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LowEr Administered Dose with highEr Relaxivity: Gadovist vs Dotarem (LEADER 75)

Bayer study drug	BAY No. 86-4875/ Gadobutrol / (GADOVIST)
Study purpose:	Comparison of Gadovist 75% standard dose to Dotarem at full standard dose
Clinical study phase:	IV **Date:** 18 MAR 2021
Study No.:	IMPACT No. 19773 **Version:** Final 2.0
Bayer Study Statistician	PPD
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Abbreviations

BR	Blinded Reader
CI	Confidence interval
FAS	Full Analysis Set
SAP	Statistical Analysis Plan
TOST	Two One -Sided Tests

1. Background of supplementary analyses

This Statistical Analysis Plan (SAP) Supplement provides details on the post-hoc supplementary analyses.

Post-hoc examination of the Average Reader mean scores for combined (unenhanced/enhanced) gadobutrol and combined gadoterate results revealed that there was less than a 1% difference for each primary efficacy parameter. This provided a compelling reason to investigate the equivalence of the performance of combined gadobutrol and combined gadoterate. A direct comparison of the complete studies (combined image sets) is consistent with clinical practice.

Supplementary Analyses of efficacy data will be performed in the Full analysis set (FAS).

A comparison of the two combined image sets will be performed. The means, medians and standard deviations will be presented for each Blinded Reader (BR) and the Average Reader.

For each primary visualization parameter, a difference of the two combined image sets will be calculated from the values already calculated in the primary analysis as described in SAP v3.0

Means, medians, standard deviations along with the 95% two-sided CIs and one-sided p-values for the difference of the combined gadobutrol minus k* times the combined gadoterate will be presented (k represents a constant for each hypothesis).

For each primary visualization parameter, an equivalence test will be considered, where the comparison will relate to a reasonable portion (5% margin) of the difference between the combined results of gadoterate and gadobutrol. The goal is to show that performance of combined gadobutrol and combined gadoterate is equivalent regarding the three visualization parameters.

Equivalence tests at level α=0.025 will be calculated using the two one-sided t-tests (TOST) procedure, see Schuirmann (1987).

The null hypotheses for equivalence are:

- H_{01}: (gadobutrol– gadoterate) $\leq$ -0.05* (gadoterate)

and

- H_{02}: (gadobutrol – gadoterate) $\geq$ +0.05* (gadoterate).

The alternative hypotheses, representing equivalence, are:

- H_{11}: (gadobutrol– gadoterate) > -0.05* (gadoterate)

and

- H_{12}: (gadobutrol – gadoterate) < +0.05* (gadoterate).

Statistical significance would be achieved if both null hypotheses could be rejected with p-values $\leq$ 0.025 for each primary efficacy variable. In each case, the overall p-value will be calculated as the maximum of the one-sided p-values of null hypotheses H_{01} and H_{02}, respectively.

2. Shells

2.1 Table shells

Table 16.4.1/11 Comparison of degree of lesion contrast enhancement detected by blinded readers for combined image sets ╥ Equivalence Test (Full analysis set)

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	one - sided p-value	p-value
1	Gadoterate 0.1 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
	Gadobutrol 0.075 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol –0.95 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol –1.05 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Equivalence Test Result										xxx
2	Gadoterate 0.1 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
	Gadobutrol 0.075 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol –0.95 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol –1.05 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Equivalence Test Result										xxx
3	Gadoterate 0.1 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
	Gadobutrol 0.075 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol –0.95 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol –1.05 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Equivalence Test Result										xxx

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	one - sided p-value	p-value
Average Reader	Gadoterate 0.1 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
	Gadobutrol 0.075 mmol/kg bw	Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol –0.95 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol –1.05 gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Equivalence Test Result										xxx

- The 95% CI is based on a t-distribution.
- An equivalence test was calculated using the two one-sided t-tests (TOST) procedure with null hypotheses H_{01}: (gadobutrol–gadoterate) ≤ -0.05* (gadoterate) and H_{02}: (gadobutrol – gadoterate) ≥ +0.05* (gadoterate). The overall p-value was calculated as max(p1,p2) where p1 and p2 are the results of null hypotheses H_{01} and H_{02}, respectively.
-The degree of lesion contrast enhancement was evaluated on an ordinal scale of 1 to 4, representing no, moderate, good and excellent enhancement respectively. The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

Table 16.4.1/12 Comparison of border delineation detected by blinded readers for combined image sets ╥ Equivalence Test (Full analysis set)

Replace footnotes by:
- The 95% CI is based on a t-distribution.
- An equivalence test was calculated using the two one-sided t-tests (TOST) procedure with null hypotheses H_{01}: (gadobutrol–gadoterate) ≤ -0.05* (gadoterate) and H_{02}: (gadobutrol – gadoterate) ≥ +0.05* (gadoterate). The overall p-value was calculated as max(p1,p2) where p1 and p2 are the results of null hypotheses H_{01} and H_{02}, respectively.
-The border delineation was evaluated on an ordinal scale of 1 to 4, representing none, moderate, good and excellent border delineation respectively. The average score over lesions evaluated for each subject was used in the analysis.
-Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

Table 16.4.1/13 Comparison of internal morphology detected by blinded readers for combined image sets ╥ Equivalence Test (Full analysis set)

Replace footnotes by:
- The 95% CI is based on a t-distribution.
- An equivalence test was calculated using the two one-sided t-tests (TOST) procedure with null hypotheses H_{01}: (gadobutrol–gadoterate) ≤ 0.05* (gadoterate) and H_{02}: (gadobutrol – gadoterate) ≥ +0.05* (gadoterate). The overall p-value was calculated as max(p1,p2) where p1 and p2 are the results of null hypotheses H_{01} and H_{02}, respectively.
- The internal morphology was evaluated on an ordinal scale of 1 to 3, representing poor, moderate and good structure and internal morphology of the lesion respectively. The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

3. Document history

Not applicable.

4. References

Schuirmann DJ. A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability. J Pharmacokinetics and Biopharmaceutics. 1987;15(6):657-81.

Statistical Analysis Plan (Supplement) Approval Form

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Statistical Analysis Plan (SAP) Version and Date	Final 2.0, 18 Mar 2021

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PPD PPD Bayer PROD Default (Useranlage) Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/19/2021 9:42:56 AM Viewed: 3/19/2021 12:00:08 PM Signed: 3/19/2021 12:01:46 PM
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Witness Events	Signature	Timestamp

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/19/2021 9:42:57 AM
Certified Delivered	Security Checked	3/22/2021 6:30:41 PM
Signing Complete	Security Checked	3/22/2021 6:34:14 PM
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Last updated: November 12, 2020.

16.1.9 Documentation of statistical methods

List of content:

Statistical Analysis Plan Supplement Final Version 1.0 dated 24 JUL 2020

Statistical Analysis Plan Final Version 3.0 dated 26 MAY 2020

LowEr Administered Dose with highEr Relaxivity: Gadovist vs Dotarem (LEADER 75)

Bayer study drug	BAY No. 86-4875/ Gadobutrol / (GADOVIST)
Study purpose:	Comparison of Gadovist 75% standard dose to Dotarem at full standard dose
Clinical study phase:	IV
Date:	24 JUL 2020
Study No.:	IMPACT No. 19773
Version:	Final 1.0
Bayer Study Statistician	PPD
Author:	PPD PPD Covance Clinical Development Services 206 Carnegie Center Princeton, NJ 08540-6233

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Medical Affairs Responsible (MAR)/Study Medical Expert)	PPD		
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Abbreviations

BR	Blinded Reader
CI	Confidence interval
FAS	Full Analysis Set
SAP	Statistical Analysis Plan

1. Background of supplementary analyses

This Statistical Analysis Plan Supplement provides details on the post-hoc supplementary analyses and also includes the correction of the formula of the standard error of the difference of rates, used for the computation of the asymptotic McNemar's test-based confidence intervals (CIs) as described in section 6.2.3 of the Statistical Analysis Plan (SAP) v3.0.

Supplementary Analyses of efficacy data will be performed in the Full analysis set (FAS).

The primary and secondary analysis as described in section 6.2.2 of the SAP v3.0 will be repeated with the Average Reader calculated now as simple mean of the arithmetic means of the values of Blinded Readers (BRs) 1, 2 and 3. No additional zero-filling across the BRs will be implemented.

Example: The primary efficacy analyses of the 3 primary efficacy variables (visualization) was done using the average (arithmetic mean) of the values of the 3 BRs, zero-filled over all detected lesions for a patient across the 3 BRs. The analysis of these variables was also performed on the data from the 3 BRs individually using the zero-filled average method. To calculate the Average Reader as simple mean, the sum of the already calculated values described above will be used and then divided by 3.

A comparison of the two unenhanced image sets (paired comparison) will be performed. The means, medians, standard deviations along with the 95% two-sided CIs and two sided p-values will be presented per for each BR and the Average Reader. As described above the Average Reader will be calculated as simple mean of the arithmetic means of the differences of unenhanced images between gadobutrol and gadorate of Blinded Readers (BRs) 1, 2 and 3 for each of the three primary efficacy variables. No additional zero-filling across the BRs will be implemented.

For each parameter, a simple difference of the two unenhanced and the combined unenhanced image sets will be calculated from the values already calculated in the primary analysis using the average (arithmetic mean) of the values of the 3 BRs. A difference of gadobutrol – gadorate will also be calculated.

Means, medians, standard deviations along with the 95% two-sided CIs and p-values for the mean difference of the gadobutrol minus the mean of both unenhanced image set scores and the gadoterate minus the mean of both unenhanced image set scores, the mean difference of gadobutrol – gadoterate will be presented.

For each parameter, a noninferiority hypothesis will be considered, where the comparison will relate to a reasonable portion (c = 0.2) of the difference between gadoterate and the mean of both unenhanced sets. The goal is to show that the loss in the visualization parameter (gadoterate minus mean unenhanced) – (gadobutrol minus mean unenhanced) is lower than 0.2 times the difference between combined unenhanced/gadoterate and the mean unenhanced.

The null and alternative hypotheses for noninferiority are:

- H_0: (gadobutrol – mean unenhanced) – (gadoterate –mean unenhanced) $\leq$ - 0.2*(gadoterate – mean unenhanced) vs
- H_1: (gadobutrol – mean unenhanced) – (gadoterate– mean unenhanced) > - 0.2*(gadoterate – mean unenhanced).

One-sided p-values will be calculated and compared to a one-sided alpha of 0.025.

The number and percentage of subjects by region, country and treatment group will be presented for all enrolled subjects.

A bar plot of the mean scores for the the average reader for the thre primary efficacy variables will be created. A bar plot of the frequency of comparison of image quality values between gadobutrol and gadorate will also be created.

The correction of the formula of the standard error of the difference of rates, used for the computation of the asymptotic McNemar's test-based CIs) as described in section 6.2.3 of the Statistical Analysis Plan v3.0, is as follows.

$$SE_{p_2-p_1} = \sqrt{\left(\left(\frac{b+c}{n}\right) - (p_2 - p_1)^2\right)\frac{1}{n}}$$

2. Shells

2.1 Table shells

Table 16.4/1 Number of subjects by region and country (All enrolled subjects)

Region	Country	Gadoterate 0.1 mmol/kg bw N = x (100.0%)	Gadobutrol 0.075 mmol/kg bw N = x (100.0%)	Total N=x (100.0%)
All	Total	xx (xx%)	xx (xx%)	xx (xx%)
Asia Pacific	Total	xx (xx%)	xx (xx%)	xx (xx%)
	China	xx (xx%)	xx (xx%)	xx (xx%)
	Taiwan	xx (xx%)	xx (xx%)	xx (xx%)
	Japan	xx (xx%)	xx (xx%)	xx (xx%)
	Add as applicable			
Eastern Europe	Total	xx (xx%)	xx (xx%)	xx (xx%)
	Czech Republic	xx (xx%)	xx (xx%)	xx (xx%)
	Hungary	xx (xx%)	xx (xx%)	xx (xx%)
	Add as applicable			
North America	Total	xx (xx%)	xx (xx%)	xx (xx%)
	Canada	xx (xx%)	xx (xx%)	xx (xx%)
	United States of America	xx (xx%)	xx (xx%)	xx (xx%)
South America	Total	xx (xx%)	xx (xx%)	xx (xx%)
	Argentina	xx (xx%)	xx (xx%)	xx (xx%)
	Brazil	xx (xx%)	xx (xx%)	xx (xx%)
	Add as applicable			
Western Europe and Australia, Israel and South Africa	Total	xx (xx%)	xx (xx%)	xx (xx%)
	Australia	xx (xx%)	xx (xx%)	xx (xx%)
	Belgium	xx (xx%)	xx (xx%)	xx (xx%)
	Add as applicable			

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/2 Comparison of degree of lesion contrast enhancement detected by blinded readers - Average reader as simple mean over reader results (Full analysis set)

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	p-value	Non-inferiority achieved
1	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol minus unenhanced) – (gadoterate minus unenhanced) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>
2	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol minus unenhanced) – (gadoterate minus unenhanced) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>
3	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	p-value	Non-inferiority achieved
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol minus unenhanced) – (gadoterate minus unenhanced) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>
Average	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (superiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol minus unenhanced) – (gadoterate minus unenhanced) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>

-The difference for superiority test is defined as the subject-wise scores of (combined unenhanced/ enhanced – unenhanced). The 95% CIs and one-sided p-values are based on a t-distribution. The superiority is achieved if the one-sided p-value<0.025.
-The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/ gadobutrol-enhanced - unenhanced) - 0.8*(combined unenhanced/ gadoterate enhanced – unenhanced). The 95% CI is based on a t-distribution. The noninferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus unenhanced) – 0.8*(gadoterate minus unenhanced) <= 0" is lower than 0.025.
-The degree of lesion contrast enhancement was evaluated on an ordinal scale of 1 to 4, representing no, moderate, good and excellent enhancement respectively. The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- The Average Reader is using the arithmetic mean of the values of the Readers 1, 2 and 3.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/3 Comparison of border delineation detected by blinded readers - Average reader as simple mean over reader results (Full analysis set)

Replace footnotes by:
-The difference for superiority test is defined as the subject-wise scores of (combined unenhanced/ enhanced – unenhanced). The 95% CIs and one-sided p-values are based on a t-distribution. The superiority is achieved if the one-sided p-value<0.025.
-The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/ gadobutrol-enhanced - unenhanced) - 0.8*(combined unenhanced/ gadoterate enhanced – unenhanced). The 95% CI is based on a t-distribution. The noninferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus unenhanced) – 0.8*(gadoterate minus unenhanced) <= 0" is lower than 0.025.
-The border delineation was evaluated on an ordinal scale of 1 to 4, representing none, moderate, good and excellent border delineation respectively. The average score over lesions evaluated for each subject was used in the analysis.
Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- The Average Reader is using the arithmetic mean of the values of the Readers 1, 2 and 3.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/4 Comparison of internal morphology detected by blinded readers - Average reader as simple mean over reader results (Full analysis set)

Replace footnotes by:
-The difference for superiority test is defined as the subject-wise scores of (combined unenhanced/ enhanced – unenhanced). The 95% CIs and one-sided p-values are based on a t-distribution. The superiority is achieved if the one-sided p-value<0.025.
-The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/ gadobutrol-enhanced - unenhanced) - 0.8*(combined unenhanced/ gadoterate enhanced – unenhanced). The 95% CI is based on a t-distribution. The noninferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus unenhanced) – 0.8*(gadoterate minus unenhanced) <= 0" is lower than 0.025.
- The internal morphology was evaluated on an ordinal scale of 1 to 3, representing poor, moderate and good structure and internal morphology of the lesion respectively. The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- The Average Reader is using the arithmetic mean of the values of the Readers 1, 2 and 3.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/5 Comparison of degree of lesion contrast enhancement detected by blinded readers – compared to mean of both unenhanced image sets (Full analysis set)

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	p-value	Non-inferiority achieved
1	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadoterate minus mean of both unenhanced)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol minus mean of both unenhanced)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol -gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference ((gadobutrol minus mean unenhanced) – (gadoterate minus mean unenhanced)) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>
2	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadoterate minus mean of both unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol minus mean of both unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	p-value	Non-inferiority achieved
		Difference (gadobutrol -gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference ((gadobutrol minus mean unenhanced) – (gadoterate minus mean unenhanced)) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>
3	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadoterate minus mean of both unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol minus mean of both unenhanced)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol -gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference ((gadobutrol minus mean unenhanced) – (gadoterate minus mean unenhanced)) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>
Average	Gadoterate 0.1 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadoterate minus mean of both unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	

Reader	Treatment	Image set	Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	p-value	Non-inferiority achieved
	Gadobutrol 0.075 mmol/kg bw	Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Combined unenhanced/enhanced	xxx	xxx	xxx	xxx	xxx	xxx				
		Difference (gadobutrol minus mean of both unenhanced)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference Unenhanced	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	
		Difference (gadobutrol -gadoterate)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Xxx	
		Difference ((gadobutrol minus mean unenhanced) – (gadoterate minus mean unenhanced)) (non-inferiority test)	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	<Yes, No>

- The 95% CIs and two-sided p-values are based on a t-distribution.
- The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/gadobutrol-enhanced – mean unenhanced) - 0.8*(combined unenhanced/gadoterate-enhanced – mean unenhanced).
-The noninferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus mean unenhanced) – 0.8*(gadoterate minus mean unenhanced) <= 0" is lower than 0.025.
-The degree of lesion contrast enhancement was evaluated on an ordinal scale of 1 to 4, representing no, moderate, good and excellent enhancement respectively. The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/6 Comparison of border delineation detected by blinded readers – compared to mean of both unenhanced image sets (Full analysis set)

Replace footnotes by:
The 95% CIs and two-sided p-values are based on a t-distribution.
The noninferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus mean unenhanced) – 0.8*(gadoterate minus mean unenhanced) <= 0" is lower than 0.025.
-The border delineation was evaluated on an ordinal scale of 1 to 4, representing none, moderate, good and excellent border delineation respectively The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/7 Comparison of internal morphology detected by blinded readers – compared to mean of both unenhanced image sets (Full analysis set)

Replace footnotes by:
The 95% CIs and two-sided p-values are based on a t-distribution.
The noninferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus mean unenhanced) – 0.8*(gadoterate minus mean unenhanced) <= 0" is lower than 0.025.
- The internal morphology was evaluated on an ordinal scale of 1 to 3, representing poor, moderate and good structure and internal morphology of the lesion respectively. The average score over lesions evaluated for each subject was used in the analysis.
- Where scans within a reader and treatment detect a different number of lesions, the zero-filled average is calculated so each average is based on the maximum number of lesions detected per reader and treatment. For the difference between treatments, the zero-filled average uses the maximum number of lesions detected per reader.
- Gadobutrol in the image set means combined unenhanced/gadobutrol enhanced image set. Gadoterate in the image set means combined unenhanced/gadoterate enhanced image set.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/8 Summary of difference of degree of lesion of contrast enhancement between gadobutrol and gadoterate unenhanced images detected by blinded readers (Full analysis set)

Reader	Subjects	mean	median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	p-value
1	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
2	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
3	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Average	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

The 95% CIs and two-sided p-values are based on a t-distribution.
-The degree of lesion contrast enhancement was evaluated on an ordinal scale of 1 to 4, representing no, moderate, good and excellent enhancement respectively. The average score of the two unenhanced images over lesions evaluated for each subject was used in the analysis.
- The Average Reader is using the arithmetic mean of the values of the Readers 1, 2 and 3.

{Program, file pathway, date/time and other details of analysis}.

Repeat for the following table(s) :

Table 16.4/9 Summary of difference of border delineation between gadobutrol and gadoterate unenhanced images detected by blinded readers (Full analysis set)

Replace footnotes by:

The 95% CIs and two-sided p-values are based on a t-distribution.
- The border delineation was evaluated on an ordinal scale of 1 to 4, representing none, moderate, good and excellent border delineation respectively.. The average score of the two unenhanced images over lesions evaluated for each subject was used in the analysis.
- The Average Reader is using the arithmetic mean of the values of the Readers 1, 2 and 3.

{Program, file pathway, date/time and other details of analysis}.

Table 16.4/10 Summary of difference of internal morphology between gadobutrol and gadoterate unenhanced images detected by blinded readers (Full analysis set)

Replace footnotes by:

The 95% CIs and two-sided p-values are based on a t-distribution.
- The internal morphology was evaluated on an ordinal scale of 1 to 3, representing poor, moderate and good structure and internal morphology of the lesion respectively The average score of the two unenhanced images over lesions evaluated for each subject was used in the analysis.
- The Average Reader is using the arithmetic mean of the values of the Readers 1, 2 and 3.

{Program, file pathway, date/time and other details of analysis}.

2.2 Figure Shells

Figure 16.4/11 Bar Plot of the mean scores of the three primary efficacy variables for the average reader (Full analysis set)

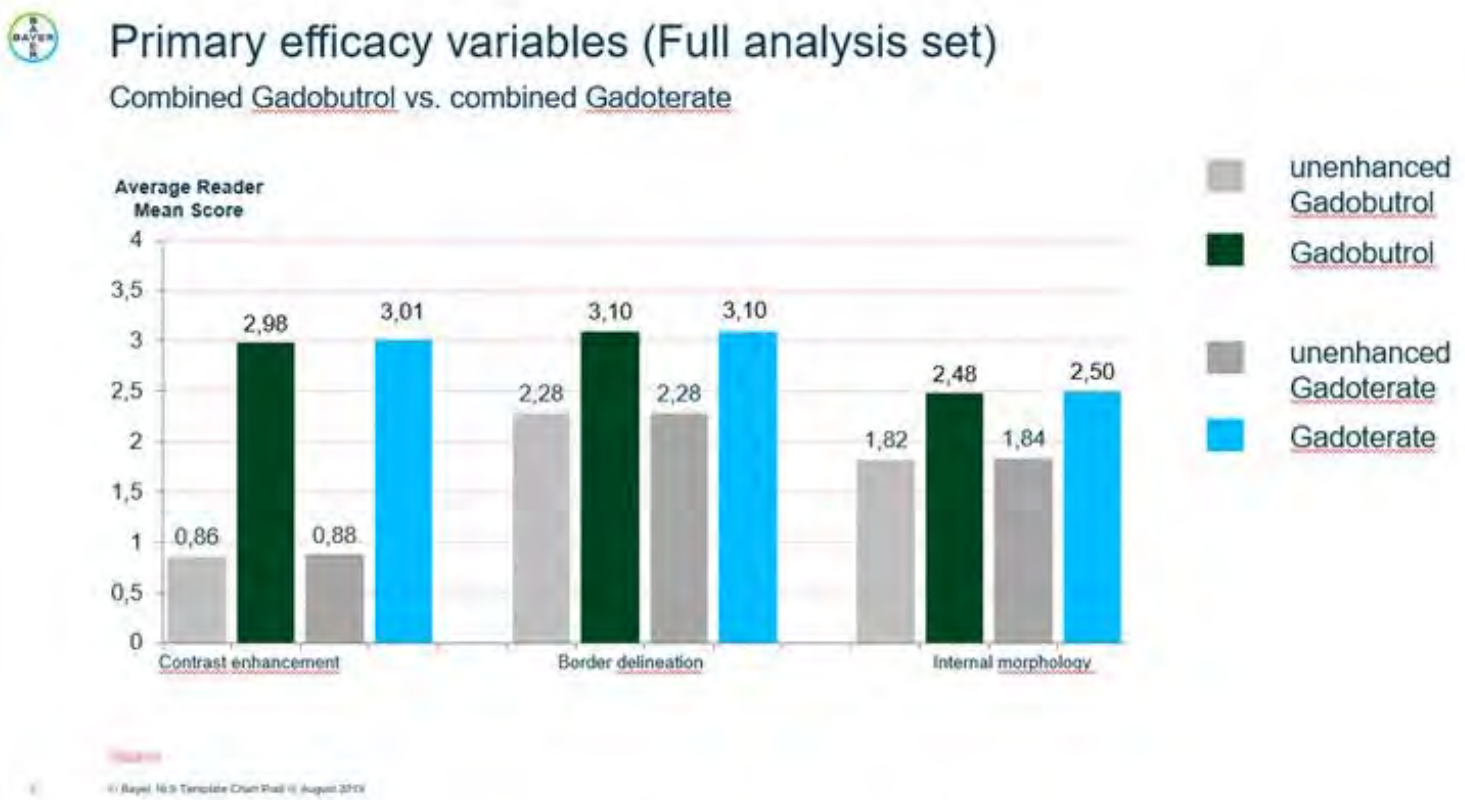
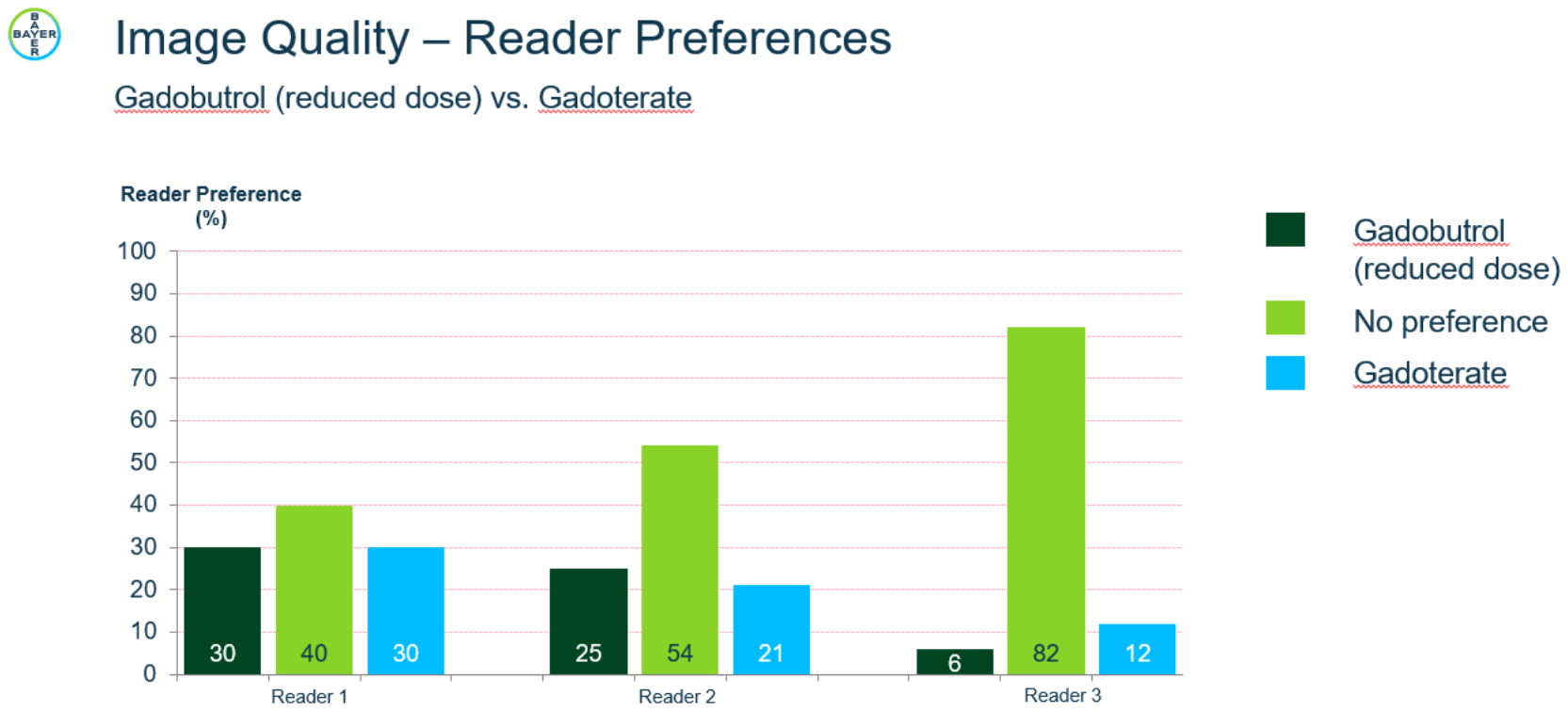


Figure 16.4/12 Bar Plot of frequency of comparison of image quality values between gadobutrol and gadoterate detected by blinded readers (Full analysis set)



3. Document history

Not applicable.

4. References

None

LowEr **A**dministered **D**ose with high**E**r **R**elaxivity: Gadovist vs Dotarem (LEADER 75)

Bayer study drug	BAY No. 86-4875/ Gadobutrol / (GADOVIST)		
Study purpose:	Comparison of Gadovist 75% standard dose to Dotarem at full standard dose		
Clinical study phase:	IV	**Date:**	26 MAY 2020
Study No.:	IMPACT No. 19773	**Version:**	Final 3.0
Bayer Study Statistician	PPD		
Author:	PPD PPD Covance Clinical Development Services 206 Carnegie Center Princeton, NJ 08540-6233		

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Statistical Analysis Plan (Amendment) Approval Form

Study Number (Bay No./IMP no.)*	BAY 86-4875/19773
Statistical Analysis Plan (SAP) Version and Date	Final 3.0, 26 May 2020

* if no IMPACT number is available, refer to the approved Study Concept

I have read and approve the SAP/SAP Amendment referred above.

	Name	Signature	Date
Author:			
Study Statistician *<plus affiliation, if not Bayer>*	PPD Covance, Inc.	PPD	
Approved by:			
Project Statistician/Internal Study Statistician[1)]	PPD		
Medical Affairs Responsible (MAR)/Study Medical Expert			
Study Statistical Analyst *<plus affiliation, if not Bayer>*	PPD Covance, Inc.	PPD	
Medical Writer *<plus affiliation, if not Bayer>*	PPD Covance, Inc	PPD	

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Abbreviations

AE	adverse event
BR	blinded reader
BW	body weight
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CNS	central nervous system
eCRF	electronic case report form
FAS	full analysis set
FLAIR	Fluid Attenuated Inversion Recovery
FN	false negative
FP	false positive
GBCA	Gadolinium-Based Contrast Agent
GCIS	General Clinical Imaging Service
eGFR	estimated glomerular filtration rate
IV	intravenous
MDRD	Modification of Diet in Renal Disease Study equation
MedDRA	Medical Dictionary for Regulatory Activities
MR	magnetic resonance
MRI	magnetic resonance imaging
NAN	not assessed negative
NAP	not assessed positive
PPS	per protocol analysis set
PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SOC	System organ class
SOT	standard of truth
T1	longitudinal relaxation time
T1w	T1-weighted
T2	transversal relaxation time
T2w	T2-weighted
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TN	true negative
TP	true positive

1. Introduction

Gadolinium-Based Contrast Agents (GBCA) are intravenous (IV) drugs used in diagnostic imaging procedures to enhance the quality of magnetic resonance imaging (MRI). Macrocyclic GBCAs, such as gadobutrol, gadoteridol, and gadoterate meglumine, have higher in-vitro and in-vivo stability and longer dissociation half-lives. The standard dose for all marketed GBCAs, including gadobutrol and gadoterate, is 0.1 mmol/kg body weight (BW) regardless of each agent's relaxivity.

This study is designed to examine if a 75% dose of gadobutrol (0.075 mmol/kg), which has a high relaxivity, is noninferior to a 100% dose of gadoterate (Dotarem) (0.1 mmol/kg) for steady state central nervous system (CNS) imaging.

Below is a list of documents this statistical analysis plan (SAP) is based on:

- Protocol Amendment 1.0, dated on 26 MAR 2018
- eCRF Final 2.0, dated on 06 Mar 2018.

2. Study Objectives

2.1 Primary Objectives

The primary objective of this study is to demonstrate noninferiority of gadobutrol-enhanced CNS imaging (at a dose of 0.075 mmol/kg BW) compared to gadoterate (0.1 mmol/kg BW) -enhanced CNS imaging (at a dose of 0.1 mmol/kg BW) for 3 lesion visualization parameters (degree of contrast enhancement, assessment of border delineation, and internal morphology of lesions) based on a blinded read.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Demonstrate noninferiority for number of lesions based on a blinded read
- Evaluate confidence in diagnosis
- Compare the 0.075 mmol/kg BW dose of gadobutrol to standard dose gadoterate for:
    - T1 (longitudinal relaxation time)-weighted (T1w) MRI image quality in a paired blinded comparison
    - Sensitivity/Specificity for presence of malignant disease based on a blinded read
- Compare the overall contrast enhancement of gadobutrol (0.075 mmol/kg BW) to the standard dose of gadoterate (0.1 mmol/kg BW) for steady-state CNS imaging. Quantitative contrast enhancement will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm.
- Assess the safety profile of the reduced dose of 0.075 mmol/kg BW of gadobutrol and standard dose gadoterate after IV administration.

3. Study Design

3.1 Overall Design

This study is a Phase 4, multicenter, controlled, cross-over study with corresponding blinded image evaluations in male and female subjects at least 18 years of age, who are referred for a contrast-enhanced MRI of the CNS based on a known or highly suspected lesion of the CNS.

Subjects will undergo an unenhanced and contrast-enhanced MRI of the CNS using gadoterate at the standard dose of 0.1 mmol/kg BW. If the investigator does not identify an enhancing lesion of the CNS, then this subject will be considered a screening failure. If an enhancing lesion is identified, then the subject will undergo a second unenhanced and contrast-enhanced MRI of the CNS using gadobutrol at a dose of 0.075 mmol/kg BW.

Safety will be assessed from the first administration of gadoterate through 24 hours after the second administration of gadobutrol. Adverse events (AEs) will be collected from the signing of informed consent through the end of the follow-up period. Serious AEs (SAEs) will be followed through resolution. Subjects who receive only the first MRI scan (considered screening failures) will be followed for SAEs only.

Gadobutrol will be administered at the dose of 0.075 mmol/kg BW by single IV injection at a rate of 2 mL/sec, followed by 20-mL 0.9% saline flush at the same rate. Gadoterate will be administered at the approved standard dose of 0.1 mmol/kg BW by single IV injection at 2 mL/sec, followed by 20-mL 0.9% saline flush at the same rate. The 2 injections will be separated by at least 24 hours, but not more than 15 days.

During the course of the study, 2 MRIs will be obtained from each subject as follows: before the administration of each of the contrast agent (unenhanced MRI) consisting of steady-state sequences (T1w, T2 [transfersal relaxation time]-weighted [T2w], and Fluid Attenuated Inversion Recovery [FLAIR]), following the gadoterate injection (gadoterate-enhanced MRI) consisting of steady-state sequences of T1; and following the gadobutrol injection (gadobutrol-enhanced MRI) consisting of steady-state sequences (T1w).

The unenhanced magnetic resonance (MR) image set, combined unenhanced and gadobutrol-enhanced MR image sets, and the unenhanced and combined unenhanced and gadoterate-enhanced MR image sets will be evaluated by 3 independent blinded readers (BRs). The BRs will also evaluate the gadobutrol-enhanced T1w images compared to the gadoterate-enhanced T1w images in a paired read for image quality.

The final clinical diagnosis will be determined by the site investigator using all available clinical information up to 30 days post the first MRI. This final clinical diagnosis will be utilized as the standard of truth (SOT) for the blinded assessment of diagnostic performance (sensitivity/specificity for malignant disease).

The safety of the subjects will be assessed by monitoring of AEs and treatment-emergent AEs (TEAEs).

An overview of the schedule of study evaluations and procedures is presented in Table 3-1.

Table 3-1 Schedule of study events

		Study Period 1[a]				Study Period 2[a]			Final Diagnosis up to 30 days Phone Call
Evaluation/Procedure	Baseline[b]	MRI		Post injection Phone Contact [C]	Baseline[c]	MRI		Post injection Phone Contact[C]	
Time Point	Up to 72 hours prior to the 1st MRI	Unenhanced	Enhanced	24 h ± 4 h	Within 24 h of the 2nd MRI	Unenhanced	Enhanced	24 h (± 4 h)	
Sign informed consent	X								
Demographic data	X								
Medical/surgical history	X								
Baseline findings	X								
Referral diagnosis	X								
Previous/concomitant medications[d]	X			X	X			X	
Weight[e]	X[i]				X[i]				
Urine pregnancy test[f]	X[i]								
Creatinine value[g]	X								
Gadoterate administration			X						
Gadobutrol administration							X		
Adverse event monitoring	X	X	X	X	X	X	X	X	
Final clinical diagnosis up to 30 days post first MRI[h]									X

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; eCRF = electronic Case Report Form; eGFR = estimated glomerular filtration rate; h = hour(s); MDRD = Modification of Diet in Renal Disease Study equation; MRI = magnetic resonance imaging; TEAE =

treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

[a] A period of 24 hours up to 15 days is required between the contrast agent injections.

[b] Baseline for Study Period 1 is from after signing informed consent up to 72 hours for gadoterate administration.

[c] Baseline for Study Period 2 is within the 24 hours prior to administration of gadobutrol. At least 2 hours is required between the 24-hour follow-up evaluations from Study Period 1 and the baseline evaluations for Study Period 2. The subject will be contacted by phone after 24-hour (± 4 hours) after each contrast agent injection. The two MRI contrast agents will be separated by at least 24 hours, but not more than 15 days. Any TEAEs or TESAEs and/or concomitant medications reported during this period will be recorded in the eCRF.

[d] All concomitant medication will be collected.

[e] Weight will be obtained at baseline and reconfirmed prior to the second MRI.

[f] Urine pregnancy test (if applicable) to be done at the site, according to the standard of the institution, and the results must be available prior to the gadoterate MRI.

[g] Serum creatinine (eGFR value calculated using either MDRD or the CKD-EPI Creatinine Equation, 2009) derived up to 4 weeks prior to the first study MRI value and date obtained and method used needs to be recorded at Screening.

[h] The final clinical diagnosis will be recorded by the investigator within 30 days of the first study MRI.

[i] Within 1 hour of injection.

3.2 Determination of Sample Size

The determination of the sample size was based on the primary noninferiority test for comparing the difference between unenhanced means and combined unenhanced/gadobutrol-enhanced means with the difference between unenhanced means and combined unenhanced/gadoterate-enhanced means.

It considers all three primary efficacy visualization parameters:

1. The contrast enhancement
2. The border delineation
3. The internal morphology.

For each parameter, a noninferiority hypothesis was considered, where the comparison was related to a reasonable portion of the difference between gadoterate and unenhanced. The goal is to show that the loss in the visualization parameter (gadoterate vs gadobutrol) is lower than a constant times the combined gadoterate and unenhanced to unenhanced.

In the Gadovist CNS pivotal study (study 310123) submitted to and agreed by the US Food and Drug Administration for the initial approval, the fixed noninferiority margin of 0.35 for the three visualization parameters (contrast enhancement, border delineation, internal morphology) for comparison of gadobutrol and gadoteridol (ProHance) was used for the secondary objective in that study.

In this study, a modified noninferiority margin for the primary efficacy variables will be used, which is 0.2*(gadoterate – unenhanced), separately for each variable. In the concept planning of the study, the constant c = 0.2 was considered reasonable as this means that it would be shown that the loss in image quality with gadobutrol at lower dose is less than 20% of the gain the comparator (gadoterate) achieves over unenhanced. The rationale for the choice of c = 0.2 is also based on the results derived from the pivotal study (study 310123) as seen in the following Table 3–2. The GBCAs like gadobutrol and gadoteridol behave similar in comparison to unenhanced within one parameter, but not across parameters.

Table 3–2 Results for average reader derived from study 310123

	Gadobutrol - unenhanced			Gadoteridol - unenhanced		
	n	mean (std)	0.2*mean	n	mean (std)	0.2*mean
Contrast enhancement	316	1.29 (0.56)	0.26	315	1.24 (0.53)	0.25
Border delineation	316	0.60 (0.53)	0.12	315	0.56 (0.48)	0.11
Internal morphology	316	0.61 (0.42)	0.12	315	0.58 (0.41)	0.12

Abbreviations: n = number; std = standard error.

The mean differences of combined gadobutrol and unenhanced to unenhanced "(gadobutrol-unenhanced)" observed in the pivotal study 310123 for these parameters were used for power calculation (1.29, 0.60, 0.61).

The related statistical hypotheses read as follows:

- H_0: (gadobutrol – unenhanced gadobutrol) – (gadoterate – unenhanced gadoterate) ≤- 0.2*(gadoterate – unenhanced gadoterate) vs
- H_1: (gadobutrol – unenhanced gadobutrol) – (gadoterate– unenhanced gadoterate) > - 0.2*(gadoterate – unenhanced gadoterate).

The study is considered successful if all 3 hypotheses related with these co-primary target variables can be rejected at a one-sided alpha of 0.025 or equivalently at a two-sided alpha of 0.05. Appropriate paired t-tests will be used.

Rejection of such a hypothesis means that it is demonstrated that gadobutrol (at reduced dose) preserves at least 80% of the effect gadoterate/Dotarem has compared to unenhanced images.

Enrolling 180 subjects allows for approximately 25% nonevaluable subjects and guarantees 90% power for border delineation. For the remaining two variables, the power will be close to 100% with this sample size. Hence, the overall power of this study will be 90%.

No type I error adjustment for multiple comparisons is needed because tests on all 3 variables must be significant to demonstrate primary efficacy.

4. General Statistical Considerations

4.1 General Principles

The primary efficacy analyses of the 3 primary efficacy variables (visualization) will be done using the average (arithmetic mean) of the values of the 3 BRs. The analysis of these variables and the analyses of the secondary efficacy variables will also be performed on the data from the 3 BRs individually.

For border delineation, contrast enhancement, and internal morphology, there will be multiple values for each subject (ratings for multiple lesions). The average (arithmetic mean) of these ratings will be used for the primary and secondary analyses. To avoid using a scoring system that rates the detection of fewer but more well-visualized lesions over the detection of more lesions, some of which may be not so well visualized, the analysis will be performed using zero-filled averages of the ratings for each subject.

In cases where the scans detect different number of lesions, enough zeros will be included with the scores for the modalities which detected fewer lesions to make the average for each modality based on the same number of scores. This zero-filled average will always reward the detection of extra lesions. This computation of zero-filled averages means that in cases where modalities (by the BRs) detect for any of the three parameters a different number of lesions in the unenhanced and enhanced image set, enough zeros will be included for the scores in the image set in which fewer lesions were detected to make the average for each modality based on the same number of scores.

Example: A reader scores in the unenhanced image of a subject two lesions regarding internal morphology and three lesions in the combined unenhanced/enhanced images. Therefore, the subject's total score of the reader will be divided by three for both images sets.

For the comparison of gadobutrol to gadoterate, the zero-filled method will be used across contrast agents.

Example: For gadobutrol, a reader scores in the unenhanced image of a subject two lesions regarding internal morphology and three lesions in the combined unenhanced/enhanced images. For gadoterate, a reader scores in the unenhanced image of a subject two lesions regarding internal morphology and five lesions in the combined unenhanced/enhanced images. Therefore, the subject's total score of the reader will be divided by five for all image sets.

Demographic variables (age, race, sex, etc.) will be summarized using frequency tables and descriptive statistics.

Safety variables will be summarized using descriptive statistics and frequency tables.

All confidence intervals (CIs) will be 2-sided, 95% intervals.

Any statistical tests used for noninferiority will be one-sided tests using the 0.025 level of significance.

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and mean, standard deviation, minimum, median, and maximum will be calculated for continuous data. Frequency tables will be generated for categorical data.

4.2 Handling of Dropouts

A subject who satisfies all eligibility criteria and discontinues study participation prior to the second MRI not due to an AE is defined as a "dropout" if the subject has already been submitted to the first study MRI.

Subjects who fail to complete both the gadoterate and gadobutrol administration as described in Section 3 will not be evaluated for the full analysis set (FAS) analyses.

Data from subjects enrolled who do not complete the study will be included in all safety analysis set (SAF) analyses.

4.3 Handling of Missing Data

No imputations will be made for missing data resulting from early termination, missed evaluations, or any other unforeseen reason.

4.4 Handling of Nonassessable (uninterpretable) Images

For the 3 primary visualization variables, the BRs must provide a numerical score for each image set; an option for uninterpretable is not available.

For evaluation of diagnoses, the readers are given the option of "not assessable," which essentially means that the image was uninterpretable for diagnostic purposes. If this evaluation occurs for the final diagnosis, the case will be excluded from the analysis of diagnoses as no SOT is available. The rare instance of a blinded-read evaluation of "not assessable" for a diagnosis based on MRI images will be considered incorrect (not a match to final diagnosis) if a final diagnosis is available for that subject.

When the BR chooses "not assessable" for diagnosis, by definition the confidence level is 1 (not confident).

4.5 Interim Analyses and Data Monitoring

No interim analyses were planned for the study.

4.6 Data Rules

Not applicable.

4.7 Validity Review

The validity of subjects to the FAS, the Per Protocol analysis set (PPS), and the SAF will be reviewed and determined before database lock. The definition for FAS, PPS, and SAF is provided in Section 5. Any changes to the statistical analysis prompted by the results of the Validity Review (or other process equivalent) will be documented in a supplement to this SAP, if applicable, or in the Clinical Study Report.

5. Analysis Sets

Full analysis set (FAS)

Analyses of efficacy data will be performed using data from all subjects for whom electronic case report form (eCRF) entries and images are available for unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and gadoterate-enhanced MRI. This population will be the FAS.

Per protocol set (PPS)

Efficacy analyses will also be performed using data from those subjects from the FAS who also fulfill all major provisions of this protocol. This set will be the PPS.

A subject will be excluded from the PPS for any one of the following reasons:

1. The subject received a dose of gadobutrol that was less than 90% or greater than 110% of the assigned dose.
2. The subject received a dose of gadoterate that was less than 90% or greater than 110% of the assigned dose.
3. An obvious error in the MRI procedure occurred either during the gadobutrol period or during the gadoterate period.
4. Pertinent images for the subject are damaged or lost.

Final decision regarding the assignment of subjects to analysis sets will be made during the Validity Review (see Section 4.7).

Safety analysis set (SAF)

The SAF will consist of all enrolled subjects (i.e., those who have signed informed consent and completed end of screening). Analysis of safety data will be performed using all available data from the SAF.

6. Statistical Methodology

For this crossover study, the study period will be divided into 3 segments:

- The **pre-treatment period** is the period after the informed consent date and before the first administration of study drug in the study.
- Two **treatment-emergent periods** (TE periods) will be defined to attribute the AEs or concomitant medications to the corresponding treatment group:
    - TE period for Study Period 1 is from the first study drug administration in Study Period 1 to 24 ± 4 hours post-injection;
    - TE period for Study Period 2 is from the first study drug administration in Study Period 2 to 24 ± 4 hours post-injection.
- The **post-treatment period** is the period after the last date of TE period for Treatment Period 2 to the date of the last study record in the clinical database or the period between the end of TE period for Treatment Period 1 and the start of TE period for Treatment Period 2.
- The baseline value is defined as the most recent nonmissing assessment (scheduled or unscheduled) collected up to 72 hours prior to first administration of study drugs in the whole study. This will include values collected at baseline visit with regard to the gadoterate scan but before signing informed consent.

6.1 Population Characteristics

6.1.1 Subject disposition

The number and percentage of total subjects in the following categories will be presented using SAF:

- Enrolled subjects
- Study drug administered in Study Period 1
- Completed Study Period 1
- Prematurely discontinued the Study Period 1
- Discontinued after Study Period 1 and before Study Period 2
- Study drug administered in Study Period 2
- Completed Study Period 2
- Prematurely discontinued the Study Period 2
- Completed study (defined as that the final clinical diagnosis is obtained, up to 30 days post the first study MRI).

Subject validity and primary reasons for exclusions from analysis sets will be presented by treatment group. The sample sizes in SAF, FAS, and PPS will also be presented by site and treatment group.

6.1.2 Protocol deviations

The number and percentage of subjects with important protocol deviations will be presented by treatment group and deviation category for all enrolled subjects.

The MRI procedure-specified protocol deviations will be summarized by treatment group and type of deviations (scanner-related or subject-related) in the SAF.

6.1.3 Demographics

Demographic and baseline characteristics will be summarized for total subjects in FAS and PPS, and by treatment group for SAF if applicable. Demographic data will include but not limited to the following:

- Age at screening
- Categorized age group at screening (< 45, ≥ 45 to 64, and ≥ 65 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and not reported)
- Ethnicity (not Hispanic or Latino, Hispanic or Latino, not reported)
- Baseline height (cm)
- Baseline weight (kg)
- Baseline body mass index (kg/m^2)
- Categorized baseline body mass index (< 25, ≥ 25 to < 30, ≥ 30 kg/m^2)
- Baseline creatinine (mg/dL)
- Baseline estimated glomerular filtration rate (eGFR; in $mL/min/1.73m^2$)

The creatinine does not require collection – Investigator must determine if eGFR is > 60 $mL/min/1.73m^2$.

6.1.4 Referral and final diagnosis

The number and percentage of subjects in each category of the referral and final diagnosis will be presented for overall subjects in the FAS, SAF, and PPS.

6.1.5 Medical history

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) during the study. Medical history will be summarized descriptively by

system organ class (SOC) and preferred term (PT) for total subjects in the SAF and total in FAS.

6.1.6 Prior and concomitant medications

Medications taken during the study will be coded using the World Health Organization Drug Dictionary Enhanced and categorized as follows:

- Prior medication: any medication that started prior to the first study drug administration, regardless of when it ended.
- Concomitant medication: medication continued or newly received during the TE period for Study Period 1 or Study Period 2. If a subject took a medication during a specific TE period, this medication will be attributed to the study drug the subject received during this study period. One medication may be attributable to more than 1 study drug for an individual subject.
- Post-treatment medication: medication continued or newly received after the TE period for Study Period 2, or between the TE periods for Study Period 1 and for Study Period 2, or after the TE period for Study Period 1 for subjects who do not have Study Period 2.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment.

For medications with partial start dates, a missing month will be imputed with January and a missing day will be imputed with 1. For medications with partial stop dates, a missing month will be imputed with December and a missing day will be imputed with the last day of the month. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment.

Prior medication summary (for medication that ended before the first study drug administration) will be presented by Anatomical Therapeutic Chemical class level 1 (anatomical class) and class level 3 (chemical level) for total subjects, and concomitant medication summary will be presented by treatment group, anatomical class, and chemical level. Both summaries of prior and concomitant medication will be based on FAS and SAF.

6.1.7 Study drug dosage and administration

The summary of drug dose and administration will be based on FAS and SAF. The actual volume (mL) and dose (mL/kg) of gadobutrol and gadoterate administered and injection rate (mL/sec) will be summarized by treatment group. The drug dose will also be presented by categories: < 90%, 90% to 110%, and > 110% relative to the assigned dose.

6.2 Efficacy

An overview of the imaging efficacy variables is provided in Table 6–1.

Table 6–1: Overview of the imaging efficacy variables

	Unenhanced MRI 1	Combined unenhanced and gadoterate-enhanced MR	Unenhanced MRI 2	Combined unenhanced and gadobutrol-enhanced MRI	Paired gadobutrol-enhanced T1w and gadoterate-enhanced T1w MRI
Variables	BR	BR	BR	BR	BR
Degree of contrast enhancement (lesions)	✓	✓	✓	✓	
Assessment of border delineation (lesions)	✓	✓	✓	✓	
Internal morphology (lesions)	✓	✓	✓	✓	
Overall contrast enhancement (Core Lab)	✓	✓	✓	✓	
Total number of lesions detected	✓	✓	✓	✓	
Malignant Disease		✓		✓	
Confidence in diagnosis		✓		✓	
Image quality					✓

Abbreviations: BR = blinded reader, MRI = magnetic resonance imaging.

6.2.1 Primary efficacy variables

The following 3 lesion visualization parameters scored by three independent BRs constitute the primary efficacy variables:

- Degree of lesion contrast enhancement
- Lesion Border delineation
- Lesion Internal morphology.

As shown in Table 6–1, the independent BRs will evaluate the 3 primary variables (visualization parameters) for up to the 5 largest lesions in each of the following images/image sets separately:

- Unenhanced and combined unenhanced (T1w, T2w, FLAIR) and gadoterate-enhanced (T1w) MR image sets.
- Unenhanced and combined unenhanced (T1w, T2w, FLAIR) and gadobutrol-enhanced (T1w) MR image sets.

The 2 image sets will be evaluated separately in 2 blinded read sessions, with 2 weeks apart between the 2 sessions to prevent reader recall.

For the evaluation of the degree of contrast enhancement, border delineation, and internal morphology, the BRs will score the lesion using the image sequence which best depicts each variable. The scores for multiple lesions of a subject will be handled by zero-filled average method as specified in Section 4.1.

6.2.1.1 Degree of contrast enhancement

A total of up to the 5 largest lesions will be selected and scored by the BRs.

The following 4-point scale will be used for lesion enhancement:

1 = No lesion is not enhanced

2 = Moderate lesion is weakly enhanced

3 = Good lesion is clearly enhanced

4 = Excellent lesion is clearly and brightly enhanced

The score will be evaluated according to Table 6–1.

6.2.1.2 Border delineation

Up to 5 of the largest lesions will be selected and scored by the BRs.

The following 4-point scale will be used for lesion delineation:

1 = None no or unclear delineation of the lesion boundaries

2 = Moderate some aspects of border delineation covered

3 = Good almost clear, but not complete delineation

4 = Excellent clear and complete delineation

The score will be evaluated according to Table 6–1.

6.2.1.3 Internal morphology

Up to 5 of the largest lesions will be selected and scored by the BRs.

The following 3-point scale will be used for lesions:

1 = Poor the structure and internal morphology of the lesion is poorly visible

2 = Moderate the structure and internal morphology of the lesion is partially visible

3 = Good the structure and internal morphology of the lesion is sufficiently visible

The score will be evaluated according to Table 6–1.

6.2.2 Analysis of primary efficacy variables

Analyses of efficacy data will be performed in Full analysis analysis set and Per Protocol analysis set.

The 3 primary analysis variables are derived from the 3 primary visualization parameters below using the following methodology:

1. The contrast enhancement (measured on an ordinal 4-point scale)
2. The border delineation (measured on an ordinal 4-point scale)

3. The internal morphology (measured on an ordinal 3-point scale)

For the 3 variables, the arithmetic mean lesion score will be calculated for each subject and each BR based on the scores for each individual lesion in a given subject. This average will be the "overall average" for each subject and each BR, and this value will be used for the primary analysis.

For example, BR 1 scores two lesions for subject X. Using border delineation as the example, he scores one lesion as a 3 and the other lesion as a 4. This reader's average lesion border delineation score for subject X will be 3.5 ((3+4)/2). This process is repeated for all 3 BRs. The average of the 3 BR overall averages for subject X is then used for the primary analysis.

The primary efficacy analysis is based on the data from the BRs' evaluation of 3 visualization parameters, which are evaluated in unenhanced and combined unenhanced and enhanced MR image sets.

A successful primary analysis is a demonstration of noninferiority for the difference between the improvement of combined unenhanced/gadobutrol in contrast to the unenhanced vs the improvement of combined unenhanced/gadoterate in contrast to the unenhanced, compared to a reasonable proportion (c = 0.2) of unenhanced vs combined gadoterate for the first 3 primary visualization parameters.

1. The contrast enhancement (measured on an ordinal 4-point scale)
2. The border delineation (measured on an ordinal 4-point scale)
3. The internal morphology (measured on an ordinal 3-point scale)

The analysis for the 3 parameters (1, 2, and 3) will be performed on the mean of the values for the 3 BRs (BR average). This analysis will be performed on the dataset including the subject average ratings for lesions.

For each parameter, a noninferiority hypothesis will be considered, where the comparison will relate to a reasonable portion (c = 0.2) of the difference between combined unenhanced/gadoterate mean and the unenhanced. The goal is to show that the loss in the visualization parameter (gadoterate minus unenhanced) – (gadobutrol minus unenhanced) is lower than 0.2 times the difference between combined unenhanced/gadoterate and the unenhanced mean. "Mean" is the mean of the BR averages.

The null and alternative hypotheses for noninferiority are:

- H_0: (gadobutrol – unenhanced gadobutrol) – (gadoterate – unenhanced gadoterate) $\leq$ - 0.2*(gadoterate – unenhanced gadoterate) vs
- H_1: (gadobutrol – unenhanced gadobutrol) – (gadoterate– unenhanced gadoterate) $>$ - 0.2*(gadoterate – unenhanced gadoterate).

The expression "(gadoterate – unenhanced gadoterate)" indicates the difference between combined unenhanced and gadoterate-enhanced mean vs the unenhanced mean.

The study is considered successful if all 3 hypotheses related to these co-primary target variables can be rejected each at a one-sided alpha of 0.025 or equivalently at a two-sided alpha of 0.05. Appropriate paired t-tests will be used as follows

The comparisons require calculations of zero-filled averages for each co-primary target variable and each subject for

- (gadobutrol minus unenhanced gadobutrol)
- (gadoterate minus unenhanced gadoterate)

Then, for each subject and each co-primary target variable, a score is derived representing

(gadobutrol minus unenhanced gadobutrol) – 0.8*(gadoterate minus unenhanced gadoterate)

For these scores, means and standard deviations will be calculated. Appropriate t-tests will be applied. For demonstration of noninferiority, p-values will be calculated for the t-test of the working hypotheses

- H_0: (gadobutrol –unenhanced gadobutrol) – 0.8*(gadoterate – unenhanced gadoterate) ≤ 0
- H_1: (gadobutrol–unenhanced gadobutrol) – 0.8*(gadoterate– unenhanced gadoterate) > 0

One-sided p-values will be calculated and compared to a one-sided alpha of 0.025.

No type I error adjustment for multiple comparisons is needed because tests on all 3 variables must be significant to demonstrate primary efficacy.

In addition, 95% two-sided CIs for the mean difference of the gadobutrol minus unenhanced score and the gadoterate minus unenhanced score will be calculated.

The other set of analysis will compare the combined enhanced and unenhanced image set to corresponding unenhanced image for both gadoterate and gadobutrol to demonstrate the superiority of the combined assessment in these 3 variables. One-sided p-values will be calculated and compared to a one-sided alpha of 0.025. This will be considered as a secondary analysis. Boxplots will be created for visualization.

Subgroup analysis will also be performed to descriptively summarize the improvement of combined unenhanced and enhanced MR image set in contrast to the unenhanced in each of the 3 primary variables (contrast enhancement, border delineation and internal morphology) by the field strength of the MRI device (1.5 or 3.0 Tesla) for gadoterate and gadobutrol groups.

6.2.3 Secondary efficacy variables

The secondary efficacy variables will be the number of lesions identified, the evaluation of the detection of malignant disease and the confidence in diagnosis. The evaluation of quantitative parameters will be performed by General Clinical Imaging Service and image quality will be evaluated by the BR(s).

The secondary efficacy variables are the:

- Comparison of contrast enhancement utilizing an Overall Contrast Enhancement Estimation Algorithm;
- Number of lesions identified (up to 10);

- Identification of benign or malignant disease;
- Confidence in diagnosis;
- Image quality.

6.2.3.1 Overall Contrast Enhancement Estimation Algorithm

Quantitative contrast enhancement estimation will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm (Relative Contrast Enhancement Score, Full Image Contrast Enhancement Score and Dice Score). The Dice Coefficient is 2 * the Area of Overlap divided by the total number of pixels in both images. The pre-contrast and post-contrast center of mass values will be calculated by the algorithm only for T1w images. The contrast enhancement will be quantified in terms of the relative difference of the centers of masses of ordinary histograms of the unenhanced and enhanced image sets. These results of the algorithm will be summarized by MRI modality using descriptive statistics and 95% CIs.

Subgroup analysis will also be performed to descriptively summarize the estimation scores by the field strength of the MRI device (1.5 or 3.0 Tesla) for gadoterate and gadobutrol groups.

Negative values of Relative and Full Image scores will be set to zero for analyses purposes.

6.2.3.2 Number of lesions able to be identified

For each image set, the BR is to record the total number of lesions, up to 10.

The number of lesions will be set to 11 for analysis purposes if > 10 lesions are reported.

For the number of lesions detected the noninferiority of gadobutrol vs gadoterate will be evaluated using tests or CIs based on the t-distribution. A noninferiority margin of 0.35 will be used in each case. This means that a 95% 2-sided CI for the mean difference gadobutrol score – gadoterate score must exceed the value -0.35 for noninferiority to be achieved.

The null and alternative hypothesis for noninferiority are:

H_0: combined unenhanced and gadobutrol MRI mean - combined unenhanced and gadoterate MRI mean $\leq$ -0.35, vs

H_1: combined unenhanced and gadobutrol MRI mean - combined unenhanced and gadoterate MRI mean > -0.35,

where “mean” is the mean of the BR averages.

6.2.3.3 Identification of benign or malignant disease

Up to 30 days post first MRI the site investigator will record in the eCRF his final clinical diagnosis, see Table 6–2 and if it confirms that the subject has malignant disease. This will serve as SOT for malignancy. A summary of final clinical diagnosis will be presented for total subjects in FAS and PPS.

The BRs will evaluate the presence of malignant lesions for each subject for the combined unenhanced and gadobutrol-enhanced MR image sets, and the combined unenhanced and gadoterate-enhanced MR image sets separately.

The SOT will be compared to the blinded read evaluations individually and per majority of BRs (at least 2 out of 3 readers).

Table 6–2: Final clinical diagnosis of CNS lesions

• Meningioma	• Chordomas
• Anaplastic/malignant meningioma	• Primary lymphoma
• Glial tumor, low grade (I/II)	• Dermoid/Epidermoid tumors
• Glial tumor, high grade (III/IV)	• Infectious disease (e.g., brain abscess, cisticercosis, etc.)
• Glial tumor, tumor grade cannot be determined	• Venous angiomas
• Metastases	• Meningeal spread of meningiomas (dural involvement)
• Multiple sclerosis (acute and chronic)	• Cerebellopontine angle tumors
• Optic neuritis	• Von Hippel Lindau syndrome
• Meningeal disease (focal enhancement)	• Hypertensive leukoencephalopathy
• Pituitary adenomas (macro and micro)	• Subacute/chronic ischemia
• Craniopharyngiomas	• Encephalitis
• Tumors of the choroid plexus	• Others, specify
• Tumors of the pineal gland	• Not assessable
• Meningeal carcinomatosis	
• Oligodendrogliomas grade II	
• Oligodendrogliomas grade III (anaplastic/malignant)	

Abbreviations: CNS = central nervous system

Diagnoses of the presence or absence of malignant tumors in each subject will be evaluated for consistency with the final diagnosis. Proportions of diagnoses consistent with the final diagnosis regarding malignancy will be calculated for gadobutrol and gadoterate, and a CI based on McNemar's test for the difference of these proportions will be given. The noninferiority of gadoterate to gadobutrol will be claimed using a noninferiority margin of 10%. These analyses will be performed for sensitivity, specificity, and overall accuracy.

Table 6–3 displays the components of the definitions for sensitivity, specificity, and accuracy.

Table 6–3: Components of the definitions for sensitivity, specificity, and accuracy

Reader Response for MRI	Final clinical diagnosis (Standard of truth)	
	Malignant	**Not Malignant**
Malignant	True positive (TP)	False positive (FP)
Not Assessable	Not assessed positive (NAP)	Not assessed negative (NAN)
Not Malignant	False negative (FN)	True negative (TN)

Sensitivity will be calculated as the number of subjects identified by MRI to have malignant lesions divided by the total number of subjects with malignant lesions according to the truth standard. Specificity will be calculated as the number of subjects identified by MRI to have no malignant lesion divided by the total number of subjects with no malignant lesion according to the truth standard. Accuracy will be calculated as the number of subjects correctly identified by MRI as having or not having malignant lesions, divided by the total number of subjects. For this analysis, a response of Benign will be considered as Not Malignant. When a response is neither benign nor malignant, then this will be considered as Not Assessable.

Using the notation of the above table,

Sensitivity = TP/(TP + NAP + FN);

Specificity = TN/(TN + NAN + FP);

Accuracy = (TP + TN)/(TP + TN + NAP + NAN + FP + FN).

Note that these calculations consider nonassessable segments as incorrect.

For the computation of the asymptotic CIs, McNemar's test-based CIs for the difference of rates between both MRI sets, the definitions in Table 6–4 are needed. With this, the standard error of the difference between p_2 and p_1 is defined as $SE_{p_2-p_1} = \sqrt{\left(p_1 + p_2 - (p_1 - p_2)^2\right)\frac{1}{n}}$

Then, the 95% asymptotic CI of the difference between p_2 and p_1 can be computed as $\left[(p_2 - p_1) - z_{0.975} \cdot SE_{(p_2-p_1)}; (p_2 - p_1) + z_{0.975} \cdot SE_{(p_2-p_1)}\right]$, with $z_{0.975} = 1.96$ as the corresponding quantile of the standard normal distribution.

Table 6–4: Components of confidence interval

Combined unenhanced/gadoterate-enhanced diagnoses agree with final diagnoses	Combined unenhanced/gadobutrol enhanced diagnoses agree with final diagnoses		
	Yes	No	
Yes	Number of subjects with matches to final diagnosis for both MRI sets: a	Number of subjects with a match for gadoterate MRI set but not for gadobutrol MRI set: b	Proportion of subjects with a match in gadoterate MRI set: $p_1 = (a+b)/n$
No	Number of subjects with a match for gadobutrol MRI set but not for gadoterate MRI set: c	The number of subjects without a match for either MRI set: d	
	Proportion of subjects with a match in gadobutrol MRI set: $p_2 = (a+c)/n$		 n = a+b+c+d

Abbreviations: MRI = magnetic resonance imaging.

The match to final diagnosis will be always considered regarding presence or absence of malignancy.

For comparing sensitivity between modalities, the match to final clinical diagnosis refers to malignancy = yes, so *n* in Table 6–4 will be the total number of subjects with malignant final clinical diagnosis by the investigator (SOT).

For comparing specificity between modalities, the match to final clinical diagnosis refers to malignancy = no, so *n* in Table 6–4 will be the total number of subjects with benign final clinical diagnosis by the investigator (SOT).

For accuracy, the match to final clinical diagnosis refers to true positive (TP) and true negative (TN) regarding malignancy, so *n* will be the total number of subjects with any final clinical diagnosis by the investigator (SOT); this will be sum of the entries for each field of the tables above for sensitivity and specificity.

These tables will be produced for each reader and for the majority reader. Majority reader is defined as the value of at least two out of three readers.

Note that truth panel diagnoses of other and not assessable will be excluded from McNemar's test or calculation of McNemar's test-based CIs.

6.2.3.4 Diagnostic confidence

The BRs will record in the eCRF his/her confidence in diagnosis for each subject for the combined unenhanced and gadobutrol-enhanced MR image sets, and the combined unenhanced and gadoterate-enhanced MR image sets separately.

Diagnostic confidence will be evaluated to determine the level of certainty that the BRs assign to a diagnosis. This is defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a subject. The degree of confidence will be rated on a 4-point scale:

1 = Not confident

2 = Somewhat confident

3 = Confident

4 = Very confident

When the BR chooses “not assessable” for diagnosis, by definition the confidence level is 1 (not confident).

Frequency tables for confidence responses (1-4) for subjects will be constructed for combined unenhanced and gadoterate-enhanced MRI, and combined unenhanced and gadobutrol-enhanced MRI. Descriptive statistics for the combined unenhanced/gadobutrol-enhanced MRI and the combined unenhanced/gadoterate-enhanced MRI will be generated. The 95% CIs for the differences based on a t-distribution will be generated.

6.2.3.5 Image quality

The BRs will evaluate the relative image quality of the gadobutrol-enhanced T1w MR images and the gadoterate-enhanced T1w MR images in a third read session different from the 2 sessions mentioned in Section 6.2.1. The assessment will be based on the overall subjective interpretation of the degree of contrast enhancement, border delineation, and internal morphology. These images will be presented in a paired fashion in a separate reading session. The gadobutrol and gadoterate images will be randomly assigned to either the left (image L) or right (image R) positions.

Image quality will be compared on a 5-point scale:

1 = Image R is worse

2 = Image R is slightly worse

3 = Image R is same

4 = Image R is slightly better

5 = Image R is better

After the data are unblinded, the above codes will be translated into the following scale:

-2 = Gadobutrol image set is worse

-1 = Gadobutrol image set is slightly worse

0 = Image sets are the same

1 = Gadobutrol image set is slightly better

2 = Gadobutrol image set is better

Frequency tables and descriptive statistics will be generated on these values and the combined values (Gadobutrol is better/slightly better) and (Gadobutrol is worse/slightly worse) yielding a 3 point scale Gadobutrol is better, same, or worse. The relative image qualities will be tested for equality using a Wilcoxon signed-rank test.

6.2.4 MRI field strengh

Field strength used in the MRI scan (1.5 Tesla, 3.0 Tesla) will be summarized for total subjects in FAS and PPS.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

6.4.1 Baseline findings

A baseline finding is defined as any untoward medical condition in a study subject who has signed the informed consent form but has not received the first dose of the study drug.

Conditions that started before signature of informed consent and for which no symptoms or treatment are present until the first administration of study drug (e.g., seasonal allergy without acute complaints) are recorded as medical/surgical history.

Conditions (e.g., abnormal physical examination findings, symptoms, diseases, or laboratory test results) present between signature of informed consent and the first administration of study drug will be documented as baseline findings and analyzed as **pretreatment AEs**.

Baseline findings will be regarded as serious if they meet the criteria used for defining SAEs and they will be reported on the SAE form.

6.4.2 Adverse events

The AE monitoring will begin with the administration of the contrast agent in Study Period 1 and will end after the last follow-up evaluation. Safety will be assessed using data from TEAEs. A **TEAE** is defined as any AE that increases in intensity or that is newly developed during the TE period for Study Period 1 or Study Period 2. If an AE starts (or increases in severity) during the TE period for a specific study period, this AE will be attributed to the treatment the subject received during the study period.

A **post-treatment AE** is defined as an AE that increase in severity or that is newly developed in post-treatment period as defined in Section 6.

The AEs are to be coded using the current MedDRA version.

Frequencies of AEs will be tabulated by contrast agent and the proportions of subjects exhibiting each AE will be displayed.

6.4.2.1 Overview of AEs

The number and percentage of subjects experiencing AEs will be summarized. Overall summary tables will be provided for all AEs, TEAEs and pretreatment AEs with following categories:

- Any such AEs
- Drug-related AEs
- AEs related to procedures required by the protocol
- AEs by intensity (mild, moderate, severe)
- Drug-related AEs by intensity
- Serious AEs (SAEs)
- Drug-related SAEs
- SAEs related to procedures required by the protocol
- AEs leading to discontinuation of study drug
- SAEs leading to discontinuation of study drug
- AEs leading to death.

The overall summary table will also be presented on AEs of subjects only receiving gadoterate but not included in the SAF.

The number and percentage of subjects with TEAEs will be summarized for the following:

- TEAEs and treatment-emergent SAEs (TESAEs) by SOC and PT
- Drug-related TEAEs and TESAEs by SOC and PT
- Nonserious TEAE by SOC and PT
- TEAEs and TESAEs resulting in discontinuation of study drug by SOC and PT
- TEAEs and TESAEs by maximum intensity, SOC, and PT
- Drug-related TEAEs and TESAEs by maximum intensity, SOC, and PT
- TEAEs and TESAEs by worst outcome, SOC, and PT
- Drug-related TEAEs and TESAEs by worst outcome, SOC, and PT

- Common TEAEs, TESAEs, drug-related TEAEs, and drug-related TESAEs with frequency ≥ 1% by SOC and PT.

Tables will be sorted alphabetically by SOC and PT.

Subject listings of all AEs as well as subset listings of AEs leading to death and AEs resulting in discontinuation of study drug will be created.

6.4.3 Other Safety Variables

No additional safety variables will be collected.

7. Document History and Changes in the Planned Statistical Analysis

- Approval of the SAP version 3.0 dated 26 MAY 2020.

1. Section 6 – Baseline definition has been updated and is defined as the most recent nonmissing assessment (scheduled or unscheduled) collected up to 72 hours prior to first administration of study drugs in the whole study. This will include values collected at baseline visit with regard to the gadoterate scan but before signing informed consent.
2. Section 5.1 – The SAF has been updated and will consist of all enrolled subjects (i.e., those who have signed informed consent and completed end of screening)
3. Section 6.1.2 Protocol deviations – The number and percentage of subjects with important protocol deviations presented by treatment group and deviation category for all enrolled subjects table was added.
4. Section 6.2.4 MRI field strength – Field strength used in the MRI scan (1.5 Tesla, 3.0 Tesla) will be summarized for total subjects in FAS and PPS was added.
5. Section 6.2.3.1 Overall Contrast Enhancement Estimation Algorithm – Relative Contrast Enhancement Score, Full Image Contrast Enhancement Score and Dice Score were added.

- Approval of the SAP version 2.0 dated 10 JUN 2019.

  The following changes have been made onto SAP version 1.0:

  1. Section 6.1.3 Demographics – A baseline characteristic summary on the number and percentage of subjects who have used 1.5 Tesla or 3.0 Tesla MRI device was added.
  2. Section 6.2.2 Primary efficacy variables – A subgroup analysis of 3 primary variables by the field strength of MRI device used (1.5T and 3.0T) was added.
  3. Section 6.2.3 Secondary efficacy variables – A subgroup analysis of contrast enhancement utilizing an Overall Contrast Enhancement Estimation Algorithm by the field strength of MRI device used (1.5T and 3.0T) was added.
  4. Section 6.4.2 Adverse events – This section was changed to remove the McNemar's test and related CIs for incidence rates of AEs as this is not Bayer standard.

- Approval of the SAP version 1.0 dated 29 AUG 2018.

8. References

None.