CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201277Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	15 February 2011
From	Lucie Yang
NDA	201277
Applicant	Bayer Healthcare
Date of Submission	13 May 2010
PDUFA Goal Date	2011 March 2011
Established (USAN) names	Gadobutrol (Proprietary Name not yet established)
Dosage forms / Strength	0.1 mmol/kg intravenous / 1 Molar
Proposed Indication(s)	To detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system
Recommended:	*Approval*

1. Introduction

The subject of this cross-disciplinary review is the New Drug Application (NDA 201277) from Bayer Healthcare for the diagnostic product Gadobutrol, a magnetic resonance imaging (MRI) contrast agent. The product is a gadolinium-based contrast agent (GBCA) with a macrocyclic structure. The applicant proposes that Gadobutrol be used with MRI for central nervous system (CNS) visualization.

The following indication statement was submitted with the application:

> "*Gadobutrol is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (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.*"

The applicant includes the results of two pivotal Phase 3 trials (123 and 124). Both trials employed a single arm design, with subjects undergoing uncontrasted (U) and contrasted (C) MRI with Gadobutrol. Paired C+U was compared with U for evaluation of the intrinsic properties of CNS lesions.

This review will mainly concentrate on issues involving benefit and risk assessment of using Gadobutrol in patients with suspected CNS abnormality. Particular attention will be paid to the risk of overdosage due to a strength that is double that of the other five GBCAs indicated for CNS imaging (same proposed dose). The efforts undertaken by the sponsor to minimize this risk will be documented.

No major disagreements between the review disciplines have been observed during the review process.

2. Background

First approved in 1998 in Switzerland, Gadobutrol is a member of a class of drugs collectively known as the gadolinium-based contrast agents (GBCAs). The gadolinium ion is bound to a ligand to form a chelate because "free" (unbound) gadolinium ion is toxic. The structure of the chelated gadolinium can be linear (open-chain) or macrocyclic, and these molecules can be further described by charge: nonionic or ionic. The paramagnetic characteristic of gadolinium results in a shortening of the T1 relaxation time, which may increase signal intensity relative to background tissue.

Gadobutrol is a macrocyclic, non-ionic GBCA. Injected intravenously, Gadobutrol remains inside vessels in the CNS because of the blood-brain barrier (BBB). This "barrier" is composed of tight junctions between endothelial cells that restrict passage of solutes across the vessel wall into tissue. In certain inflammatory or cancerous lesions, the BBB becomes more permeable and GBCAs can "leak" from the vessel into tissue. In such cases, GBCA molecules enter tissue and change the signal characteristics of the tissue.

There are currently seven GBCAs approved in the U.S. for use with MRI. Five of these seven GBCAs are indicated for use in the CNS (some have additional indications). If approved, Gadobutrol will differ most notably from the other GBCAs in its molar strength. The proposed strength for Gadobutrol is 1.0 Molar whereas the strength for the other five marketed GBCAs with a CNS indication is 0.5 Molar. Given that the proposed Gadobutrol dose is the same as that for the other GBCAs with a CNS indication (0.1mmol/kg), the Gadobutrol volume would be half that of the other five GBCAs. This difference in strength raises the possibility for Gadobutrol overdosage if healthcare providers mistakenly assume all six GBCAs with a CNS indication are of the same strength.

Since 2007, the GBCAs carry a boxed warning on the risk of Nephrogenic Systemic Fibrosis (NSF). There was no stratification of NSF risk among labels of GBCAs marketed in the U.S. The association between GBCAs and NSF was made in 2006. NSF is a fibrotic condition characterized by pain, skin thickening / hardening, and joint contractures. The widespread fibrosis and collagen deposition can extend beyond the skin to affect many other organs. NSF usually presents within months following GBCA administration, though the range is from days to years after exposure. NSF can be severely debilitating and progress to death.

In 2010, FDA revised the labels of GBCAs to include new risk minimization information and to contraindicate the use of Omniscan, Optimark, and Magnevist among patients with acute kidney injury or severe, chronic kidney disease. This revision was largely based on a post-marketing drug safety review which included evaluation of spontaneous reports, epidemiology literature, drug usage patterns, nonclinical data, and physicochemical properties. Macrocyclic GBCAs have been considered to confer lower risk of NSF than linear GBCAs.

Given that NSF risk has been associated with higher GBCA doses, an Advisory Committee meeting on January 21, 2010 focused on NSF risks associated with Gadobutrol in the context of the potential for Gadobutrol overdosage errors. Post-marketing experience for Gadobutrol outside of the U.S. includes reports of NSF.

3. CMC

At the time this review is filed, the CMC review had not been finalized. To the best of this reviewer's knowledge, there are no unresolved CMC issues.

The Product Quality Microbiology Review (finalized 13 January 2011) indicates no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Overall, nonclinical studies did not reveal any major safety signals associated with a single administration of Gadobutrol. Single administration did result in a dose-related, reversible vacuolation of the proximal tubules of the kidneys, and an increase in kidney weight (relative and absolute).

Regarding NSF, nonclinical studies evaluated skin deposition of various GBCAs in animals with and without surgically-induced renal impairment. Propensity for skin deposition was higher for linear-nonionic GBCAs and lower with linear, ionic and macrocyclic GBCAs.

5. Clinical Pharmacology/Biopharmaceutics

At the time of filing this review, the Clinical Pharmacology review had not been finalized. To the best of this reviewer's knowledge, there are no outstanding clinical pharmacology issues.

A thorough QT Study Review has been finalized without outstanding issues. At a dose that is five times the proposed dose (0.5 mmol/kg), the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline corrected QTc (Fridericia's correction) was 11.9 ms at 1 minute post-dose.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

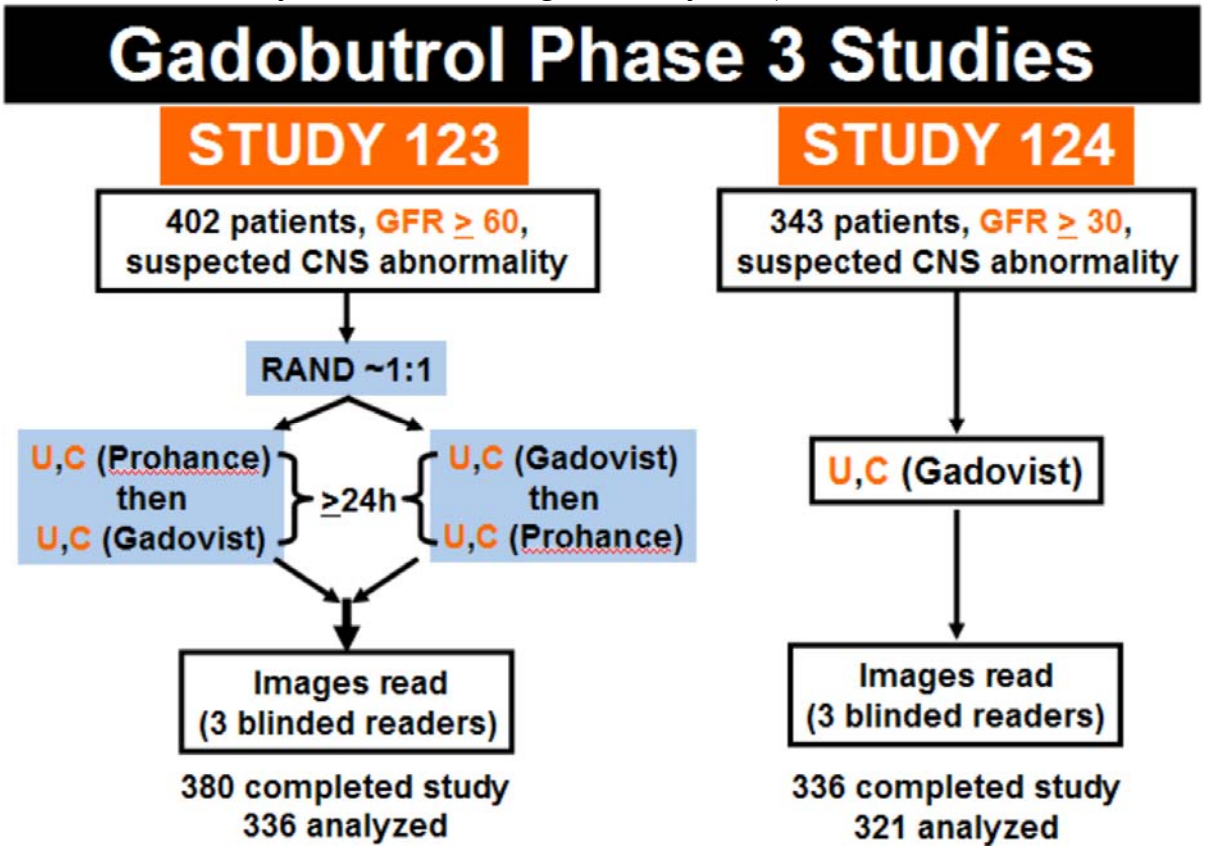
Although the biometrics review had not been finalized by the time this review is filed, this reviewer is not aware of any outstanding statistical issues.

The sponsor bases the claim of efficacy of Gadobutrol primarily on the results of two pivotal Phase 3 trials (123 and 124). Study 123 is titled, "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)." Study 124 is titled, "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)."

Please refer to the primary clinical review for a detailed description of the design, conduct, and results of these studies. The key elements are summarized below.

Studies 123 and 124 share design features (Figure 1). All subjects were suspected of having a CNS lesion. Subjects underwent an uncontrasted (U) scan followed by a contrasted (C) scan. The 1.0 Molar strength Gadobutrol was dosed at 0.1 mmol/kg. Three readers blinded to clinical information evaluated U and then paired U+C images to assess the added value of Gadobutrol. Intrinsic properties of lesions (contrast enhancement, border delineation, and internal morphology) were evaluated for superiority of U+C compared to U, and the number of lesions was assessed for non-inferiority of U+C versus U alone.

Figure 1. Study design of two Phase 3 trials (excerpted from the primary clinical reviewer's slides for the Advisory Committee meeting 21 January 2011)



The two studies importantly differed in that Study 124 subjects were administered only Gadobutrol whereas Study 123 was a randomized, double-blind crossover study. Subjects in Study 123 underwent two uncontrasted scans and two contrasted scans. On one day, the subject would be scanned without contrast and then with Gadobutrol or Prohance. On a second visit, the subject would be scanned without contrast and then with the other GBCA (Prohance if Gadobutrol was administered during the first visit or vice versa). Subjects were randomized to Gadobutrol then Prohance or to Prohance then Gadobutrol. Comparison between Gadobutrol and Prohance was a secondary endpoint.

Because Study 123 administered two GBCAs, subjects were enrolled only if they had normal renal function.

For both studies, visualization outcomes achieved statistical significance except for the average number of lesions in Study 123 (Table 1).

Table 1. Efficacy results of Phase 3 studies (excerpted from the primary clinical reviewer's slides for the Advisory Committee meeting 21 January 2011)

Variable	123			124		
	C + U	U	Δ	C + U	U	Δ
Contrast enhancement	2.26	0.97	1.29 (p<0.001)	2.86	0.93	1.94 (p<0.001)
Border delineation	2.58	1.98	0.60 (p<0.001)	2.94	1.92	1.02 (p<0.001)
Internal morphology	2.58	1.98	0.60 (p<0.001)	2.35	1.57	0.78 (p<0.001)
Avg # lesions detected	8.25	8.08	0.17 *	2.97	2.65	0.32

* Did not meet noninferiority margin of -0.35

8. Safety

Sources of safety data included Phase 2-4 studies, global pharmacovigilance data, and NSF data.

Clinical Trials

The clinical development program included 4549 subjects, 138 were pediatric subjects. Approximately 78% were dosed with the 1.0 Molar strength Gadobutrol and 54% were administered the proposed 0.1 mmol/kg dose.

Notably, in the Phase 3 trials, 7 of 716 subjects were administered a double dose. Most of these mis-administrations were the first patients at the clinical research site. According to the sponsor, after a reminder on the appropriate Gadobutrol dosing was posted on a newsletter to all investigators, the mis-administrations stopped.

There were 17 serious adverse events (SAE) among the 4549 subjects in Phase 2-4 trials. The sponsor reports that most SAEs were related to the underlying clinical condition. One SAE was crystalluria which occurred in a pediatric patient and was reported by investigators as related to Gadobutrol exposure. According to the sponsor, the patient was also exposed to augmentin for pneumonia, and crystalluria is a labeled adverse event for augmentin.

In the Phase 2-4 trials, the most common clinical adverse events (>1%) were: headache (1.5%) and nausea (1.2%). In a Phase 1 study, one subject experienced an anaphylactic reaction described in detail in the primary clinical review.

Global pharmacovigilance

Since marketing in 1998, the sponsor reports 15 deaths, including 8 anaphylaxis / anaphylactoid shock cases. As of September 2010, the sponsor reports 1175 adverse event case reports, including 317 SAEs and 3 cases of “overdose” without known sequelae. Anaphylaxis is reported at a rate of <1 / 1000, which is similar to other GBCAs.

NSF

As of 31 December 2010, the sponsor reports 10 cases of NSF associated with gadobutrol: six reports of more than one GBCA administered to the subject (confounded), two reports with only Gadobutrol administration (single-agent) and two reports considered non-assessable due to missing or incomplete information. The primary clinical reviewer agreed with the sponsor’s assessment of two single-agent Gadobutrol NSF cases among over 6 million administrations.

In the slides for the 21 January 2011 Advisory Committee meeting (Table 2), the primary clinical reviewer noted that two other macrocyclic agents, Prohance and Dotarem, each had one confirmed single-agent case among double or quadruple the number of worldwide administrations.

Table 2. Global NSF reports based on EMEA data, with the addition of Gadovist. Excerpted from the primary clinical reviewer's slides for the Advisory Committee meeting 21 January 2011.

GBCA	# NSF reports		# Administrations (millions)
	Single-agent	Confounded	
Omniscan	438	90	47
Optimark	7	11	0.8
Magnevist	135	276	95
MultiHance	0	8	6
Primovist*	0	0	0.15
Vasovist**	0	0	0.05
Gadovist* **	**2**	**8**	**6.0 (Oct. 2010)**
ProHance	1	13	12.3
Dotarem***	1	11	22.4

* Primovist is Eovist in the U.S.
** Vasovist is Ablavar in the U.S.
*** Not marketed in the U.S. Gadovist is the tradename for Gadobutrol outside of the U.S.

The primary clinical reviewer recommends that Gadobutrol be labeled without a contraindication for NSF in at-risk patients for the following reasons:

- 2 single agent Gadobutrol cases among over 6 million administrations
- animal studies suggest low risk of NSF-like skin lesions following Gadobutrol administration in animals with renal impairment
- physico-chemical data supporting gadobutrol stability as a macrocyclic agent, thus less likely to undergo dechelation

These conclusions of the primary clinical reviewer are consistent with the nonclinical reviewer and preliminary conclusions of the CMC reviewer.

The CDTL reviewer does not fully agree with the primary reviewers regarding NSF risk of Gadobutrol for the following reasons.

First, Gadobutrol has been administered to fewer patients than the other macrocyclic GBCAs (Prohance and Dotarem) and yet has at least as many (if not more) single-agent cases (if any of the currently inconclusive cases are actually single-agent cases).

Second, according to some studies, Gadobutrol has the lowest conditional stability of all the globally marketed GBCAs. Conditional stability is thermodynamic stability constant at pH 7.4.

The high thermodynamic stability reported by the sponsor is not at physiologic pH and therefore less clinically relevant.
The following paragraphs are excerpted from a clinical review on GBCAs and NSF finalized in DARRTS on 23 August 2010 under NDA 201277.

> All published studies reporting conditional stability indicate that the conditional stability of Gadobutrol (14.7) is in the same low range as those for the linear nonionic GBCAs such as Omniscan (14.9) and Optimark (15.0). Among the nonionic GBCAs, the macrocyclic GBCA Prohance has the highest conditional stability (16.9 – 17.2). The linear ionic GBCAs (Magnevist, Multihance, Eovist, Ablavar) all have conditional stabilities, ranging from 17.7 to 18.9. Dotarem has the highest conditional stability (18-8-19.3). For references, see the clinical review finalized in DARRTS on 23 August 2010 under NDA 201277.
>
> Although the range of conditional stabilities across GBCAs appears quite narrow (14.5 – 19.5), these numbers represent log K_{cond}. Therefore, the conditional stability is actually $10^{14.7}$ M^{-1}, whereas that for Dotarem is $10^{19.3}$ M^{-1}, making the difference in equilibrium constants at pH 7.4 (physiologic) for these two GBCAs quite large.
>
> The low thermodynamic stability of Gadovist at physiologic pH suggests that at equilibrium, the concentration of the free gadolinium ion and ligand relative to that of the chelate is similar to that for Omniscan and Optimark. The high kinetic stability of Gadovist simply suggests that achieving equilibrium may take longer for Gadovist than for Omniscan and Optimark.
> The prolonged GBCA exposure time in those with severely impaired renal function may likely be long enough for equilibrium to be achieved and significant dissociation to occur for Gadovist. As mentioned in section 2.3, in patients with a creatinine clearance <10 mL/min, the mean recovery of Gadovist in urine is only ~75% after 5 days.
>
> Although *in vitro* measurements of Gadovist dissociation in human serum at 37^{o}C showed no release of gadolinium ion after 15 days, the reported lower limit of quantitation of the assay (0.1%, 1mmol/L GBCA) may be higher than that necessary to trigger a fibrotic reaction *in vivo*. In addition, formation of insoluble precipitates upon GBCA dechelation *in vivo*, for which there is evidence [130, see article for potential conflict of interest;131-133], would tend to drive the equilibrium toward dissociation of Gd^{3+} from the ligand that is in the Gadovist formulation.
>
> The amount of excess ligand in the Gadovist formulation is similar to that in Magnevist, 1 mmol/L Despite being a macrocyclic GBCA, the amount of excess ligand in the Gadovist formulation is greater than for the other macrocyclic GBCAs Prohance (0.5 mmol/L) and Dotarem (0 mmol/L). Excess ligand is usually added to complex with free Gd^{3+} since free Gd^{3+} is toxic. According to a Bayer publication, the excess ligand was added to Gadovist for a reason unrelated to stability: to trap metal traces from glass vials during heat sterilization.

Of note, not all macrocyclic gadolinium complexes are more inert or stable than their linear counterparts.

For the reasons stated above, the CDTL reviewer does not agree with the primary reviewers regarding the intrinsic NSF risk for Gadobutrol relative to other GBCAs. However, given the declining overall incidence of NSF for all GBCAs since 2007, at this time, the CDTL reviewer will support the primary reviewers in their recommendation to not contraindicate Gadobutrol in patients at risk for NSF. However, if there are any additional single-agent NSF cases attributed to Gadobutrol, the CDTL reviewer highly recommends a re-evaluation of the NSF risk of Gadobutrol with careful consideration given to the physico-chemical properties.

In the mean time, a comparison of physico-chemical properties under identical conditions for all GBCAs is much needed.

Minimizing risk of overdose

The sponsor proposes to (b) (4) In addition, the sponsor proposes to include a detailed dosing chart as part of the package insert and to use conspicuous packaging to display Gadobutrol's higher concentration and lower dosing volume.

9. Advisory Committee Meeting

The Peripheral and Central Nervous System Advisory Committee held a meeting on 21 January 2011 primarily to consider the risk of NSF in light of the potential for Gadobutrol overdosage due to its double strength relative to other GBCAs with a CNS indication. Whether the benefits outweighed the risks to justify approval was also discussed.

There were two voting questions. In response to the question of whether the clinical trial and postmarketing data support Gadobutrol approval, the committee unanimously voted yes. The committee also voted on whether to label Gadobutrol without a contraindication in the at-risk population; 15 voted yes, one voted no, and none abstained. Some committee members expressed uncertainty about classifying Gadobutrol as a "lower" risk agent given the NSF cases and the number of administrations relative to other agents.

The committee was asked to discuss ways to minimize the risk of Gadobutrol overdosage. Recommendations included education of radiology technicians and radiologists, adding signs and warnings on container labels and on dosing charts, and modifications of dosing charts to include the extremes of the population in terms of body mass.

10. Pediatrics

As a new molecular entity, pediatric studies are to be considered under the Pediatric Research and Equity Act (PREA).

Bayer submitted a safety and pharmacokinetic data supporting the use of Gadobutrol in children 2-17 years of age. The sponsor also submitted a request for deferral of studies in children 0-23 months of age on the basis that adult studies are completed and ready for approval.

On 27 September 2010, FDA informed the sponsor that the Proposed Pediatric Study Request (PPSR) was inadequate on the grounds that there is concern for the safety of Gadobutrol in children, the PPSR should fully address NSF concerns for young patients with potentially immature renal function, and the need for preclinical studies to characterize elimination of Gadobutrol in the setting of renal immaturity.

On 12 October 2010, Bayer submitted a study report on the single dose toxicity study in neonatal rats in support of a human study in young children.

The sponsor is proposing to submit a final clinical protocol to study the safety of Gadobutrol in children ages 0-2 years in (b) (4), with the final Clinical Study Report to be submitted to FDA in June (b) (4)

The reviewer recommends granting the deferral of a pediatric study for children ages 2 years or less. This deferred pediatric study should be a required postmarketing study.

(b) (4) which is after this review is finalized.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations conducted six good clinical practice (GCP) inspection (applicant, four clinical sites, one contract research organization). Although there were isolated regulatory violations with respect to monitoring, the data submitted by the sponsor was deemed acceptable for use in support of the NDA since the deficiencies were not thought to significantly impact the efficacy or safety outcomes of the study. These findings were preliminary at the time this CDTL review was finalized.

12. Labeling

The labeling review is ongoing. No major labeling issues which may interfere with drug approval have been identified. The Pharmacology / toxicology reviewer and the maternal health team have provided recommendations that will be considered during labeling

discussions. The CDTL reviewer has identified language and visuals within the label that may appear promotional; these will likely be revised.

One unresolved issue of major importance is the unacceptability of two proposed proprietary names. The most recent proposal, (b) (4) A teleconference on 11 February 2011 was held to outline steps forward. The sponsor agreed to withdraw the proposed proprietary name (b) (4) and send a few proposed names for DMEPA to comment on before submitting a new proprietary name for review.

13. Recommendations/Risk Benefit Assessment

Cross-disciplinary Team Leader recommends approving Gadobutrol as a MRI contrast agent for detecting and visualizing central nervous system lesions.

The diagnostic efficacy of the drug has been demonstrated in two Phase 3 confirmatory trials. Both trials showed the added value of Gadobutrol compared to uncontrasted MRI.

Overall, the safety profile of Gadobutrol is similar to that for other approved GBCAs.

The main safety concern with Gadobutrol is the risk of overdose due to the double strength of Gadobutrol relative to that of the other five GBCAs approved for a CNS indication. The sponsor has proposed risk reduction plans which appear acceptable.

The primary reviewers and the Advisory Committee recommend against contraindicating Gadobutrol in patients at risk for NSF. Although the CDTL reviewer disagrees with this recommendation, the CDTL reviewer will support this perspective at the current time given the overall declining incidence of NSF. If, however, there are any additional single-agent NSF cases attributed to Gadobutrol, the CDTL reviewer highly recommends re-evaluation of the NSF risk associated with Gadobutrol, with particular attention paid to the physico-chemical properties of Gadobutrol.

Given the demonstrated benefit of Gadobutrol and its limited risk, the risk/benefit assessment favors approval. The approval, if issued, may be under its established name (Gadobutrol) if the sponsor does not submit an acceptable proprietary name prior to the goal date.

The CDTL reviewer recommends that the sponsor's proposed pediatric study for children 0-2 years be a required postmarketing study. No post-marketing requirement or commitment for NSF is being considered.

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/s/

LUCIE L YANG
02/16/2011