Gadobutrol 0.3

| | Gadobutrol 0.3 ΔPR | Placebo ΔPR | $\Delta\Delta$PR | |
|-----------------|---|--|--------------------------------------|--------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | 2.1 | 0.3 | 1.8 | (-1.0, 4.5) |
| 0.033 | 1.3 | 0.3 | 1.0 | (-1.6, 3.5) |
| 0.067 | 2.7 | -1.2 | 3.9 | (1.4, 6.4) |
| 0.1 | 1.2 | 1.1 | 0.1 | (-2.6, 2.8) |
| 0.13 | 1.1 | 1.2 | -0.1 | (-2.6, 2.4) |
| 0.17 | 2.2 | 0.6 | 1.6 | (-0.9, 4.0) |
| 0.2 | 0.1 | -2.6 | 2.6 | (-0.1, 5.4) |
| 0.25 | 0.3 | -2.5 | 2.8 | (0.1, 5.5) |
| 0.5 | 1.8 | -0.1 | 1.9 | (-0.7, 4.5) |
| 1 | -0.6 | 1.2 | -1.7 | (-4.7, 1.2) |
| 2 | -0.3 | -1.6 | 1.3 | (-1.5, 4.1) |
| 3 | -3.4 | -3.8 | 0.4 | (-2.8, 3.7) |
| 4 | -5.0 | -4.1 | -0.8 | (-3.8, 2.1) |
| 6 | -6.9 | -8.1 | 1.3 | (-1.9, 4.4) |
| 8 | -5.2 | -6.9 | 1.7 | (-1.0, 4.4) |
| 22 | -4.9 | -8.1 | 3.2 | (-0.4, 6.8) |

Table 19: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Gadobutrol 0.5

| | Gadobutrol 0.5 ΔPR | Placebo ΔPR | $\Delta\Delta$PR | |
|-----------------|---|--|--------------------------------------|--------------------|
| Time/(h) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 1 | 3.3 | 0.3 | 3.0 | (0.3, 5.7) |
| 2 | 1.3 | 0.3 | 1.0 | (-1.6, 3.5) |
| 4 | 1.3 | -1.2 | 2.6 | (0.1, 5.0) |
| 6 | 1.6 | 1.1 | 0.5 | (-2.2, 3.2) |
| 8 | 1.3 | 1.2 | 0.1 | (-2.4, 2.6) |
| 10 | 0.8 | 0.6 | 0.2 | (-2.3, 2.6) |
| 12 | 1.3 | -2.6 | 3.9 | (1.2, 6.6) |
| 15 | -0.1 | -2.5 | 2.4 | (-0.2, 5.1) |
| 30 | -0.9 | -0.1 | -0.8 | (-3.4, 1.7) |
| 1 | 1.4 | 1.2 | 0.2 | (-2.7, 3.1) |
| 2 | -2.2 | -1.6 | -0.6 | (-3.3, 2.2) |
| 3 | -4.9 | -3.8 | -1.1 | (-4.2, 2.1) |
| 4 | -5.3 | -4.1 | -1.2 | (-4.1, 1.7) |
| 6 | -9.4 | -8.1 | -1.2 | (-4.4, 2.0) |
| 8 | -7.0 | -6.9 | -0.1 | (-2.8, 2.6) |
| 22 | -5.0 | -8.1 | 3.1 | (-0.5, 6.7) |

Table 20: Categorical Analysis for PR

| Treatment Group | Total | | Value≤200 ms | | Value>200 ms | |
|-----------------|---------|--------|--------------|--------------|--------------|-----------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| Baseline | 64 | 6808 | 62 (96.9%) | 6713 (98.6%) | 2 (3.1%) | 95 (1.4%) |
| Gadobutrol 0.1 | 57 | 896 | 51 (89.5%) | 877 (97.9%) | 6 (10.5%) | 19 (2.1%) |
| Gadobutrol 0.3 | 56 | 851 | 52 (91.2%) | 822 (96.6%) | 5 (8.8%) | 29 (3.4%) |
| Gadobutrol 0.5 | 59 | 901 | 56 (94.9%) | 894 (99.2%) | 3 (5.1%) | 7 (0.8%) |
| Moxifloxacin | 59 | 897 | 58 (98.3%) | 889 (99.1%) | 1 (1.7%) | 8 (0.9%) |
| Saline | 58 | 914 | 54 (93.1%) | 902 (98.7%) | 4 (6.9%) | 12 (1.3%) |

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in the following tables. The largest upper bounds of the 2-sided 90% CI for the mean difference between gadobutrol 0.1-mmol/kg, 0.3-mmol/kg, 0.5-mmol/kg groups and placebo were 3.5 ms, 2.6 ms and 3.3 ms, respectively.

The outlier analysis results for QRS are presented in Table 24. Two subjects in gadobutrol 0.3-mmol/kg group and one subject in gadobutrol 0.5-mmol/kg treatment group have observations of QRS>110 ms.

Table 21: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Gadobutrol 0.1

| | Gadobutrol 0.1 Δ QRS | Placebo Δ QRS | $\Delta\Delta$ QRS | |
|-------|-----------------------------------|-------------------------|--------------------|--------------|
| | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | -0.0 | -0.1 | 0.1 | (-1.5, 1.7) |
| 0.033 | 0.7 | -1.1 | 1.8 | (0.1, 3.4) |
| 0.067 | 0.8 | -1.0 | 1.8 | (0.1, 3.5) |
| 0.1 | -1.8 | 0.5 | -2.3 | (-4.0, -0.5) |
| 0.13 | 0.4 | 0.4 | 0.0 | (-1.7, 1.7) |
| 0.17 | 0.4 | 1.0 | -0.6 | (-2.2, 1.0) |
| 0.2 | -0.2 | 1.2 | -1.4 | (-3.2, 0.3) |
| 0.25 | -0.3 | 0.6 | -0.8 | (-2.5, 0.9) |
| 0.5 | -0.4 | -0.3 | -0.1 | (-1.8, 1.6) |
| 1 | 0.2 | 0.8 | -0.5 | (-2.2, 1.2) |
| 2 | -0.3 | -1.0 | 0.8 | (-0.8, 2.3) |
| 3 | -0.6 | 0.2 | -0.8 | (-2.5, 0.9) |
| 4 | -0.7 | -0.4 | -0.3 | (-2.0, 1.4) |
| 6 | 0.9 | 0.4 | 0.5 | (-1.3, 2.3) |
| 8 | -1.8 | -0.4 | -1.4 | (-3.2, 0.4) |
| 22 | -1.9 | -0.7 | -1.2 | (-3.2, 0.8) |

Table 22: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Gadobutrol 0.3

| | Gadobutrol 0.3 ΔQRS | Placebo ΔQRS | $\Delta\Delta$QRS | |
|-------|--|---|--------------------------------------|--------------------|
| | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | -0.8 | -0.1 | -0.7 | (-2.3, 0.9) |
| 0.033 | -1.3 | -1.1 | -0.2 | (-1.8, 1.4) |
| 0.067 | -0.4 | -1.0 | 0.6 | (-1.2, 2.3) |
| 0.1 | -0.9 | 0.5 | -1.4 | (-3.2, 0.4) |
| 0.13 | 0.0 | 0.4 | -0.4 | (-2.1, 1.3) |
| 0.17 | -0.6 | 1.0 | -1.5 | (-3.1, 0.1) |
| 0.2 | -1.1 | 1.2 | -2.3 | (-4.1, -0.6) |
| 0.25 | -1.4 | 0.6 | -1.9 | (-3.7, -0.2) |
| 0.5 | 0.5 | -0.3 | 0.8 | (-1.0, 2.6) |
| 1 | -1.5 | 0.8 | -2.2 | (-4.0, -0.5) |
| 2 | -0.6 | -1.0 | 0.5 | (-1.1, 2.1) |
| 3 | -0.4 | 0.2 | -0.6 | (-2.3, 1.2) |
| 4 | -0.3 | -0.4 | 0.1 | (-1.7, 1.8) |
| 6 | -0.9 | 0.4 | -1.3 | (-3.1, 0.5) |
| 8 | -0.8 | -0.4 | -0.3 | (-2.1, 1.5) |
| 22 | -2.0 | -0.7 | -1.4 | (-3.4, 0.7) |

Table 23: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Gadobutrol 0.5

| | Gadobutrol 0.5 Δ QRS | Placebo Δ QRS | $\Delta\Delta$ QRS | |
|-------|-----------------------------------|-------------------------|----------------------------|--------------|
| | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0.017 | -0.4 | -0.1 | -0.2 | (-1.8, 1.4) |
| 0.033 | -1.4 | -1.1 | -0.3 | (-1.9, 1.3) |
| 0.067 | -1.1 | -1.0 | -0.2 | (-1.9, 1.6) |
| 0.1 | -0.7 | 0.5 | -1.1 | (-2.9, 0.6) |
| 0.13 | -0.8 | 0.4 | -1.2 | (-2.9, 0.5) |
| 0.17 | -0.6 | 1.0 | -1.6 | (-3.2, -0.0) |
| 0.2 | -1.8 | 1.2 | -3.0 | (-4.8, -1.3) |
| 0.25 | -0.7 | 0.6 | -1.3 | (-3.0, 0.4) |
| 0.5 | -0.4 | -0.3 | -0.0 | (-1.8, 1.7) |
| 1 | -0.4 | 0.8 | -1.1 | (-2.8, 0.6) |
| 2 | -0.6 | -1.0 | 0.4 | (-1.2, 2.0) |
| 3 | 0.1 | 0.2 | -0.1 | (-1.8, 1.6) |
| 4 | -1.0 | -0.4 | -0.7 | (-2.4, 1.1) |
| 6 | 0.4 | 0.4 | -0.0 | (-1.8, 1.8) |
| 8 | 0.6 | -0.4 | 1.0 | (-0.8, 2.8) |
| 22 | 0.7 | -0.7 | 1.3 | (-0.7, 3.3) |

Table 24: Categorical Analysis for QRS

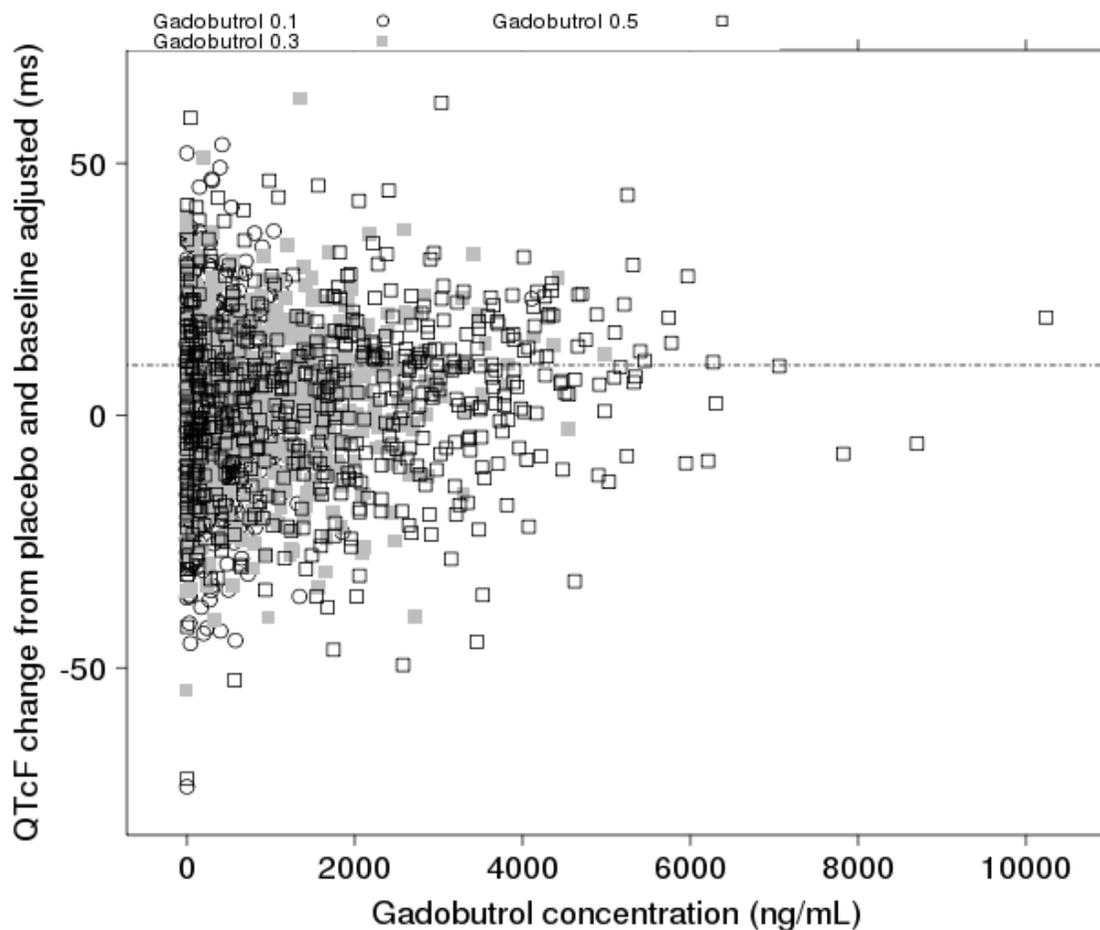
| Treatment Group | Total | | Value≤100 ms | | 100 ms<Value≤110 ms | | Value>110 ms | |
|-----------------|---------|--------|--------------|--------------|---------------------|-----------|--------------|----------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| Baseline | 64 | 6808 | 61 (95.3%) | 6718 (98.7%) | 3 (4.7%) | 90 (1.3%) | 0 (0.0%) | 0 (0.0%) |
| Gadobutrol 0.1 | 57 | 896 | 50 (87.7%) | 875 (97.7%) | 7 (12.3%) | 21 (2.3%) | 0 (0.0%) | 0 (0.0%) |
| Gadobutrol 0.3 | 56 | 851 | 53 (93.0%) | 836 (98.2%) | 2 (3.5%) | 12 (1.4%) | 2 (3.5%) | 3 (0.4%) |
| Gadobutrol 0.5 | 59 | 901 | 54 (91.5%) | 885 (98.2%) | 4 (6.8%) | 15 (1.7%) | 1 (1.7%) | 1 (0.1%) |
| Moxifloxacin | 59 | 897 | 53 (89.8%) | 887 (98.9%) | 5 (8.5%) | 8 (0.9%) | 1 (1.7%) | 2 (0.2%) |
| Saline | 58 | 914 | 52 (89.7%) | 903 (98.8%) | 5 (8.6%) | 10 (1.1%) | 1 (1.7%) | 1 (0.1%) |

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean gadobutrol concentration-time profile is illustrated in Figure 1.

The relationship between $\Delta\Delta\text{QTcF}$ and gadobutrol concentrations is visualized in Figure 4. The slope of the exposure-response relationship is slightly but significantly greater than 0 (slope: 0.0015 with p-value: 0.001). However, the upper 90% confidence boundaries at the expected values of C_{max} for all doses are below 10 ms. Hence, the potential effect of gadobutrol on QT prolongation is likely to be small and should not have important clinical significance.

Figure 4: $\Delta\Delta$ QTcF vs. Gadobutrol Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

One subject discontinued the study due to chest discomfort and T-wave inversion, developed immediately after receiving gadobutrol 0.3 mmol/kg injection. Both AEs were judged by the investigator as mild in intensity. The chest discomfort was considered probably related to study medication and the T-wave inversion was considered possibly related to study medication. No QT prolongation was observed in this subject.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 94% of the ECGs were annotated in the primary lead II, with less than 89% of

ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Nine subjects treated with gadobutrol experienced PR >200 ms, 5 in the 0.1 mmol/kg arm, 5 in the 0.3-mmol/kg arm and 3 in the 0.5-mmol/kg arm. Maximum PR achieved was 215 ms, none of these changes were clinically relevant and all increases over baseline were <25%.

Two subjects treated with gadobutrol had QRS > 110 ms, one in the 0.3-mmol/kg arm and the other in the 0.5-mmol/kg arm. Changes were not clinically relevant..

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

(b) (4)

| | | |
|---|---|---|
| Therapeutic dose | 0.1 mmol gadobutrol/kg BW | |
| Maximum tolerated dose | 1.5 mmol gadobutrol/kg BW | |
| Principal adverse events | The most frequent ($\geq 0.5\%$) adverse reactions are nausea, feeling hot, injection site reactions, headache, and dysgeusia. Adverse reactions following gadobutrol administration are usually mild to moderate in severity and transient in nature | |
| Maximum dose tested | Single Dose | 1.5 mmol gadobutrol/kg BW (safety only, no PK) 0.5 mmol gadobutrol/kg BW (including PK) |
| | Multiple Dose | 2 x 0.1 mmol gadobutrol/kg BW with 30 min dosing interval between both injections |
| Exposures Achieved at Maximum Tested Dose | Single Dose | C_{max} : 4437 \pm 1458 $\mu\text{mol/L}$ (arith. mean \pm SD) AUC: 6357 \pm 1554 $\mu\text{mol}\cdot\text{h/L}$ (arith. mean \pm SD) |
| | Multiple Dose | C_{max} : 1792 (15.9) $\mu\text{mol/L}$ (geomean (CV%)) AUC: 2070 (14.3) $\mu\text{mol}\cdot\text{h/L}$ (geomean (CV%)) |
| Range of linear PK | 0.04 – 0.4 mmol gadobutrol /kg BW | |
| Accumulation at steady state | Not applicable | |
| Metabolites | Gadobutrol is not metabolized | |
| Absorption | Absolute/Relative Bioavailability | Not applicable (iv administration) |
| | t_{max} | 2- 10 min (min - max) |
| Distribution | V_{ss} | 0.21 \pm 0.02 L/kg (arith. mean \pm SD) |
| | % bound | Protein binding of gadobutrol is negligible: <ul style="list-style-type: none"> 2.7 \pm 0.8% (arith. mean \pm SD) (ultrafiltration) (9139/II) 5.4% (dialysis at steady state) |
| Elimination | Route | Exclusively via renal elimination |
| | Terminal $t_{1/2}$ | 1.88 \pm 0.19 h (arith. mean \pm SD) |
| | CL | 1.50 \pm 0.13 $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ (arith. mean \pm SD) |
| Intrinsic Factors | Age | In elderly patients (aged 65 years and above) systemic exposure (AUC) is increased by 33% (men) and 54% (women) in the mean |
| | Sex | No effect |
| | Race | No effect |
| | Renal | After intravenous injection of 0.1 mmol |

| | | |
|--|---|--|
| | Impairment | gadobutrol/kg BW, the systemic exposure increased 3.6-fold (AUC: 4015 ± 1818 µmol*h/L, arith. mean ± SD) in mild to moderately impaired patients (80>CL _{CR} >30 mL/min) and 10.3 fold (AUC: 11531 ± 4255 µmol*h/L, arith. mean ± SD) in severely impaired patients (CL _{CR} < 30 mL/min, not depending on dialysis) (B245) in comparison to healthy volunteers (AUC: 1117 ± 93.7 µmol*h/L, arith. mean ± SD). |
| Extrinsic Factors | Drug interactions | No drug-drug interaction studies were performed. |
| | Food Effects | Not applicable (iv administration) |
| Expected High Clinical Exposure Scenario | The extent of exposure correlates with the degree of renal impairment. In severely impaired patients (CL _{CR} < 30 mL/min, not depending on dialysis), an about 10.3 fold increase in mean exposure was observed as compared to healthy subjects with normal renal function. | |

6.2 TABLE OF STUDY ASSESSMENTS

Table 2 Time schedule of clinical study activities for study periods 1 – 5

| | Baseline | | | | | Inj./Inf. | | On-Drug Period | | | | | | | | | | | | | | | | | 24(±4) | | |
|--|-------------------|----------------|-----|-----|-----|------------------|----------------|----------------|---|---|---|---|----|----|-----------------|----|----|-------|---|---|---|---|---|----|--------|----------------|---|
| | -110 ¹ | -90 | -80 | -70 | -65 | -60 ² | 0 ³ | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 15 | 30 | 45 | 60 | 2 | 3 | 4 | 6 | 8 | 22 | | | |
| | minutes | | | | | | | | | | | | | | | | | hours | | | | | | | | | |
| Medical history: Changes from previous recordings | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug Screen ⁴ | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test ⁴ | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical Exam. | X | | | | | | | | | | | | | | | | | | | | | X | | | | X | |
| Injection arm eval. | X ⁹ | | | | X | | X | | | | | | | | X ¹⁰ | | | | | | | X | | | | X | |
| Mini-mental status | X | | | | | | | | | | | | | | X | | | | | | | X | | | | X | |
| Blood pressure | | | X | X | | X | | | X | | | X | | | | X | X | X | | | | X | X | | | X | |
| Respiratory rate | | | X | X | | | | | X | | | X | | | | X | X | | | | | | X | | | X | |
| Body temperature | | | X | | | | | | | | | | | | | | X | | | | | | X | | | X | |
| Conventional 12-lead ECG (10 sec) | | | X | X | | X | | X | X | | | X | | | | X | X | X | | | | X | X | | | X | |
| Continuous ECG recording ⁶ | | | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Time-points for QT analysis by Core lab ⁵ | | X ⁷ | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pharmacokinetics ⁶ | X | | | | | | | | X | X | X | | | | X | X | X | X | X | X | X | X | X | | | X | |
| Hematology | X | | | | | | | | | | | | | | | | | | | | | X | | | | X | |
| Blood chemistry | X | | | | | | | | | | | | | | | | | | | | | X | | | | X | |
| Adverse Events | | | | | | | | | | | | | | | | | | | | | | | | | | X ⁸ | |

1 = comprises period from -120 to -91 minutes. Additionally: establish peripheral venous access, place ECG electrodes (12 leads)

2 = start of the moxifloxacin infusion

3 = defined as the end of the saline flush

4 = Drug screen & pregnancy test to be done in-house, not by the central laboratory, and results must be available prior to study drug administration.

5 = also includes heart rate which is not to be measured separately as it is included in ECG measurements

6 = Blood pressure not be measured at the injection site arm, always 30-60 seconds after marked time point in order not to interfere with QT measurement/PK sampling.

7 = QT analysis for individual regression curve will be performed/ used every 5 minutes for the period from -90 min. until - 60min.

8 = Adverse events are recorded for subject's entire study participation. However, for study period one AEs are collected from the time of study drug injection

9 = Injection arm evaluation performed before venous line is established

10 = Injection arm evaluation performed after venous line is discontinued

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/s/

MONICA L FISZMAN
11/18/2010

QIANYU DANG
11/19/2010

JOANNE ZHANG
11/19/2010

JIANG LIU
11/26/2010

HAO ZHU
11/28/2010

NORMAN L STOCKBRIDGE
11/29/2010

DSI CONSULT: Request for Clinical Inspections

Date: September 7, 2010, 2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Thompson
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Barbara Stinson, D.O., Clinical Reviewer*
Alexander Gorovets, M.D., Clinical Team Leader
Rafel Rieves, Division Director

From: *James Moore, Regulatory Health Project Manager/DMIP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-201-277, Gadovist (Gadobutrol)
Applicant: Bayer HealthCare Pharmaceuticals
Applicant contact information: Phillip Johnson (973) 487-2181
phillip.johnson@bayer.com
Drug Proprietary Name: Gadovist (Gadobutrol)
NME :**Yes**:
Review Priority (Standard or Priority): Standard

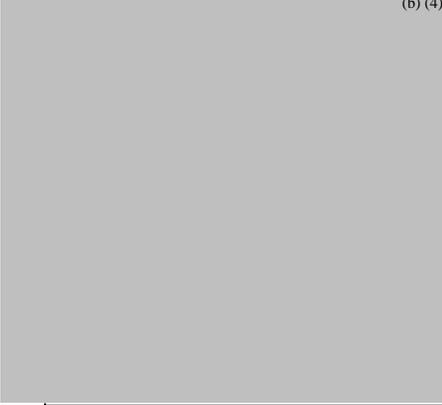
Study Population includes < 17 years of age Yes: Ages 2-17
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): A new gadolinium based contrast agent for magnetic resonance imaging (MRI) of the Central Nervous System (CNS)

PDUFA: March 14, 2010
Action Goal Date: March 10, 2010
Inspection Summary Goal Date: November 16, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table. This is an additional DSI Consult to add a clinical Site for Inspection for comparison of treatment related events.

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication |
|--|-------------|--------------------|--|
| 14004 | 310124 | 15 | For comparison of treatment related events The inspection of data forms was requested by DSI |
| Investigator-Jae K. Kim, M.D., Ph.D. 677 N. Wilmot Road Tuscon, Arizona 85711 Phone 520-514-7600 Email dr.jae.k.kim@gmail.com | | | |
|  (b) (4) | | | |
| | | | |
| | | | |

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): numbers of adverse events reported- Comparison of AEs (see table above)

Should you require any additional information, please contact James Moore, *RPM* at 301-796-1986
Barbara Stinson at 301-796-1470.

Concurrence: (as needed)

- _____ Medical Team Leader
- _____ Medical Reviewer
- _____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|--|----------------------|
| NDA-201277 | ORIG-1 | BAYER HEALTHCARE PHARMACEUTICALS INC | GADOBUTROL INJECTION |

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/s/

JAMES W MOORE
09/08/2010

RAFEL D RIEVES
09/08/2010

DSI CONSULT: Request for Clinical Inspections

Date: August 16, 2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Thompson, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Barbara Stinson, D.O., Clinical Reviewer, DMIP*
Alexander Gorovets, M.D., Clinical Team Leader, DMIP
Rafel Rieves, M.D., Director, DMIP

From: *James Moore, Regulatory Health Project Manager, DMIP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-201-277, Gadovist (Gadobutrol)
Applicant: Bayer HealthCare Pharmaceuticals, Inc.
Applicant contact information: Phillip Johnson (973) 487-2181
phillip.johnson@bayer.com
Drug Proprietary Name: Gadovist (Gadobutrol)
NME :**Yes**:
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age Yes: Ages 2-17
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): A new gadolinium based contrast agent for magnetic resonance imaging (MRI) of the Central Nervous System (CNS)

PDUFA: March 14, 2011
Action Goal Date: March 10, 2011
Inspection Summary Goal Date: November 16, 2010

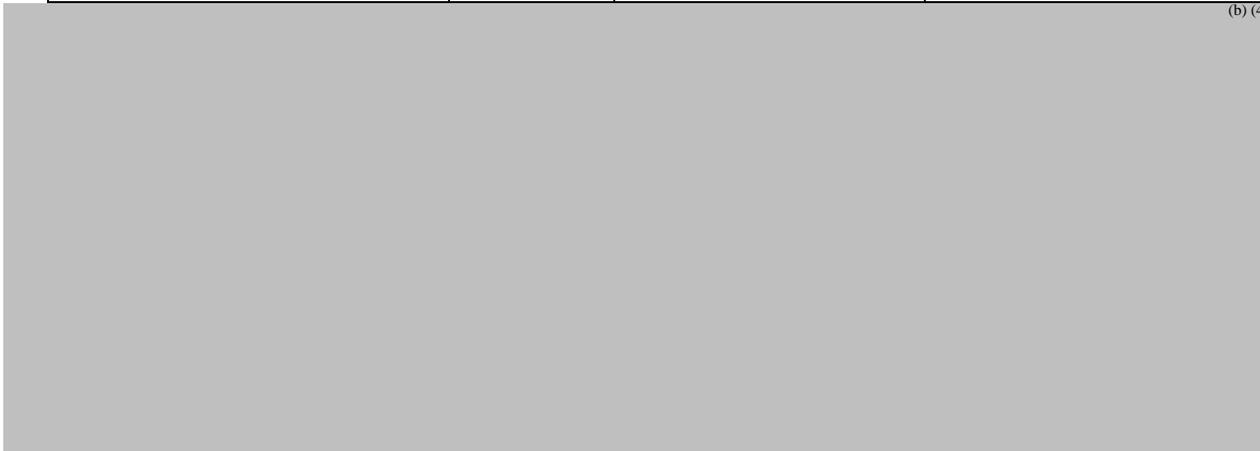
II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication |
|--|--------------------|---------------------------|------------------------------|
| Site 10006 Hr. Prof. Dr. Rudiger Von Kummer Universitätsklinikum Carl-Gustav Carus Abteilung Neuroradiologie (Haus 59) Fetscherstrasse 74 01307 Dresden, Germany Telephone: 011 49 351 458 2660 Email: ruediger.vonkummer@uniklinikum-dresden.de | 310123 | 27 | 19 protocol violations |
| Site 14002 Dr. Elias Melhem University of Pennsylvania Health System 3400 Spruce Street 2 nd floor Dulles Building Philadelphia, PA, 19104 USA Telephone: 215-662-6865 Email: emelhem@rad.upenn.edu | 310123 | 19 | 68 treatment emergent events |
| Site 14001 Dr. Robert Booth UF College of Medicine-C90 655 West Eighth Street Jacksonville, FL, 32209 USA Telephone: 904-244-4487 Email: Robert.booth@jax.ufl.edu | 210124 | 19 | 24 treatment emergent events |

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication |
|--|-------------|--------------------|------------|
|--|-------------|--------------------|------------|

(b) (4)



| | | | |
|--|--|--|--|
| | | | |
|--|--|--|--|

The title of Protocol number 310123 is: “A multicenter, randomized, double-blind, crossover, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS).” This was conducted under IND number 56,410.

The title of Protocol Number 310124 is: “A multicenter, open-label, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS).” This was conducted under IND number 56,410.

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI’s thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): numbers of adverse events reported

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study). This drug is considered an NME and will probably be presented at an advisory committee meeting; sites were chosen from 2 pivotal phase 3 studies for reasons of protocol violations and adverse events. The international site had a large number of protocol violations for the subject number. The second international is the core lab responsible for the independent interpretation of study efficacy results necessary for licensure. The compliance with the pre-specified blinded image charter is of particular concern.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact James Moore, RPM at 301-796-1986
Barbara Stinson at 301-796-1470.

Concurrence: (as needed)

- _____ Medical Team Leader
- _____ Medical Reviewer
- _____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|--|----------------------|
| NDA-201277 | ORIG-1 | BAYER HEALTHCARE PHARMACEUTICALS INC | GADOBUTROL INJECTION |

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/s/

JAMES W MOORE
08/16/2010

RAFEL D RIEVES
08/16/2010