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Title Page

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Multicenter, single-blind, adaptive dose finding study of single intravenous injections of BAY 1747846 with corresponding blinded read in adult participants with known or highly suspected CNS lesions referred for contrast-enhanced MRI of the CNS

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Medical Monitor name and contact information will be provided separately.

Name: PPD MD MS Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 4	5.0	06 JAN 2022	
Amendment 3	4.0	29 JUL 2021	
Amendment 2	3.0	15 OCT 2020	
Amendment 1	2.0	12 FEB 2020	
Clinical Study Protocol	1.0	24 OCT 2019	*Version submitted to the HAs*

Protocol Amendment Summary of Changes Table

Amendment 4 (06 JAN 2022)

This is a global amendment and is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment was primarily implemented to fulfill the FDA request to add secondary endpoints to the study and clarify the algorithm for dose decision. In addition, editorial, administrative, and typographical corrections were made that do not affect the overall document. These changes are not described in this section. The description of changes and a brief rationale for each change are as follows:

Section # and Name	Description of Change	Brief Rationale

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis **3.0** Objectives and Endpoints **8.1.3** Secondary Endpoints **8.1.3.1** Lesion Visualization Parameters **8.1.3.2** Number of lesions **9.4** Statistical Analyses **9.4.1** Efficacy Analyses **9.4.1.2.1** Lesion Visualization Parameters at 5 min post injection **9.4.1.2.2** Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on pre-contrast and combined pre- and post-contrast (5 min pi) images **9.4.1.2.3** Number of Lesions **9.4.1.3.2** Number of Enhanced Lesions on Post-Contrast Images at 5 min Post Injection	The following secondary objective and corresponding endpoints were implemented: Secondary Objective: • Compare pre- and post-contrast images with respect to lesion visualization parameters and number of lesions Corresponding Secondary Endpoints: • Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on pre-contrast and combined pre- and post-contrast (5 min pi) images • Number of lesions on pre-contrast and combined pre- and post-contrast (5 min pi) images The identified subsections under Sections 8 and 9 were revised to accommodate the analyses of visualization parameters, lesion number and statistical variables corresponding with the additional secondary objective and endpoints.	As per FDA request, the study protocol was modified to facilitate a secondary analysis comparing lesion visualization parameters (border delineation, contrast enhancement, and internal morphology) and number of lesions between pre-contrast and combined pre- and post-contrast images.
4.3 Justification of Dose **9.2** Sample Size Determination	In case “Prefer gadobutrol” and Prefer BAY 1747846” are equally balanced in favor of both compounds, dose adjustment will not be needed.	Clarification for the dose decision algorithm (option 2-no dose adjustment) to rely solely on the primary endpoint
9.5 Interim Analyses	Revised wording to specify that an interim analysis is optional and ‘‘may’’ be performed (changed from ‘‘is planned’’). If performed, it will not affect the blinding design of the study.	Clarification that the interim analysis is not mandatory. Only participants (and central readers) are blinded as per study design and this will not be affected by the interim analysis, if performed.
6.1 Study Interventions Administered	Table 6-1 was revised to remove mention of specific country sourcing, packaging, and label procedures. Additional text indicating that local requirements for the applicable countries will be followed as to ensure compliance.	Clarification of text to prevent confusion of the local country requirements used for sourcing, packaging and labeling of study intervention.

Table of Contents

Table of Tables

Table of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: Multicenter, single-blind, adaptive dose finding study of single intravenous injections of BAY 1747846 with corresponding blinded read in adult participants with known or highly suspected CNS lesions referred for contrast-enhanced MRI of the CNS

Short Title: Adaptive dose finding study

Rationale:

This study is conducted to establish a dose of BAY 1747846 in participants with known or highly suspected central nervous system (CNS) pathology which shows similar image quality and signal enhancement (at a reduced gadolinium [Gd] dose) to the established comparator gadobutrol. Gadobutrol is a macrocyclic gadolinium-based contrast agent (GBCA) approved worldwide for various indications and populations (incl. all age groups) with broad utilization (more than 50 million administrations [Scott 2018]). Hence, it is well suited to serve as comparator and to ensure that similar imaging performance can be achieved with BAY 1747846 while relevantly reducing the Gd burden per contrast-enhanced magnetic resonance imaging (MRI) examination.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Identify a dose for further development that has an overall diagnostic preference rate similar to that of the comparator gadobutrol at 5 min post injection (pi).	• Overall diagnostic preference based on a randomized paired blinded read using a 5-point scale (greatly prefer BAY 1747846, prefer BAY 1747846, no preference, prefer gadobutrol, greatly prefer gadobutrol) at 5 min pi
Secondary	
• Show non-inferiority of BAY 1747846 compared to gadobutrol at 5 min pi with respect to sum of lesion visualization parameters • Compare pre- and post-contrast images with respect to lesion visualization parameters and number of lesions	• Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on post-contrast images at 5 min pi • Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on pre-contrast and combined pre- and post-contrast (5 min pi) images • Number of lesions on pre-contrast and combined pre- and post-contrast (5 min pi) images

Overall Design:

This is a multicenter Phase 2 study with a single-blind design with blinded read in participants with known or highly suspected CNS pathology. Participants will be enrolled in up to 3 cohorts. Gadobutrol will serve as active comparator.

Intervention Model:

Intra-individual comparison, single-blind design

Primary Purpose:

Diagnostic

Number of Arms:

Not applicable.

A maximum of 3 cohorts will be needed for the dose finding of BAY 1747846.

Masking:

Blinded participants, blinded readers

Number of Participants:

Approximately 60 participants per cohort will be assigned to study intervention such that at least 50 evaluable participants per cohort complete the study. Enrolment should continue until 50 participants have completed the MRIs in both study periods and the corresponding required images are fully evaluable for efficacy (i.e. central image quality control [QC] by General Clinical Imaging Services [GCIS] passed). If the primary endpoint is met in the first cohort, there will be the option to investigate another cohort with an adapted lower or higher dose level to evaluate the robustness and dose range of that result in a no preference outcome for BAY 1747846 and the comparator.

In total, approximately 180 participants (i.e. if all 3 cohorts will be conducted) will be assigned to study intervention such that at least 150 evaluable participants complete the study.

Intervention Groups and Duration:

Each participant will be assigned to receive gadobutrol as intervention for contrast-enhanced MRI as single intravenous (IV) administration during Period 1 and then a single IV administration of BAY 1747846 during Period 2.

There will be a washout period of 3 to 14 days between each study intervention administration during the study.

The individual study duration will be approximately 2 to 4 weeks including screening and last measurements in Period 2, which will be conducted 24 h after the last study MRI. The total duration of the study will be approximately 1 year until final clean data base.

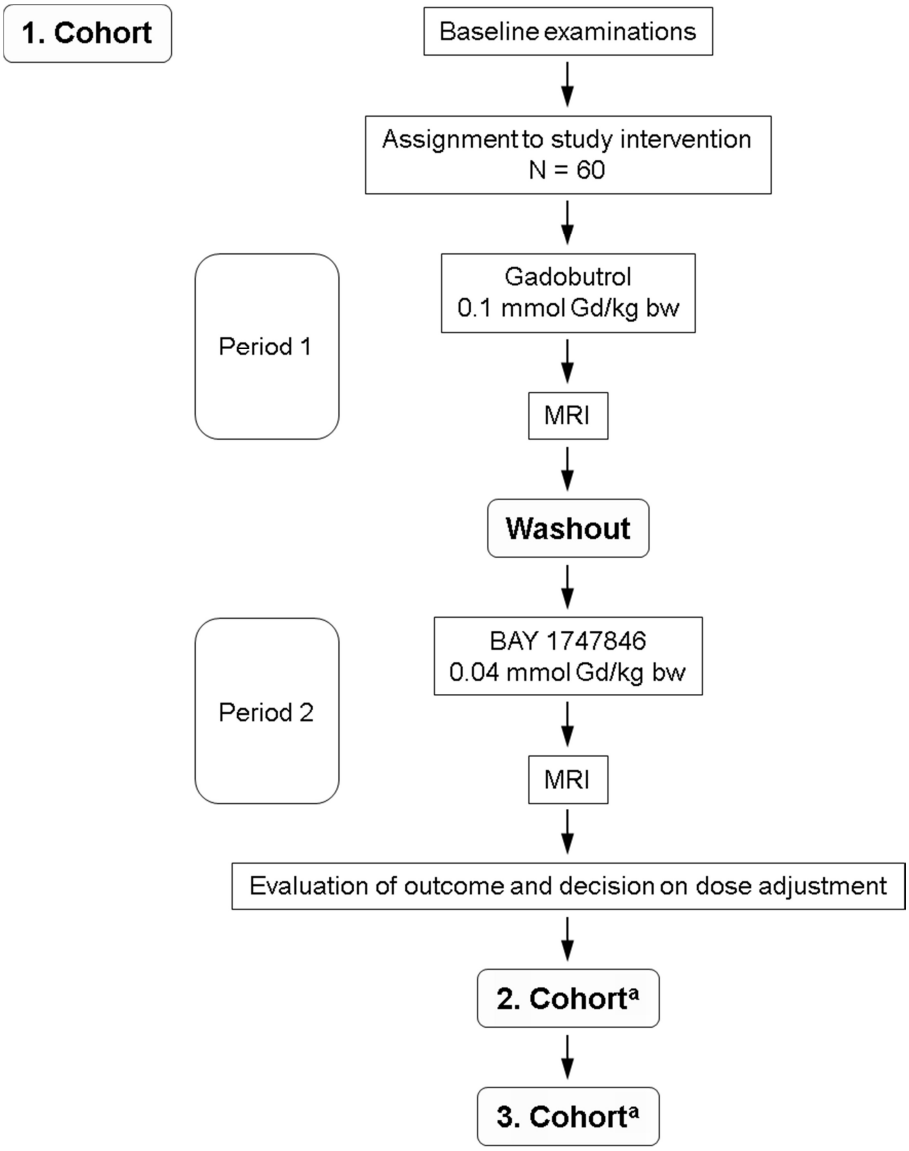
Data Monitoring Committee:

No

1.2 Schema

This is a multicenter, single-blind, adaptive dose finding study with corresponding blinded read. The first cohort of participants will receive BAY 1747846 at the initial dose of 0.04 mmol Gd/kg body weight (bw). Up to two dose adjustments (in steps of about 0.005 mmol Gd/kg bw higher or lower) will be performed depending on the outcome of the preceding cohort. The active comparator for this study will be gadobutrol (Gadovist/Gadavist) at the approved standard dose for CNS imaging of 0.1 mmol Gd/kg bw. Each cohort will consist of at least 50 evaluable participants. The overall study design is shown in Figure 1-1.

Figure 1-1: Overall study design



bw = Body weight; Gd = Gadolinium; MRI = Magnetic resonance imaging, N = Number of participants
a Decision on study continuation with a further cohort depends on outcome of previous cohort

1.3 Schedule of Activities (SoA)

Table 1-1 provides the SoA presenting the study-related measures/actions planned for this study. Screening activities might be combined with baseline measurements on the same day. In that case, the participant needs to sign the informed consent form (ICF) by documenting the time point in addition to the signature date before any baseline activity starts. Baseline activities are scheduled within 48 h prior to study intervention administration (see Section 10.1.3) and need to be done for each study period, including check of inclusion and exclusion criteria as relevant changes might occur in between (e.g. eGFR, medical condition).

The reference point (Day 1, relative time: 00d00h00 min) for the time matrix to be used for data evaluation will be the administration of study intervention. All measures/actions to be performed **before this reference point** will be assigned to **negative** time points, all subsequent measures/actions will have positive time points.

Table 1-1: Study SoA

Evaluation/procedure	**Scr**	**Baseline[k]**	**MRI and injection phase in Period 1 and 2**			**Post injection phase in Period 1 and 2**			
Time point		**≤48 h before dosing**	**Prior to injection**	**Dosing**	**5 min pi**	**Immediately after MRI (20 – 60 min pi)**	**2 – 4 h**	**6 – 8 h**	**24 ± 4 h[m-n]**
Relative time point		**-2d 00h 00min**	**0d 00h 00min (PRE)**	**0d 00h 00min**	**0d 00h 05min**	**0d 00h 20min**	**0d 02h 00min**	**0d 06h 00min**	**1d 00h 00min**
Written informed consent[a]	X								
Demographic data	X								
Medical/surgical history	X								
Prior medication	X								
Concomitant medication	X	X					X		X
Urine pregnancy test[b]		X	X						
Determination of eGFR[c]		X							
Body height and weight, BMI		X							
Complete physical examination		X						X	X
In/exclusion criteria	X	X							
At-hospital[d]			X→	→	→	→	→	→X	
Administration of study intervention				X					
Blood pressure, heart rate or pulse[e]		X				X	X		X
Body temperature		X	X			X			
Respiratory rate		X				X			
Short physical check[f]						X			
Examination of injection site[g]			X			X			X
Short mental status check		X							X
12-lead ECG[e]		X				X	X		X
Placement of IV line for dosing			X						
MRI phase			X→[l]	→	→X	→X			
Pulse oximetry[h]			X→	→	→	→X			
Blood sampling for safety		X					X		X
Blood sampling for PK[i]		X				X	X	X	X
Blood sampling for centralized serum creatinine[j]		X							
Urinalysis		X					X		X
AE monitoring		X→	→	→	→	→	→		→ X

Table continued

Table 1-1: Study SoA – continued

AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; IV = Intravenous; MRI = Magnetic resonance imaging; pi = post injection; PK = Pharmacokinetics; Scr = Screening

X Measure/action to be done at the time point indicated.

→ Measure/action to be done continuously, starting/ending from/at the time point indicated.

a The informed consent has to be obtained within 8 weeks before any study-related procedures and assessments are conducted. If screening and baseline activities are to be performed on the same day, time of signature needs to be documented on the informed consent form in addition to signature date.

b For women of child-bearing potential only. At the day of study intervention administration, the result must be available prior to administration of contrast media injection.

c With regards to baseline of period 1, eGFR can be derived from a serum creatinine result obtained within 4 weeks prior to the first study MRI. If a serum creatinine result is not available, it will be determined by the study site (creatinine that is part of blood sampling for safety at each baseline can be used to derive eGFR for the respective baseline period as long as the result is available prior to administration of the intervention).

d patient may be hospitalized throughout each period for participant convenience or site operations, based on operational feasibility, participant health condition and willingness, after a positive benefit/risk assessment by the Investigator for such hospitalization

e After 5 min resting phase.

f Done by observation and asking the participant about his/her physical condition.

g Before and after placement of IV line as well as after discontinuation of IV line.

h Continuously monitored, starting prior to the beginning of the first MRI and continuing throughout until completion of the second MRI.

i A second indwelling cannula will be required for PK sampling. Population PK samples time windows: 20 – 60 min, 2 – 4 h, 6 – 8 h and 24 ± 4 h (together with blood sample for safety) after administration of study intervention. Actual sampling times will be documented in the eCRF. The first 3 time windows will be subdivided in 3 sub-windows, see Table 8-2.

j Only performed once.

k Baseline assessment to be done in Period 1 and 2. All baseline values will be assessed before placement of IV line.

l MRI prior to study intervention administration is an unenhanced MRI (i.e. without contrast media). Details can be found in Section 8.1.1.

m In Period 2, this time point will be the follow-up visit. For participants with premature study termination, the same assessments scheduled for follow-up will be conducted during an early discontinuation visit.

n 24 ± 4 h procedures for period 1 and/or period 2 may be conducted at hospital, at a local facility or at home based on operational feasibility, local regulations, participant health condition and willingness. At hospital procedures are preferred when possible.

2. Introduction

BAY 1747846 is a new macrocyclic GBCA with high relaxivity for enhancing magnetic resonance (MR) images. The clinical utility of GBCAs in contrast-enhanced MRI is well established and demonstrated in various indications and populations for more than 3 decades and in over 500 million procedures.

BAY 1747846 is in development as multi-purpose GBCA for contrast-enhanced MRI in adults and children of all ages. So far, it has been studied in two Phase 1 trials. The initial first-in-human (FiH) study (Study 19324) examined increasing doses of BAY 1747846, ranging from 0.025 up to 0.2 mmol Gd/kg bw in healthy men and women, and confirmed similar safety and pharmacokinetics (PK) compared to marketed GBCAs. In Study 19325, signal enhancement of various selected regions in the head and neck area at increasing dose levels (0.01 to 0.06 mmol Gd/kg bw) was evaluated in healthy men and women in comparison to gadobutrol at the standard dose of 0.1 mmol Gd/kg bw. Also in this study, the safety profile was similar to gadobutrol and the FiH Study 19324. A dose proportional enhancement pattern was observed and could be compared quantitatively to gadobutrol.

2.1 Study Rationale

This study is conducted to establish a dose of BAY 1747846 in participants with known or highly suspected CNS pathology which shows similar image quality and signal enhancement (at a reduced Gd dose) to the established comparator gadobutrol. Gadobutrol is a macrocyclic GBCA approved worldwide for various indications and populations (incl. all age groups) with broad utilization (more than 50 million administrations [Scott 2018]). Hence, it is well suited to serve as comparator and to ensure that similar imaging performance can be achieved with BAY 1747846 while relevantly reducing the Gd burden per contrast-enhanced MRI examination.

2.2 Background

Since their introduction almost 30 years ago and after 500 million administrations worldwide, GBCAs have been established as a crucial element in transforming MRI into a high performance. GBCAs are complexes of Gd, a paramagnetic metal acting as the signal and contrast-enhancing component, with different organic chelators. Depending on the structure of the chelator, they are differentiated in linear or macrocyclic compounds. Macrocyclic GBCAs are generally more stable than linear GBCAs.

In 2006, the administration of GBCAs was identified as a risk factor for the development of Nephrogenic Systemic Fibrosis (NSF) in patients with severe renal impairment (glomerular filtration rate [GFR] <30 mL/min) (Grobner 2006). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs. The risk for NSF was found to be higher for linear compounds with lower stability of the Gd-chelate.

In 2014, increased signal intensity (SI) in the dentate nucleus and the globus pallidus was reported on unenhanced T1-weighted ($T1_w$) MR images in patients who had received multiple injections of GBCAs before (Kanda et al. 2014). Further non-clinical and clinical investigations have shown that traces of Gd may remain in parts of the body, including bone, skin, brain, blood, urine, and other areas, for long periods of time after injection of all

GBCAs. The less stable linear agents resulted in higher concentrations of Gd than the macrocyclic agents. In animals, no histopathological change was detectable in brain tissue after repeated high doses of even the least stable agents (Radbruch 2016, Runge 2016).

Although no symptoms or diseases linked to Gd in the brain have been reported, the European Medicines Agency (EMA) took a precautionary approach, requesting the lowest Gd doses that enhance images sufficiently should be used (EMA 2017).

Health authorities worldwide either requested label updates to reflect the above-mentioned findings or requested in the case of the EMA the suspension of the less stable linear multipurpose GBCAs as a precautionary measure. In addition, health authorities consistently request the lowest dose resulting in diagnostic enhancement. BAY 1747846 addresses this request by substantially lowering the Gd burden per administration while maintaining sufficient enhancement.

The scientific and medical evidence to date continues to support a favorable benefit-risk profile for GBCAs in the vast majority of patients, in accordance with the product information.

Gadobutrol

Gadobutrol is a macrocyclic GBCA and is indicated for contrast enhancement in MRI in adults and children for MRI of the brain and spine, MR angiography and whole-body MRI. Clinical safety, efficacy and PK are well characterized (see local product label for gadobutrol). Gadobutrol is approved for various indications in most regions/countries worldwide including the European Union (EU), USA and Japan.

Preclinical Data of BAY 1747846

The effect of a GBCA on relaxation times in tissues, and consequently enhancement in SI and contrast on MR images, depends on its relaxivity and its concentration in the tissue of interest, i.e. its PK behavior.

For BAY 1747846, the relaxivities measured *in vitro* were more than 2-fold higher compared to other macrocyclic GBCAs like gadobutrol, when normalized to Gd. MRI studies in rats, rabbits, and minipigs confirmed that BAY 1747846 shows similar signal enhancement at less than half the Gd dose as other available macrocyclic GBCAs (see Section 4.1.2 of the Investigator's Brochure [IB] and report PH-40545).

The PK profile of BAY 1747846 was investigated in several animal species, including rats, rabbits and cynomolgus monkeys. It was found to be identical to that of marketed multipurpose/macrocyclic GBCAs with superimposable concentration-time profiles when administered at the same dose. Elimination was almost exclusively via the kidneys and at the same excretion rates. The elimination rate of BAY 1747846 was similar to the GFR. *In vitro* studies showed a negligible protein binding, no uptake into hepatocytes and no potential for drug-drug interactions. Further details can be found in Section 4.2 of the IB.

Clinical Data of BAY 1747846

<u>First-in-Human (FiH) Study 19324</u>

The FiH Study 19324 was a randomized, single-blind, placebo-controlled, escalating single-dose study on the safety, tolerability, and PK of IV administered BAY 1747846 in healthy women and men.

The main objective of this study was to investigate safety, tolerability and PK including gender differences, excretion pathways and analysis for potential metabolites. The first 3 cohorts received single ascending doses of 0.025, 0.05 or 0.1 mmol Gd/kg bw of BAY 1747846 or placebo (0.9% sodium chloride) as a 5-min IV infusion; cohorts 4, 5 and 6 received 0.03, 0.1 or 0.2 mmol Gd/kg bw of BAY 1747846 or placebo (0.9% sodium chloride) as IV injection at 2 mL/s. In total, 49 participants were recruited in this study and received BAY 1747846 or placebo in Study 19324.

BAY 1747846 was found to be very well tolerated at single IV doses up to 0.2 mmol Gd/kg bw. The safety assessment based on adverse events (AEs), vital signs, electrocardiogram (ECG) parameters, pulse oximetry, and laboratory examinations indicated that IV administration of BAY 1747846 was very well tolerated. The incidence and severity of AEs was independent from the dose administered and similar to placebo. No relevant effects on cardiac or respiratory function were observed. Laboratory examinations were without clinically relevant observation.

PK results of participants in Study 19324 revealed - as expected - a rapid decline of the plasma concentration-time profile shortly after the end of the administration. Main PK parameters (AUC_{norm} and CL/bw) are summarized in Table 2-1.

Maximum concentration (C_{max}) was reached shortly after the end of the infusion in most cases. Following injection (2 mL/s), C_{max} was observed either at 2 or 5 min after injection.

C_{max} and area under the concentration versus time curve (AUC) increased dose proportionally from 0.025 to 0.2 mmol Gd/kg bw. The total body clearance of drug normalized by bw (CL/bw), volume of distribution at steady state normalized by bw (V_{ss}/bw), mean residence time and effective $t_{1/2}$ remained constant within the dose range tested. BAY 1747846 showed a clearance similar to the GFR and V_{ss} indicated distribution into the extracellular water space of the body.

For the main PK parameters, the variability was low (between 8.23 and 22.1%). For C_{max}, variability was slightly higher (up to 34%) as can be expected during the early time after IV administration for a compound with such a rapid distribution phase.

As expected and similar to other marketed macrocyclic GBCAs, the major part of the Gd dose was excreted within 12 h pi. On average, about 84 – 101% of the dose was already excreted within 12 h via urine, except for the highest dose group, where on average 74% was excreted during that time frame. However, in this group, two participants had a low recovery during the first 4 h (32 and 57%) post dose which may indicate loss of urine during collection. Exemption of these 2 participants from average calculations showed a recovery of 84%.

The PK results of BAY 1747846 were in the expected range based on the preclinical data and were very similar to those reported for marketed macrocyclic GBCAs, e.g. gadobutrol and gadoterate meglumine, when corrected for dose.

The CL/bw values determined for all dose levels were around 0.09-0.1 L·kg/h and essentially the same as determined for gadobutrol (0.09 L·kg/h) and gadoterate meglumine (0.08 L·kg/h).

The same holds true for the average dose normalized AUC for all dose groups of BAY 1747846, gadobutrol and gadoterate meglumine, as listed in Table 2-1.

Table 2-1: Dose normalized AUC and CL/bw (mean [CV%]) obtained from dose groups 1 – 6 in the FiH Study 19324 for ascending doses of BAY 1747846 in comparison to the same parameters reported for gadobutrol and gadoterate meglumine

Compound / administration	Dose [mmol Gd/kg bw]	AUC_{norm} [kg·h/L]	CL/bw [L·kg/h]
BAY 1747846 5 min infusion	0.025	10.1 [8.23]	0.0985 (8.23]
BAY 1747846 5 min infusion	0.05	9.78 [8.51]	0.102 [8.51]
BAY 1747846 5 min infusion	0.1	10.7 [11.4]	0.0936 [11.4]
BAY 1747846 injection	0.03	9.73 [17.2]	0.103 [17.2]
BAY 1747846 injection	0.1	10.2 [22.1]	0.0984 [22.1]
BAY 1747846 injection	0.2	10.2 [12.0]	0.0978 [12.0]
Gadobutrol[a] injection	0.1	11.1 [N/A]	0.094 [8.90]
Gadoterate meglumine[b] injection	0.1	9.87 [N/A]	0.08 [12.6]

a Report No. 9746; Report No A44213
b Le Mignon et al. 1990; Dotarem SmPC

In addition, the amount of BAY 1747846 excreted within 12 to 24 h is matching the amount of macrocyclic GBCAs (gadobutrol: 86 – 100% of the administered dose, see Report No 9746; gadoterate meglumine: 89 – 95% of the administered dose, see Dotarem Summary of Product Characteristics [SmPC]) excreted via the kidneys.

Overall, these results confirm the expected safety and PK of BAY 1747846 that was already shown pre-clinically in several animal species. The determined PK profile, with its rapid extracellular distribution and elimination (according to GFR) and its similarity to other marketed macrocyclic GBCAs, supports the implemented minimum washout period of 3 days between the administration of BAY 1747846 and gadobutrol, respectively.

Dose-response Study 19325 in healthy participants

This was a randomized, single-blind, 4 x 4 cross-over, dose-response study of 3 single IV injections of increasing doses of BAY 1747846 compared to gadobutrol in healthy

participants. The primary objective of the study was to determine relative signal enhancement (RSE) of BAY 1747846 in relation to dose and compare it to the RSE achieved with gadobutrol at the standard dose (0.1 mmol Gd/kg bw). The secondary objective of the study was to investigate the safety of BAY 1747846 in healthy participants.

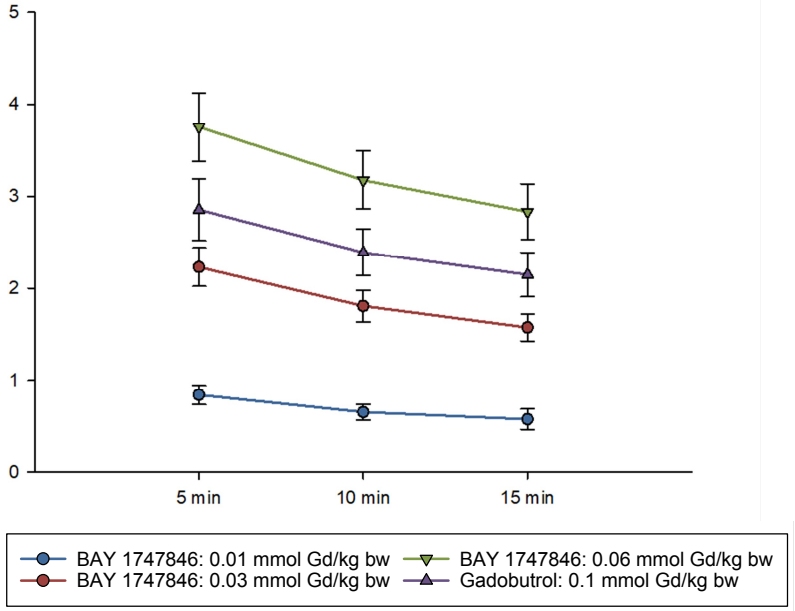
In this study, 43 participants were treated. 42 participants received 3 doses of BAY 1747846 (0.01, 0.03 and 0.06 mmol Gd/kg bw) and one dose of gadobutrol (0.1 mmol Gd/kg bw) in a randomized order with at least 7 days between injections.

The conduct of the study was completed; preliminary results for safety and dose response are available.

The preliminary safety assessment confirmed the good safety profile observed in the FiH Study 19324. There were 16 participants with treatment-emergent adverse events (TEAEs), 12 were of mild and 4 of moderate intensity. There was a balanced distribution among treatments. No AE led to discontinuation and no serious adverse events were observed.

To establish a dose response, SI was measured in five enhancing areas of the head and neck region before (pre) and at approximately 5, 10 and 15 min after each injection: Sagittal sinus, sigmoidal sinus, parotid gland, submandibular gland, and internal carotid artery. MR Images were acquired with a $T1_w$ 3D gradient echo sequence on a 1.5 T MR Scanner. BAY 1747846 showed an increase in signal enhancement in relation to Gd dose in all regions of interest for each imaging time point. RSE for all treatments and time points for an exemplary area (sigmoidal sinus) is shown in Figure 2-1.

Figure 2-1: RSE (% ± SD) determined in the sigmoidal sinus at 5, 10 and 15 min after injection of 0.01, 0.03 or 0.06 mmol Gd/kg bw of BAY 1747846 or 0.1 mmol Gd/kg bw of gadobutrol.



RSE for each area was determined by dividing the difference between pre and post SI by pre SI. Based on the RSE values a dose response curve was established for each area by inverse regression which was then compared to the RSE determined after injection of gadobutrol. Overall, BAY 1747846 leads to the same enhancement as gadobutrol with less than half the Gd dose. The estimated dose to reach the same signal enhancement was in the range from 0.038 to 0.065 mmol Gd/kg bw.

These results are well in line with the $T1_w$ relaxivity differences of BAY 1747846 (11.8 $L \cdot mmol^{-1} \cdot s^{-1}$) and gadobutrol (5.2 $L \cdot mmol^{-1} \cdot s^{-1}$), which is approximately 2.3 and underline that signal enhancement is independent of different organs and depends mainly on relaxivity of the GBCA and its presence in the area of interest.

2.3 Benefit/Risk Assessment

This study will be performed in male and female participants with known or highly suspected CNS pathology. The participants will benefit from the contrast-enhanced MRI examination which they will receive based on the underlying clinical need. They will not directly benefit from the additional MRI being performed in relation to the study. However, the data obtained from this study will contribute to the development of BAY 1747846 for contrast-enhanced MRI in adults and children of all ages, with the goal to relevantly reduce the dose of Gd.

The overall safety profile of GBCAs is favorable and well established with more than 500 million administrations of all GBCAs since 1988. Adverse reactions following their administration are usually mild to moderate in severity and transient in nature. The most commonly reported adverse reactions following administration of GBCAs are headache, nausea and dizziness.

Hypersensitivity/anaphylactoid reactions consisting primarily of cutaneous, respiratory, and cardiovascular symptoms have been recognized to occur in association with all GBCAs. The mechanism by which anaphylactoid reactions occur is not fully understood but may involve release of active mediators, such as histamine and bradykinin. The vast majority of hypersensitivity reactions to GBCAs are mild to moderate in nature, and transient, consisting of events such as urticaria and usually occur within 30 min after administration (Prince et al. 2011). As a precaution, hypersensitivity reactions will be monitored narrowly as adverse event of special safety interest (AESI) and reported within the same timelines as any serious adverse event (SAE).

Post-marketing experience with GBCAs identified rare adverse reactions, such as anaphylactoid reactions/anaphylactoid shock, which may be severe or life-threatening, seizures, and NSF as further risks (Prince et al. 2011). NSF was observed in patients with severe renal impairment (GFR <30 mL/min) or with acute renal failure, populations excluded from participation in this study (Kanal 2016).

Recently, increased SI was reported in some brain areas on unenhanced scans after repeated injections of primarily linear GBCAs (Kanda et al. 2014). However, to date, none of the many studies have shown an association between the observed increased SI in the brain after repeated GBCA administrations and the occurrence of any clinical AEs. Additionally, no causal relationship has been reported between clinical signs and symptoms and the presence

of traces of Gd in the body in patients with normal renal function following use of a GBCA (see Section 5.3.3.3 of the IB).

The safety and tolerability of BAY 1747846 was assessed in the FiH Study 19324 based on the incidence and severity of AEs during a study period of 7 days post dose. This included the serial evaluation of cardiac (heart rate, blood pressure [BP], ECG) and respiratory function (peripheral hemoglobin oxygen saturation), hematology, biochemistry, and monitoring of markers for complement activation and histamine release. In addition, plasma, urine, and feces were collected over a period of 72 h post dose to investigate the PK of BAY 1747846, including investigation of metabolism and excretion.

No SAE was observed during the study conduct.

The incidence of TEAEs was similar in all dose groups and in placebo participants. Most TEAEs were mild, two were of moderate intensity (creatine kinase increase after intense physical activity and brief lymphocyte decrease in the context of laboratory evidence of a short inflammatory reaction) and none were severe. All AEs were recovered or recovering at the end of the study close out visit one week after administration.

The preliminary overall safety assessment based on TEAEs, vital signs, ECG, pulse oximetry, and laboratory examinations indicates that IV administration of BAY 1747846 was very well tolerated. The incidence and severity of AEs was independent of the dose administered and was similar to placebo. No relevant effect on cardiac or respiratory function was observed.

Also, no clinically relevant change in laboratory examinations attributable to treatment with BAY 1747846 was observed.

Based on nonclinical data and preliminary data from the FiH Study 19324, the safety and PK profiles of BAY 1747846 are assumed to be similar to other GBCAs.

The safety monitoring activities that are part of this clinical study are considered appropriate to detect any effect with relevance to the safety of the study participants. The principal investigator or his/her delegate will be present at the MRI unit from study intervention administration until at least 1 h after administration to promptly and efficiently manage any acute reaction, should it occur.

Repeated pregnancy testing and the required use of highly effective contraception will minimize the risk of inadvertent administration to a pregnant woman or prenatal exposure in this study.

Based on the favorable non-clinical and clinical safety data of BAY 1747846 at the doses investigated, it is concluded that female and male participants will not be exposed to any relevant health risk in this cross-over study. Therefore, their inclusion in this study is justified considering the potential benefit that the development of a low-dose, macrocyclic GBCA may provide to patients undergoing contrast-enhanced MRI examinations.

This clinical study does not involve invasive procedures other than single IV administration of the test and comparator GBCAs and a very limited number of venous blood samples for safety and PK analysis.

The typical contraindications for MRI are reflected in the selection criteria. When properly performed, the MRI examination is painless and no harmful effects are currently known.

In conclusion, the procedure-related risks of study participation are considered to be minimal.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BAY 1747846 can be found in the IB and for Gadovist/Gadavist within the respective local product label.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Identify a dose for further development that has an overall diagnostic preference rate similar to that of the comparator gadobutrol at 5 min pi	• Overall diagnostic preference based on a randomized paired blinded read using a 5-point scale (greatly prefer BAY 1747846, prefer BAY 1747846, no preference, prefer gadobutrol, greatly prefer gadobutrol) at 5 min pi
Secondary	
• Show non-inferiority of BAY 1747846 compared to gadobutrol at 5 min pi with respect to sum of lesion visualization parameters • Compare pre- and post-contrast images with respect to lesion visualization parameters and number of lesions	• Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on post-contrast images at 5 min pi • Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on pre-contrast and combined pre- and post-contrast (5 min pi) images • Number of lesions on pre-contrast and combined pre- and post-contrast (5 min pi) images
Other pre-specified	
• Evaluate SI/enhancement • Evaluate efficacy at 15 min pi • Evaluate efficacy at 10 min pi • Determine plasma concentrations of Gd following administration of BAY 1747846 and gadobutrol • Evaluate safety profile of BAY 1747846 in comparison to gadobutrol • Number of enhanced lesions on post-contrast images	• Quantitative parameters: SI, contrast to noise ratio (CNR), signal to noise ratio (SNR) • Lesion visualization parameters at 15 min pi • Lesion visualization parameters at 10 min pi • Plasma concentrations of Gd within 3 time windows on Day 1 and after 24 ± 4 h following administration of BAY 1747846 and gadobutrol • Incidence and severity of TEAEs and other parameters • Number of enhanced lesions on post-contrast images at 5 min pi

4. Study Design

4.1 Overall Design

This is a multicenter Phase 2 study with a single-blind design with blinded read. The study will permit up to two adaptive dose changes (i.e. increase or decrease) to ensure that the dose of BAY 1747846 shows similar overall diagnostic preference and enhancement as the selected active comparator gadobutrol.

Each participant will receive an IV gadobutrol administration during Period 1 and an IV BAY 1747846 administration during Period 2 followed by recording of a contrast-enhanced MRI in each period.

Between each study intervention administration there will be a washout period of 3 – 14 days.

The individual study duration will be approximately 2 to 4 weeks including screening and last measurements in Period 2, which will be conducted 24 h after the last study MRI. The total duration of the study will be approximately 1 year until final clean data base.

4.2 Scientific Rationale for Study Design

The decision for the study design is primarily based on the following considerations:

- The non-randomized design was selected to enable a diagnostic MRI for the study participants during Period 1 as the participants are patients with CNS lesions requiring a contrast-enhanced MRI, and they need to be provided with standard medical care with the first imaging. Therefore, the comparator (gadobutrol)-enhanced MRI will always be done in Period 1, whereas the MRI including the injection of BAY 1747846 will be done during Period 2. Based on the gadobutrol-enhanced MRI, the investigator may identify the need for immediate treatment or that the participant has no lesions, both may yield in exclusion from further study participation.
- The single-blind design is addressing primarily an unbiased assessment of safety parameters. The study participants will be blinded to the study intervention. Only the investigator and site staff will be unblinded to the study intervention, obeying to the need for participants to receive the best medical care as urgently as needed based on clinical judgment.
- The single-blind design might potentially lead to a bias with regard to safety assessment on the investigators side. Safety bias is minimized by the blind in the participants and evaluation of images for efficacy. The risk for bias was evaluated vs. the benefit for the participants in obtaining a diagnostic MRI in the study Period 1 and was regarded acceptable.
- The efficacy analysis is done in an independent blinded read which is unaffected by the single-blind non-randomized study design.

4.3 Justification for Dose

BAY 17147846

The starting dose of BAY 1747846 of 0.04 mmol Gd/kg bw was selected based on the results of the dose response Study 19325. Based on the RSE values determined in five different areas of the head and neck, a dose response curve was established for each area by inverse regression which was then compared to the RSE determined after injection of gadobutrol. Overall, BAY 1747846 led to the same enhancement as gadobutrol with less than half the Gd dose. The estimated dose to reach the same signal enhancement was in the range of 0.038 to 0.065 mmol Gd/kg bw (see Section 2.2). A starting dose was chosen at the lower end of the range.

The primary and secondary endpoints will be based on the images acquired 5 min pi, as this time point is representative of steady-state when the GBCA has been distributed in the extracellular space. In addition, 5 min pi image acquisition is used broadly in clinical routine for CNS contrast-enhanced MRI.

There are 3 possible outcomes from the first cohort of at least 50 evaluable participants (see Section 9.2 for determination of sample size):

1) If the confidence intervals (CIs) for the choices “Prefer gadobutrol” and “Prefer BAY 1747846” are not overlapping and the proportion expressing “Prefer gadobutrol” is greater than the proportion “Prefer BAY 1747846”, then the dose needs to be adjusted upward and an additional cohort with a higher dose will be enrolled.
2) In case, the choices “Prefer gadobutrol” and “Prefer BAY 1747846” are equally balanced in favor of both compounds, dose adjustment will not be needed.
3) If the CIs for the choices “Prefer gadobutrol” and “Prefer BAY 1747846” are not overlapping and the proportion expressing “Prefer BAY 1747846” is greater than the proportion “Prefer gadobutrol”, then the dose needs to be adjusted downward and an additional cohort with a lower dose will be enrolled.

For outcome 1, a second participant cohort will be studied with an adjusted dose of BAY 1747846 which will be about 0.005 mmol Gd/kg bw higher than the initial dose. If that cohort does not result in outcome 2 or 3, an additional dose adjustment of about 0.005 mmol Gd/kg bw will be performed in a third cohort of additional 50 evaluable participants.

The starting dose was selected to be unlikely to require more than one upwards dose adjustment.

For outcome 2, which means that the primary endpoint is met, there will be no investigation of another cohort.

For outcome 3, one downward adjustment of about 0.005 mmol Gd/kg bw with additional 50 evaluable participants will be performed.

The final determination of the dose will also consider the individual visualization parameters which are evaluated as secondary endpoints as well as quantitative SI measurements using dedicated software.

Gadobutrol

Gadobutrol will be the active comparator for this study. It will be administered at the approved standard dose for CNS imaging of 0.1 mmol Gd/kg bw.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including completion of the 24 h post MRI measurements in Period 2.

The end of the study is defined as the date when the clean database is available.

Primary completion

The primary completion event for this study is the availability of the blinded read results for all participants.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Known or highly suspected CNS pathology (contrast-enhancing CNS lesion) referred for contrast-enhanced MRI of the CNS. The suspicion of a CNS pathology can be based on current clinical symptoms and/or on a previous imaging procedure. Types of CNS lesions and pathologies which could be included are:
    - Glial tumor (low grade [I/II], high grade [III/IV], grade cannot be determined)
    - Oligodendrogliomas grade II and III (anaplastic/malignant)
    - Metastases
    - CNS lymphoma
    - Meningiomas, anaplastic/malignant meningiomas, meningeal spread of meningiomas [dural involvement], swannomas, neurinomas/accusticus neurinomas
    - Craniopharyngiomas
    - Ependymomas.

    Participants who are referred for follow-up MRIs after treatment or for treatment planning (e.g. targeted radiosurgery) are eligible if there is a possibility to schedule an additional MRI exam.

Sex

3. Male and female.
4. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Sexually active men, who have not been surgically sterilized, and women of child-bearing potential must agree to use reliable and acceptable methods of contraception. This applies for the time period between signing the informed consent form (ICF), until 24 h after the last study MRI. Men must not to act as sperm donor. Acceptable

methods of contraception include user-independent (e.g. implantable hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion) and user-dependent methods (e.g., hormonal contraception with inhibition of ovulation, vasectomized partner if sole sexual partner, sexual abstinence). Preference should be given to user-independent methods of contraception (detailed guidance see Section 10.4).

Informed Consent

5. Capable of giving informed consent within 8 weeks before any study-related procedures and assessments are conducted as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other

6. Estimated glomerular filtration rate (eGFR) value ≥60 mL/min/1.73m^2 at baseline. With regards to baseline of period 1, eGFR value can be derived from a serum creatinine result within 4 weeks prior to the first study MRI determined by local hospital lab.
7. Ability and willingness to understand and follow study-related instructions, including two contrast-enhanced MRI examinations with both BAY 1747846 and gadobutrol.
8. Confirmation of the participant's health insurance coverage prior to the baseline examinations, if required by country (e.g. Germany).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Considered clinically unstable or has a concomitant/intercurrent condition (e.g. COVID-19 infection) that would not allow participation for the full planned study period (i.e. period 1, 2 or both) in the judgement of the investigator.
2. Severe cardiovascular disease (e.g. known long QT syndrome, acute myocardial infarction [<14 days], unstable angina, congestive heart failure New York Heart Association class IV or acute stroke [<48 h]).
3. Patients undergoing liver transplantation.
4. Any contraindication to MRI examinations (e.g. metallic implants, pacemaker, claustrophobia).
5. History of severe allergic or anaphylactic/anaphylactoid reaction to any allergen including drugs and contrast agents, foods, chemicals or other substances.
6. History of allergic asthma and/ or atopic dermatitis.
7. Suspected lesions or suffering from any of the following CNS diseases/lesion types as the main indication for MRI. Secondary findings identified by the investigator might not lead to exclusion of the participant, e.g. a small venous angioma:

- Lepto-meningeal disease (e.g. leptomeningeal carcinomatosis). Dural lesions (e.g. meningiomas) fulfilling inclusion criteria #2 are not excluded.
- Pituitary adenomas (macro and micro)
- Tumors of the choroid plexus
- Tumors of the pineal gland
- Dermoid/epidermoid tumors
- Infectious disease (e.g. brain abscess, cisticercosis, etc.)
- Venous angiomas
- Subacute/chronic ischemia
- Encephalitis
- Multiple sclerosis (acute and chronic)
- Optic neuritis
- Chordomas
- Von Hippel Lindau syndrome
- Hypertensive leukoencephalopathy.

Prior/Concomitant Therapy

8. Receipt of any contrast agent <72 h prior to the study MRIs, or planned receipt of any contrast agent within 72 h after the second study MRI.
9. Planned or expected biopsy in the region of interest or any interventional therapeutic procedure from the first study MRI up to 24 h after the second study MRI.
10. Planned or expected change in any treatment or procedure between the two study MRIs that may alter image comparability, e.g. corticosteroid and /or chemotherapy which is changed between the two MRI procedures.

Prior/Concurrent Clinical Study Experience

11. Has been previously enrolled in this study.
12. Has received any investigational product within 30 days, or within 5 times half-life of the investigational product, whichever is shorter, prior to enrolling in this study. Note: Participants who have entered the follow-up period of or have been discontinued from an investigational study may participate as long as it has been 30 days after the last dose of the previous investigational product, or 5 times half-life of that investigational product, whichever is shorter.
13. Contraindications to the administration of gadobutrol, as specified in the local product label (e.g. history of severe hypersensitivity reaction to gadobutrol).

Other Exclusions

14. Women of child-bearing potential with a positive urine test at the day of study intervention administration.
15. Breast feeding women.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Fasting is recommended according to clinical practice.

No water is allowed from 1 h prior to and until 1 h after study intervention administration.

5.3.2 Activity

Participants will abstain from excessive or unusual exercise in the period from signing of the ICF until 24 h after the last study MRI.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently receiving study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. A maximum of 10% of participants may be enrolled in the study after re-screening. Re-screened participants should be assigned a new participant number. The previous participant number of the participant will be documented in the electronic case report form (eCRF).

Re-starting the defined set of screening procedures to enable the “screen failure” to participate at a later time point is not allowed – with the following exceptions:

- The participant had successfully passed the screening procedures but could not start subsequent study intervention administration on schedule.
- The in-/exclusion criteria preventing the participant’s initial attempt to take part in the study have been changed (via protocol amendment).

In any case, the investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. Also, for re-screening, the participant has to re-sign the ICF, even if it was not changed after the participant’s previous screening.

6. Study Intervention

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study participant according to the study protocol.

Note: In this study, study intervention refers to administration of test intervention BAY 1747846 and comparator intervention gadobutrol.

6.1 Study Interventions Administered

Regarding the selection of doses in the study, refer to Section 4.3.

The identity of the study interventions is described in detail in Table 6-1.

Table 6-1: Identity of study intervention

Arm name	Active drug	Active drug
Intervention Name	BAY 1747846	Gadobutrol
Type	Test drug	Comparator drug
Dose formulation	Solution for IV injection	Solution for IV injection
Unit dose strength	193.43 mg BAY 1747846/mL (equivalent to 0.3 mmol Gd/mL); 4 ml (773.70 mg) per vial (nominal amount)	604.72 mg gadobutrol/mL) (equivalent to 1.0 mmol Gd/mL)
Dosage level(s)	1. cohort: 0.04 mmol Gd/kg bw 2. cohort: 0.04 + 0.005 or 0.04 - 0.005 mmol Gd/kg bw 3. cohort: 0.04 + 0.01 or 0.04 - 0.01 mmol Gd/kg bw	0.1 mmol Gd/kg bw
Route of administration	IV injection	IV injection
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided locally by the study site as marketed product or provided centrally by the sponsor (depending on local requirements).
Packaging and Labeling	Will be supplied in 10 mL vials, colorless glass type I for injection with stopper. Each glass vial will be labeled as required per country requirement.	Will be supplied in vials. Study intervention will be used as unchanged product with market authorization or each vial will be labeled as required per country requirement (depending on local requirement).
Current/Former Name(s) or Alias(es)	BAY 1747846	Gadovist/Gadavist

bw = body weight; Gd = gadolinium; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product

Administration procedure

An IV injection line consisting of a large bore indwelling catheter will be placed in an antecubital vein. The location of the IV injection line has to be documented in the eCRF.

The study intervention will be administered as a bolus at the rate of 2 mL/s either using an automated MR-compatible injection system or by hand injection via the IV injection line, each followed by a 20 mL 0.9% saline flush at the same flow rate. Dose and volume of study intervention will be recorded in the eCRF.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

6.3 Measures to Minimize Bias: Randomization and Blinding

This is a single-blind study. Participants will remain blinded to the sequence of the study intervention throughout the course of the study. In order to maintain this blind, the study intervention must be prepared without the study participant being able to witness it. Furthermore, the investigator's team has to ensure that the participants remain blinded throughout the study.

Blind readers will not be provided with information on study intervention throughout the course of the study.

6.4 Study Intervention Compliance

The IV administration of the study intervention will be done by a member of the investigator's team. This person will ascertain and document that the participant receives the treatment as planned.

6.5 Prior and Concomitant Therapy

Participants are not to receive any contrast agent <72 h prior to the study MRIs or within 72 h after the second study MRI (see Section 5.2).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving within 4 weeks before signing of the ICF or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and stop dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The regular use of contraceptives and the occasional use of paracetamol, aspirin, or ibuprofen are permitted prior and during the study.

Medication other than the study intervention must not be taken during the study without consulting the investigator. Participants will be instructed to not use any medication without consulting the investigator, unless prescribed by a physician to treat an AE. Participants will be instructed to report any used concomitant medication, including herbal remedies or food supplements, to the investigator. All concomitant medication is to be recorded in the source documentation and the appropriate pages of the eCRF. For concomitant medication administered on days of study intervention administration each dose will be documented with time of administration.

6.6 Dose Modification

See Section 4.3.

6.7 Intervention after the End of the Study

After the end of this study, no further treatment is planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

No further participant will be dosed with BAY 1747846 and the study findings will be evaluated thoroughly at this point to decide on further progress of the study, if one of the following occurs:

- Occurrence of any SAE assessed as related to BAY 1747846 which is not in line with the safety profile of current macrocyclic GBCAs.
- Occurrence of severe AEs related to BAY 1747846 in more than 3 participants. This includes changes of laboratory parameters qualifying as severe.
- Any relevant information, from this study or from outside of this study, indicating a relevant deterioration of the risk-benefit ratio.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Dropout

A participant who discontinues study participation prematurely for any reason is defined as a “screen failure” if the participant has not received any study intervention (Section 5.4).

A participant who at the time of premature withdrawal, has received any study intervention is a “drop out”.

7.3 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit

should be conducted. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If, in the investigator's opinion, continuation of the study which includes start of Period 2 would be harmful to the participant's well-being the participant will be permanently discontinued. Participants that suffer a severe hypersensitivity reaction related to gadobutrol during Period 1 of the study, must not be advanced into Period 2 of the study.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he/she fails to return for Period 2 and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

The independent review and centralized measurements will be planned and conducted by GCIS (Bayer). Details on blinded image evaluation and centralized procedures will be provided by GCIS in the Image Review Charter. The blinded readers will be experienced independent certified radiologists not affiliated with the imaging facilities and not involved in the conduct of the study and/or the recruitment of participants. Prior to the conduct of the blinded read, the readers will be trained by GCIS on the alignment of the assessment rules for image evaluation.

8.1.1 MRI Procedure

8.1.1.1 MRI Equipment

The MRI will be performed at MRI units with readily available emergency and intensive care facilities. State of the art 1.5 Tesla MRI scanners that can perform the required pulse sequences with a dedicated head or head/neck coil will be used. The same scanner, coil and MR techniques per participant must be used for both the gadobutrol and BAY 1747846 contrast-enhanced MRIs.

8.1.1.2 Sequence Parameters for Brain Imaging

Protocol-defined sequences for CNS MRI will be used to obtain unenhanced and contrast-enhanced image presentations.

The same parameter setting must be used for unenhanced $T1_w$ images and for contrast-enhanced $T1_w$ images in each participant. The required pulse sequences for BAY 1747846 and gadobutrol are:

- Unenhanced:
    - Localization sequence for brain according to the study site's standard
    - 2D $T1_w$ images of the whole brain (axial)
    - 3D $T1_w$ images of the whole brain (axial or sagittal, consistent across visits per participant)
- Contrast-enhanced:
    - 3D $T1_w$ images of the whole brain (axial or sagittal, consistent to unenhanced and across visits per participant), starting 5 min pi.
    - 2D $T1_w$ images of the whole brain (axial), starting directly after prior sequence at about 10 min pi.

- 3D $T1_w$ images of the whole brain (axial or sagittal, consistent across visits per participant), starting 15 min pi.

- General considerations:
  - The MRI scanner must NOT be actively retuned after the unenhanced sequences.
  - It is crucial that all imaging parameters are as consistent as possible throughout both image visits of each study participant.

Further sequences (e.g. DWI or T2/FLAIR) can be run for local clinical use, as long as no active retuning or shimming is ensured between the mandatory study sequences.

The date and start time of the study intervention injection will be recorded in the eCRF as well as any deviation from the specified MRI procedures and the reason for it (scanner-related problem or participant-related problem).

The recommended MRI parameters for the mandatory study sequences are displayed in Table 8-1 below.

Table 8-1: Recommended MRI sequence parameters

	2D $T1_w$ [a]	**3D $T1_w$ [a]**
Plane	Axial	Sagittal or axial[b]
Pulse sequence	Spin echo (SE)	Inversion recovery gradient recall echo (IR-GRE)[c]
Patient position	Supine	Supine
Coil	Head/head-neck	Head/head-neck
Slice thickness (Gap/spacing)	≤5 mm (0 mm)	1 mm (isovoxel) (0 mm)
Frequency	≥256	≥256
Phase	≥256	≥256
Inplane resolution	1.5 x 1.5 mm	1 x 1 mm
NEX/NSA	≥1	≥1
Parallel imaging	Up to 2x	Up to 2x
TR	According to site's standard	According to site's standard[d]
TE	According to site's standard	Minimum value[d]
TI	–	According to site's standard[d]
Acquisition	2D	3D
Contrast media	Unenhanced Starting about 10 min pi (directly after prior sequence)	Unenhanced Starting 5 and 15 min pi

2/3D = 2/3 dimensional, IR-GRE = inversion recovery gradient recall echo, NEX = number of excitations, NSA = number of acquisitions, pi = post injection, SE = spin echo, $T1_w$ = T1-weighted, TE = echo time, TI = inversion time, TR = repetition time.

a All parameters must be as consistent as possible across both image visits per participant and equivalent for pre- and post-contrast $T1_w$ images per image visit.
b Either axial or sagittal anatomic orientation can be performed, but must be consistent for both image visits and for unenhanced and contrast-enhanced images per study participant.
c Equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi), inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
d Recommended TR/TE values based on Ellingson et al.: TR = 2100 msec (Siemens, Hitachi) or 5 to 15 msec (GE, Philips, Toshiba); TI = 1100 msec (Siemens, Hitachi) or 400 to 450 msec (GE, Philips, Toshiba).

8.1.1.3 Quality Assurance of Images

The investigator must assure that the MRI image set is of acceptable diagnostic quality.

All image sets will be de-identified and sent to GCIS. GCIS will conduct QC and quality assurance (QA) of the MR images.

Further details and guidance for the sites will be provided in the Imaging Manual by GCIS.

8.1.1.4 Image Archiving and Copying

Once all the study-related images are acquired, all sets of images and related documents are considered to be source data and therefore must be stored on appropriate archival media at the site according to local requirements, but at least for 15 years.

8.1.2 Primary Endpoint

To assess the primary study endpoint, 3 blinded readers (i.e. blinded to the treatment allocation and any other information on the participant) will independently compare the following contrast-enhanced image sets of each study participant in a matched pairs approach:

- Contrast-enhanced $T1_w$ (BAY 1747846) 5 min pi
- Contrast-enhanced $T1_w$ (gadobutrol) 5 min pi.

The gadobutrol and BAY 1747846 image sets will be randomly assigned to either the left (image L) or right (image R) position in the image visualization system. Qualitative technical efficacy is measured by the reviewers overall diagnostic preference based on the randomized paired blinded read using the following 5-point scale:

1 = greatly prefer image R

2 = prefer image R

3 = no preference

4 = prefer image L

5 = greatly prefer image L.

8.1.3 Secondary Endpoints

8.1.3.1 Lesion Visualization Parameters

The following 3 lesion visualization parameters will be scored by the 3 blinded readers for assessing the secondary endpoint “lesion visualization parameters” for each enhanced (5 min pi) MR image set separately (no matched pairs approach), as well as for assessing the secondary endpoint “lesion visualization parameters” for comparison of pre- and post-contrast images on pre-contrast and combined pre- and post-contrast images (5 min pi) separately (no matched paired approach):

- Lesion border delineation (see Section 8.1.3.1.1)
- Degree of lesion contrast enhancement (see Section 8.1.3.1.2)
- Lesion internal morphology (see Section 8.1.3.1.3).

8.1.3.1.1 Lesion Border Delineation

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

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.

8.1.3.1.2 Contrast Enhancement

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

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.

8.1.3.1.3 Internal Morphology

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

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.

8.1.3.2 Number of lesions

The 3 blinded readers will record the total number of lesions for each pre-contrast and combined pre- and post-contrast (5 min pi) MR image set separately (no matched pairs approach). The upper limit of lesions to be counted is 20.

8.1.4 Other Endpoints

8.1.4.1 Quantitative Signal Intensity

For each image set, one additional blinded reader will perform quantitative measurements on unenhanced and contrast-enhanced (5 min pi, 10 min pi, and 15 min pi) images of both image sets for each study participant. The following quantitative parameters will be calculated (for further details see Section 9.4.1.3):

- Percentage of lesion enhancement
- CNR
- SNR.

In addition, an algorithm-based evaluation of weighted mean contrast enhancement may also be conducted centrally using dedicated software.

8.1.4.2 Efficacy Evaluation at 10 and 15 min Post Injection

Efficacy evaluation as described in Sections 8.1.3 and 8.1.4 (lesions visualization parameters, number of lesions and quantitative SI) will additionally be performed for enhanced images 10 and 15 min pi.

8.1.4.3 Number of Enhanced Lesions

The 3 blinded readers will record the total number of enhanced lesions for each enhanced (5 min pi) MR image set separately (no matched pairs approach). The upper limit of lesions to be counted is 20.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

The complete physical examination (by means of inspection, palpation, auscultation) will be performed by a physician, or by another qualified healthcare professional under the responsibility of the investigator or physician designee, and cover at least the organs of the cardiovascular, respiratory and abdominal systems. Orientating tests of neurological function will be included.

The short physical check will be done by a qualified healthcare professional by observation and asking the participant about his/her physical condition. Additionally, participants will be asked using open questions about any symptoms that they experience, i.e. AEs.

The performance of the physical examination will be documented in the eCRF. Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 10.3.1).

8.2.2 Vital Signs

The following vital signs will be assessed at the time points specified in the SoA (Section 1.3):

- BP (systolic and diastolic)
- Heart rate or pulse
- Body temperature
- Respiratory rate.

BP and heart rate or pulse will be assessed by a member of the investigator's team under the following conditions:

- Position: Supine (small pillow under head allowed), resting period of at least 5 min in a quiet setting without distractions (e.g. television, cell phones).
- Measuring site: cuff to be placed on the right/left upper arm (if possible, the same arm will be used for all measurements in one participant); cuff location will be documented. BP will not be measured at the arm used for injection of the study intervention.
- Method: oscillometric measurement of systolic and diastolic BP by automatic measurement device.

Body temperature will be measured by a member of the investigator's team with an appropriate thermometer. The location of temperature measurement will be documented in the eCRF.

8.2.3 Electrocardiogram

Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) by a member of the investigator's team under the following conditions:

- Position: supine (small pillow under head allowed) for at least 5 min
- Device: computerized ECG device, representing paper velocity of 25 mm or 50 mm per second as preferred by the site, same velocity for all ECGs
- Automatic calculation of the following parameters: Heart rate (HR), PR interval (PR), QRS duration, QT interval uncorrected (QT) and corrected for HR (QTc).
- Safety evaluation of all ECG recordings by a site physician, in a timely manner during the timeframe of the visit, providing diagnosis including an overall assessment of the findings and the overall clinical relevance (normal, abnormal clinically insignificant or abnormal clinically significant).
- All ECGs recorded during the study at one site will be evaluated by a cardiologist from the institutions, including measurements of intervals and a diagnosis. Only these ECG measurements will be used for the statistical data evaluation.

8.2.4 Pulse Oximetry

In both study periods, non-invasive monitoring of pulse oximetry will be performed during the MRI phase. The continuous assessment will be done while the participant is in the MR scanner. Results of the pulse oximetry monitoring will not be recorded within the eCRF unless the results qualify for an AE.

8.2.5 Short Mental Status Check

A short mental status check will be performed, which is an interview of the participants to do a basic assessment of orientation, memory, and cognitive function, for time points see SoA (Section 1.3).

8.2.6 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected by a member of the investigator's team. Detailed information about the collection, processing, storage and shipment of laboratory samples is provided in the laboratory manual.
- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- Additional safety assessments may be conducted at the discretion of the investigator. These may be laboratory examinations at additional time points or additional laboratory parameters.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 h after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the eCRF.
- In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study. AESIs have to be followed up regardless of causality or relationship to study intervention (see Section 8.3.6).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from signing of the ICF until follow-up at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after signing the ICF will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section, if they:

- Are surgical procedures that were planned prior to the start of the study by any physician treating the participant.

- Started before signing the ICF and for which no symptoms or treatments are present until signing of ICF (e.g. seasonal allergy without acute complaints).
- Started before signing of ICF and for which symptoms or treatment are present after signing ICF at an unchanged intensity (e.g. allergic pollinosis).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 h, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will

review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 24 h after the second study MRI during Period 2. Any outcome of the mother and the child at delivery should be reported.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered as SAEs.
- The child's health should be followed up until 6 to 8 weeks after birth.

8.3.6 Adverse Event of Special Safety Interest

Any AESI is to be reported within 24 h of the investigator's awareness, independently from seriousness and causality assessments.

For the purpose of this study, the following AEs are defined as AESI:

- Reactions indicating hypersensitivity, e.g. bronchial asthma, rhinosinusitis, anaphylaxis, urticarial, and any type of skin reactions including late cutaneous and organ-specific reactions.
- All AEs which are "severe" in intensity.

Hypersensitivity/anaphylactoid reactions have been reported to occur rarely for all GBCAs, as discussed in Section 2.3. The definition of hypersensitivity/anaphylactoid reactions as AESI is intended as a precaution, to assure that the sponsor is informed within short timelines about their occurrence and to allow thorough investigation of all circumstances, e.g. concomitant medications or environmental factors.

SAEs may represent a stopping criterion for the study (Section 7.1) and, therefore, need to be followed closely.

8.3.7 Expected Adverse Events

For this study, the applicable reference document is the current version 2.0 of the IB for BAY 1747846 and the SmPC of gadobutrol (available at (https://www.medicines.org.uk/emc/product/2876/smpc). If relevant new safety information for BAY 1747846 is identified, the information will be integrated into an update of the IB and distributed to all participating study centers.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

Expected Conduct-related Adverse Events

The frequent blood sampling (by single vein puncture and/or indwelling cannula) may be accompanied by mild pain, hematoma and, in rare cases, inflammation of the vessel wall or injury of a nerve. Awareness should be raised to the possibility of a vasovagal attack or syncope (marked by pallor, nausea, sweating, bradycardia, decrease in arterial BP, which, when below critical level, results in dizziness and/or loss of consciousness) during the sampling procedure.

The use of adhesive electrodes (ECG leads) and/or adhesive dressings may be accompanied by mild and transient reddening and/or itching of the skin.

8.3.8 Reporting of Medical Device Failures (Japan Only)

Medical device failure is defined as a medical device event which is related to an SAE or could cause health damage to participants or healthcare professionals in a clinical study. The investigator must report immediately all non-approved medical device failures. For this reporting, the forms provided are to be used and sent to the designated recipient.

8.4 Treatment of Overdose

For this study, any dose of BAY 1747846 greater than 0.2 mmol Gd/kg bw (corresponding to the highest dose applied in the FiH Study 19324) and any dose of gadobutrol greater than 0.3 mmol Gd/kg bw within a 24-h time period will be considered an overdose. This dose is below the currently approved maximum dose for GBCAs. It is assumed that overdosing with the study intervention is highly unlikely. No signs of intoxication from an overdose of gadobutrol have so far been reported during clinical use (see local product label of gadobutrol). GBCAs like BAY 1747846 and gadobutrol are quickly eliminated via glomerular filtration, which is not-dose depended. Patients with impaired renal function will be excluded from the study.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities (cardiovascular monitoring [including ECG] and control of renal function recommended as a measure of precaution) until BAY 1747846 or gadobutrol can no longer be detected systemically (at least 7 days).
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose in the eCRF.

8.5 Pharmacokinetics

8.5.1 Drug Measurements

In total, 5 blood samples will be collected per participant per period for measurement of Gd in plasma at the time points specified in the SoA (Section 1.3). Instructions for the collection

and handling of biological samples will be provided by the sponsor in the laboratory manual. The actual date and time (24-h clock time) of each sample will be recorded in the eCRF.

Plasma concentrations of Gd will be determined using a validated inductively coupled plasma mass spectrometry method. Calibration samples and QC samples will be analyzed concurrently with study samples. The results of calibration and QC samples will be reported in the Bioanalytical Report, which will be included in the Clinical Study Report for this study.

Whenever possible, all efforts should be made to adhere to the sampling time windows in the SoA as it is important to have these data thoroughly and accurately documented in the eCRF. Sampling times outside the suggested time windows will be listed as "other protocol deviations" only.

8.5.2 Population Pharmacokinetic Evaluation

Per period, a baseline blood sample will be taken prior to and 4 blood samples will be taken after administration of BAY 1747846 or gadobutrol and after the imaging MRI scans are complete in all participants. Each blood sample will be drawn during a pre-defined time-window (20 min – 1 h, 2 – 4 h, 6 – 8 h after study intervention administration) or at 24 ±4 h after study intervention administration. The first time window starts after the MRI acquisition is completed. The 3 time windows and the late time point on the following day were chosen based on the well-established PK profile of GBCAs and the determined similarity of the PK profile of BAY 1747846 in the FiH Study 19324.

The 3 time windows on the dosing day will be subdivided into 3 further sub-windows (see Table 8-2). In order to achieve an approximately equal distribution of blood samples over the whole time window, the time points (sub-windows) at which the samples are taken will be randomized. This means that the sampling time point for each participant will be allocated to a sub-window. The PK sample scheduled for the next day (24 ± 4 h) can be taken together with the safety blood sample.

The PK calculation will be based on the actual sampling and dosing times. Therefore, it is of importance to have this data thoroughly documented in the eCRF. Deviations from the specified time points will be documented and taken into account when calculating the PK parameters. Those deviations do not qualify as protocol violations.

Randomization of the sub-windows will be performed for each participant on the basis of a computer-generated randomization list. Each study site will be provided with a randomization list for a balanced participant assignment to all sub-windows per time point.

Table 8-2: Sampling schedule for sparse PK sampling

Time window/time frame for blood sampling	Sampling times points as defined by randomization
Immediately pre-injection	Randomization not applicable
20 min – 1 h	20 min to <30 min 30 min to <45 min 45 min to 1 h
2 h – 4 h	2 h to <2 h 40 min 2 h 40 min to <3 h 20 min 3 h 20 min to 4 h
6 h – 8 h	6 h to <6 h 40 min 6 h 40 min to <7 h 20 min 7 h 20 min to 8 h
24 ± 4 h	Randomization not applicable

Gd plasma concentration data for BAY 1747846 collected in the present study will be evaluated using non-linear mixed effects models together with data collected from other clinical studies investigating BAY 1747846. Mixed effects models, or population-type PK models, describe the relationship between dose, time and variables, such as drug plasma concentrations. The population PK model to be developed based on PK data from the FiH study data will be applied and adjusted, if appropriate. PK of BAY 1747846 will be compared to gadobutrol.

The results of this evaluation may be presented in a separate Modelling and Simulation Evaluation Report.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

Not applicable.

8.8 Biomarkers

Not applicable.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

8.10 Population Characteristics

8.10.1 Demographics

For demographic assessment the following parameters will be recorded: year of birth/age, sex, race/ethnicity, weight and height.

Body weight and height, body mass index

Body weight will be measured by a member of the investigator's team under the following conditions:

- Light clothing without shoes after having emptied the bladder.
- Electronic physician (column) scale with digital display, measurement units 0.1 kg.

The participant's height will be measured (without shoes). The body mass index (BMI) will be calculated in RAVE, see Section 10.1.7.

8.10.2 Medical and Surgical History

Medical and surgical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Not pertaining to the study indication,
- Starting before signing of the ICF,
- Considered relevant for the participant's study eligibility.

Detailed instructions on the differentiation between medical history and AEs can be found in Section 10.3.1.

9. Statistical Considerations

9.1 Statistical Hypotheses

The main objective of this study is to identify a BAY 1747846 dose similar to the comparator gadobutrol in diagnostic preference. Therefore, only point estimators and CIs will be considered and no formal hypothesis testing will be performed to compare differences between treatments or between individual doses.

9.2 Sample Size Determination

The justification of sample size was based on the proportion of participants for whom "No preference", "Prefer BAY 1747846" and "Prefer gadobutrol" is expressed for each cohort along with a corresponding two-sided 95% CI.

Number of Participants

For each BAY 1747846 dose cohort, approximately 60 participants will be enrolled. Based on the experience from previous studies, it is expected that up to 18% of the participants will discontinue prematurely and thus have images with only one of the two study interventions available. Therefore, participants will be enrolled on an ongoing basis until 50 participants have completed the MRIs in both study periods to ensure 50 evaluable participants per cohort for the analysis.

A maximum of two dose adjustments will be used, so that a maximum of approximately 180 participants (3 cohorts) will be enrolled into the study.

Dose Finding Algorithm

The decision criteria for dose adjustment will consider both the proportion of participants for whom no preference is selected, and the difference between the proportion preferring gadobutrol and preferring BAY 1747846.The following algorithm for dose adjustment will be used:

- If the CIs for the choices “Prefer gadobutrol” and “Prefer BAY 1747846” are not overlapping and the proportion expressing “Prefer gadobutrol” is greater than the proportion “Prefer BAY 1747846”, then the dose needs to be adjusted upward and an additional cohort with a higher dose will be enrolled.
- In case, the choices “Prefer gadobutrol” and “Prefer BAY 1747846” are equally balanced in favor of both compounds, dose adjustment will not be needed.
- If the CIs for the choices “Prefer gadobutrol” and “Prefer BAY 1747846” are not overlapping and the proportion expressing “Prefer BAY 1747846” is greater than the proportion “Prefer gadobutrol”, then the dose needs to be adjusted downward and an additional cohort with a lower dose will be enrolled.

Simulation

The reads of the blinded readers will be treated as independent confirmations of the results. For each cohort, 3 readers will be used as independent replications of the result, therefore the number of participants is 50 even though there will be 150 reads available. Having 2 or 3 readers giving the same result lends confidence to the conclusion. If 2 or 3 readers reach the same conclusion on the recommended action (no dose adjustment needed, dose increase needed, dose decrease needed), then that will be the recommended action taken.

If all 3 readers reach different conclusions, then no dose adjustment is needed.

If 50% of choices are no preference, with 50 evaluable participants the 95% CI would be (36%, 64%). Based on simulations and assuming that the true percentage of no preference responses is 50%, and that there are no differences between the proportions preferring BAY 1747846 and comparator, with 50 patients the above decision algorithm would conclude no dose adjustment greater than 95% of the time. This is equivalent to saying that with 50 patients and these assumptions there is greater than 95% power to conclude that no dose adjustment is needed. If we assume that there is a 30% difference in proportions between preferring BAY 1747846 and comparator, there is 77% power to conclude that a dose adjustment is needed.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 9-1: Analysis sets

Population	Description
Enrolled	All participants who sign the ICF.
Full analysis set (FAS)	All participants who have complete MR image datasets that qualify for blinded read.
Safety analysis set (SAF)	All participants who receive any dose of study intervention.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

For the primary objective

- The estimand is then the proportion of participants for whom no preference is chosen for the image preference in the overall diagnostic preference based on a randomized paired blinded read using a 5-point scale (see Section 8.1.2) at 5 min pi in all participants who have 2 image sets (gadobutrol and BAY 1747846) available. No imputations or adjustments will be made for those participants who have no images or only one image set as these participants will be excluded from the analysis.
- The estimand is then the difference between the proportion of participants for whom the BAY 1747846 image sets are preferred and the proportion of participants for whom the gadobutrol image sets are preferred in the overall diagnostic preference based on a randomized paired blinded read using a 5-point scale (see Section 8.1.2) at 5 min pi in all participants who have 2 image sets available. No imputations or adjustments will be made for those participants who have no images or only one image as these participants will be excluded from the analysis.

For the secondary objectives

- The estimand is then the sum of lesion visualization parameters between both image sets (BAY 1747846 and gadobutrol) in all participants who have 2 image sets available. No imputations or adjustments will be made for those participants who have no images or only one image set as these participants will be excluded from the analysis.
- The estimand is then the mean of lesion visualization parameters between both image sets (pre-contrast and combined pre- and post-contrast) in all participants who have 2 image sets available. No imputations or adjustments will be made for those participants who have no images or only one image set as these participants will be excluded from the analysis.

For objectives and endpoints see also Section 3.

For the analysis of preference, a participant needs to have two image sets (gadobutrol and BAY 1747846) available. No imputations for missing data will be performed. A low number of missing values will be expected due to the short duration for each participant and the expected high adherence to the study protocol. Imputations might introduce bias due to the small sample size and the study design (for drop-outs, the experimental intervention will always be missing).

9.4.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
• Overall diagnostic preference based on a randomized paired blinded read using a 5-point scale (greatly prefer BAY 1747846, prefer BAY 1747846, no preference, prefer gadobutrol, greatly prefer gadobutrol) at 5 min pi	• For overall diagnostic preference 95% two-sided CIs for the proportion of participants for whom “No preference” was expressed will be calculated. • Treatment difference will be tested with McNemar’s test.
Secondary	
• Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on post-contrast images at 5 min pi	• For the sum of lesion visualization parameters, 95% two-sided CIs for the mean difference between BAY 1747846 and gadobutrol will be calculated.
• Lesion visualization parameters (border delineation, contrast enhancement, internal morphology) on pre-contrast and combined pre- and post-contrast (5 min pi) images	• For lesion visualization parameters, 95% two-sided CIs for the mean difference between pre-contrast and combined pre- and post-contrast will be calculated.
• Number of lesions on pre-contrast and combined pre- and post-contrast (5 min pi) images	• The number of lesions will be analyzed descriptively.
Other pre-specified	
• Quantitative parameters: SI, contrast to noise ratio (CNR), signal to noise ratio (SNR) • Lesion visualization parameters at 15 min pi • Lesion visualization parameters at 10 min pi • Number of enhanced lesions on post-contrast images	• The percentage of enhancement of the lesion post administration of study intervention injection in comparison to baseline (i.e. prior to administration of study intervention) will be calculated. • Sum of lesion visualization parameters at 15 min pi will be analyzed descriptively. • Sum of lesion visualization parameters at 10 min pi will be analyzed descriptively. • The number of enhanced lesions will be analyzed descriptively.

9.4.1.1 Primary Efficacy Analysis – Overall Diagnostic Preference at 5 min post injection

The blinded readers will evaluate the relative image quality of the BAY 1747846-enhanced $T1_w$ MR images and the gadobutrol-enhanced $T1_w$ MR images. 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 BAY 1747846 and gadobutrol 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 = greatly prefer image R
2 = prefer image R
3 = no preference
4 = prefer image L
5 = greatly prefer image L.

As part of the randomization and blinding process, R and L will represent either the BAY 1747846 or gadobutrol image. After the data is unblinded, the above codes will be translated into the following scale:

1 = greatly prefer BAY 1747846,
2 = prefer BAY 1747846,
3 = no preference
4 = prefer gadobutrol,
5 = greatly prefer gadobutrol.

For each cohort, the proportion of participants for whom "No preference", "Prefer BAY 1747846" and "Prefer gadobutrol" is expressed, will be calculated along with a corresponding two-sided 95% CI. The three categories are collapsed from the 5-point preference scale.

Additionally, the distribution of the choices other than "No preference" will be examined descriptively using frequency tables and histograms.

The null and alternative hypotheses for an exploratory analysis of a treatment difference are as follows:

$$H_0: \pi_{\text{prefer BAY 1747846}} = \pi_{\text{prefer gadobutrol}}$$

$$vs \quad H_1: \pi_{\text{prefer BAY 1747846}} \neq \pi_{\text{prefer gadobutrol}},$$

where $\pi_{\text{prefer BAY 1747846}}$ is the proportion of participants for whom the BAY 1747846-enhanced image was preferred and $\pi_{\text{prefer gadobutrol}}$ is the proportion of participants for whom the gadobutrol-enhanced image was preferred. For this exploratory analysis, a McNemar's test will be used.

A table displaying frequencies and percentages of the results of the 5-point scale will also be provided.

9.4.1.2 Secondary Efficacy Analysis

For the secondary endpoints, there will be multiple values for each subject (ratings for multiple lesions). The average of these ratings will be used for the 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. A more detailed description will be provided in the SAP.

9.4.1.2.1 Lesion Visualization Parameters at 5 min Post Injection on Post-Contrast Images

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

1. Contrast enhancement (measured on an ordinal 4-point scale)
2. Border delineation (measured on an ordinal 4-point scale)
3. Internal morphology (measured on an ordinal 3-point scale).

In order to reduce multiplicity, the 3 variables will be combined by adding them up for each participant and each blinded reader, leading to only one variable on an ordinal 11-point scale. Average reader will be used in addition to the 3 individual readers.

The analysis is based on the data from the blinded readers' evaluation of the 3 visualization parameters, which are evaluated in the MR image sets.

For the combined visualization parameter, the non-inferiority of BAY 1747846 versus gadobutrol will also be evaluated using CIs based on the t-distribution. A non-inferiority margin of 1 will be used.

The non-inferiority margin was determined by the 95%-95% method described in the FDA Guidance "Non-Inferiority Clinical Trials to Establish Effectiveness" and is based on the past performance of the comparator in the Gadavist Study 310123. Data from this study were re-analyzed using the combined approach described above. After combining the visualization parameters of Study 310123 and calculating the two-sided 95% CI for the mean difference gadobutrol – unenhanced, the observed mean difference was 2.49 and the corresponding 95% CI [2.337; 2.651]. As described in the FDA Guidance, the lower bound of the 95% CI was selected as the known effect of gadobutrol to the unenhanced imaging $M_1 = 2.337$. To retain at least half of the effect of the original treatment, the non-inferiority margin is set to $M_2 = 0.5 * M_1 = 1.16785$. Due to the fact that in Study 310123 the averaged reader was used for evaluation, which helped lowering the variability, the non-inferiority margin was even further lowered to 1.

This means that a 95% two-sided CI for the mean difference BAY 1747846 score – gadobutrol score must exclude the value -1 for non-inferiority to be achieved. A one-sided test conducted at the 0.025 level of significance would be a statistically equivalent procedure. The null and alternative hypotheses for non-inferiority are:

$$H_0: \mu_{\text{BAY 1747846}} - \mu_{\text{gadobutrol}} < -1 \text{ vs } H_1: \mu_{\text{BAY 1747846}} - \mu_{\text{gadobutrol}} \geq -1,$$

where $\mu_{BAY\ 1747846}$ and $\mu_{gadobutrol}$ are the mean of the score evaluated by blinded readers after administration of BAY 1747846 and gadobutrol, respectively.

The analyses of the visualization efficacy variables will be performed on the data from each blinded reader, as well as the data obtained by averaging across the 3 blinded readers, producing one mean value per participant.

Inter-reader agreement for each of the 3 visualization variables will be assessed using the intra-class correlation coefficient. Separate coefficients will be generated by imaging modality.

9.4.1.2.2 Lesion Visualization Parameters on Pre-Contrast and Combined Pre- and Post-Contrast (5 min pi) Images

The analysis is based on the data from the blinded readers' evaluation of the 3 visualization parameters, which are evaluated in the MRI sets.

A comparison of the pre-contrast and combined pre- and post-contrast images will be performed for each of the 3 visualization parameters. Summary statistics for absolute values and difference of the pre-contrast and combined pre- and post-contrast will be presented for each Blinded Reader and the Average Reader along with the 95% two-sided CIs for the difference of the pre-contrast and combined pre- and post-contrast.

9.4.1.2.3 Number of Lesions on Pre-Contrast and Combined Pre- and Post-Contrast (5 min pi) Images

A table displaying frequencies and percentages of different numbers of lesions detected by pre- and combined pre- and post-contrast will be generated. A CI for the difference in number of lesions detected in the two image sets will be constructed.

9.4.1.3 Other Efficacy Analysis

9.4.1.3.1 Efficacy Evaluation at 10 and 15 min Post Injection

Summary statistics and frequency table will additionally be provided for contrast-enhanced images at 10 and 15 min pi.

9.4.1.3.2 Number of Enhanced Lesions on Post-Contrast Images at 5 min Post Injection

A table displaying frequencies and percentages of different numbers of contrast-enhanced lesions detected by BAY 1747846 and gadobutrol will be generated. A CI for the difference in enhanced lesions detected by the 2 study interventions will be constructed.

9.4.1.3.3 Signal Intensity Measurements

Quantitative measurements will be done in order to evaluate the percentage of lesion enhancement in the $T1_w$ sequence after injection of BAY 1747846 or gadobutrol compared to the unenhanced $T1_w$ sequence. Furthermore, the CNR of the lesions will be determined.

One additional independent blinded reader will perform SI measurements on the image sets. The blinded reader will have knowledge if the $T1_w$ sequence is pre-injection or post-injection, but will be blinded to knowledge of contrast agent (i.e. BAY 1747846 or gadobutrol). The images will be evaluated as follows:

- Contrast-enhanced $T1_w$ MRI: the image giving the best visualization of the lesion will be chosen (either BAY 1747846-enhanced or gadobutrol-enhanced sequence). The region of interest (ROI) will be placed in that area of the lesion that shows best enhancement, avoiding necrotic regions. A second ROI will be drawn in normal brain tissue on the contralateral white matter or in normal spine tissue. A third ROI will be positioned in an area outside the brain or spine to determine the background.
- All ROIs of the chosen contrast-enhanced sequence will be copied and pasted into the corresponding images of the other contrast-enhanced sequence and the unenhanced sequence in order to assure same location and size of ROIs in all $T1_w$ images (BAY 1747846-enhanced, gadobutrol-enhanced, and unenhanced).

The percentage of enhancement of the lesion will be based on SI measurements obtained from the combined results of unenhanced MRI – BAY 1747846 and unenhanced MRI – gadobutrol-enhanced MRI as follows:

$$\frac{SI_{L,post} - SI_{L,pre}}{SI_{L,pre}} \times 100\%,$$

where $SI_{L,post}$ is the SI of the contrast-enhanced lesion and $SI_{L,pre}$ is the SI of the unenhanced lesion. For heterogeneous lesions, multiple ROIs can be placed over different areas, and the region that shows the maximum relative enhancement will be used for analysis.

SNR and CNR will be calculated based on SI measurements obtained as follows:

$$SNR = \frac{SI_{N,post}}{SD_{noise}}$$

and

$$CNR = \frac{SI_{L,post} - SI_{N,post}}{SD_{noise}},$$

where $SI_{L,post}$ is the SI of the lesion on the contrast-enhanced image, $SI_{N,post}$ is post injection SI of normal tissue of the brain or spine, and SD_{noise} is the standard deviation of the noise (background).

The ROI size of the same lesion will be identical in all measurements within a single participant. SI measurements will be summarized by MRI modality using descriptive statistics and CIs.

9.4.2 Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	
• Not applicable	• Not applicable
Secondary	
• Not applicable	• Not applicable
Other pre-specified	
• Incidence and severity of TEAEs and other parameters • Determine plasma concentrations of Gd within 3 time windows on Day 1 and after 24 ± 4 h following administration of BAY 1747846 and gadobutrol	• The number of participants with TEAEs will be displayed in a frequency table. Descriptive results will be displayed for vital signs, ECG and safety laboratory. • Individual concentration versus time curves will be provided.

All safety analyses will be performed on the SAF population, unless otherwise stated.

9.4.2.1 Adverse Events

Individual listings of AEs will be provided.

TEAEs

AEs are considered to be treatment-emergent if they have started or worsened after first application of study intervention GBCA injection up to 24 h ± 4 h follow-up time point (i.e. per period).

The incidence of TEAEs and study intervention-related TEAEs, respectively, will be summarized by treatment using System Organ Class (SOC) and Preferred Terms (PTs) according to the current Medical Dictionary for Regulatory Activities (MedDRA) version.

SAEs and Deaths

For SAE outcomes, AEs leading to discontinuation and deaths, listings of participants will be provided by treatment sequence, participant and/or AE.

9.4.2.2 Other Safety Examinations

Quantitative data (hematology, blood chemistry, vital signs) will be described by the following summary statistics: arithmetic mean, standard deviation, minimum, median and maximum for quantitative data. These summary statistics will be presented by treatment for the original data and for the difference to the respective baseline for quantitative data (i.e. pre-dose measurements, performed prior to the first administration of the study intervention per treatment period). Frequency tables will be provided for qualitative data. Laboratory data outside the reference range will be listed and flagged with ‘L’ for low and ‘H’ for high. Additional tables with all abnormal (out-of-range) values will be presented.

Graphical displays of individual data and mean values with standard deviations will be included.

Data from the standard ECGs will be reported in a descriptive way.

Pulse oximetry during MRI will only be done for monitoring purposes without documenting values within the eCRF. Only time interval and occurrence of AEs will be documented from these measurements.

9.4.2.3 Demographic and Other Baseline Characteristics Analyses

Participant Validity and Disposition

Study sample size will be summarized by treatment sequence and total. Participant validity with reason for exclusion from analysis sets, participant disposition, end of study medication, and important deviations/validity findings will be summarized by total using frequency tables over appropriate analysis sets like FAS or 'All enrolled participants'.

Demographics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented for all patients in the analysis population being summarized. Frequency tables for qualitative data will be provided. If the FAS population differs from the SAF population, summary statistics and frequency tables for FAS will be provided as well.

Medical/Surgical History

The number of participants with medical history findings will be summarized by classified data using frequency tables. The classification will be done according to MedDRA using SOC, high level terms and PTs. The most recent MedDRA version will be used.

Prior and Concomitant Medication

The number of participants that used prior or concomitant medication will be analyzed using frequency tables based on classified data. The classification will be done according to the World Health Organization Drug Dictionary (WHO-DD).

9.4.3 Analyses of Gd Plasma Concentration

Individual Gd plasma concentrations will be listed per study intervention (i.e. BAY 1747846 and gadobutrol). Individual concentration versus time curves of Gd plasma will be provided separately for each treatment, for each participant and for all participants.

9.5 Interim Analyses

A non-binding interim analysis (IA) may be perfomed for this study to facilitate informed planning of the next phases of development.

The IA can be triggered at any time when at least 25 participants have been enrolled in a dose cohort and have completed both MRI periods (i.e., at least 50% completion of the dose-cohort).

Enrollment in the dose-cohort will continue while the IA is ongoing. Independent of the outcome from the IA, the cohort will be completed.

The Statistical Analysis Plan (SAP) will describe the planned interim analyses in detail.

In brief, the IA will evaluate the primary efficacy endpoint for the selected dose-cohort.

In case a trend of "no-preference" between BAY 1747846 and gadobutrol (or a trend of "preference of BAY 174846") is observed, further efficacy analyses will be performed for the secondary endpoint and the number of enhanced lesions. In addition, safety analysis will be conducted including the incidence and severity of TEAEs along with other safety parameters and Gd plasma concentrations.

If no trend is observed or if deemed inconclusive, no further analysis will be performed until the primary completion of the selected dose-cohort.

Since the assessment of the final dose finding algorithm is not based on a formal hypothesis test, the type I error (i.e., the alpha level) will not be adjusted for the IA.

This is a single-blind study and the IA will not affect the blinding design as only participants are blinded and will remain blinded to the sequence of treatment administration. The central independent readers evaluating the primary and secondary endpoints will remain blinded during the IA and the results.

Data will be processed and analyzed by the sponsor and there will not be an independent data monitoring committee. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection while maintaining sufficient blinding in the study.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

- Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.
- Participants who are re-screened are required to sign a new ICF.
- If the baseline activities are to be performed on the same day as the ICF is signed, the time needs to be documented in addition to the signature date.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical QA auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Not applicable.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in participants are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (e.g. MRI data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet-based validated electronic data capture (EDC) software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.
- All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

- All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.
- The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all participants enrolled in this study.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the investigator site file.

10.1.9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- Blood and urine sampling for laboratory analysis will be taken as outlined in the SoA (see Section 1.3).
- The tests detailed in Table 10-1 will be performed by local laboratories or the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Urine pregnancy testing will be performed before each administration of study intervention to evaluate eligibility of female participants (see Section 5.2 criterion 14).

Table 10-1: Parameters of laboratory analyses

Parameters (by category)	Sample destination
Blood / Plasma / Serum	
Hematology: Leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes	Local laboratory
Serum chemistry: Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, lactate dehydrogenase, creatinine, urea, creatine kinase, chloride, potassium, sodium, calcium, phosphate, glucose, total protein, albumin, high-sensitivity C-reactive protein	Local laboratory
Creatinine	Central laboratory
Plasma concentration: BAY 1747846	Central laboratory
Urine	
Urinalysis – dipstick (spot urine): pH value, urobilinogen, erythrocytes/hemoglobin, leukocytes, protein, ketone, bilirubin, nitrite, glucose	Local laboratory
Sediment (spot urine): Only in case of abnormal urinalysis results for protein, leukocytes, erythrocytes/ hemoglobin, or nitrite	Local laboratory
Pregnancy test (spot urine) before administration of study intervention	To be performed at study site

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, after providing written informed consent, whether or not considered related to the study intervention.
  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
    - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Important factors to be considered in assessing the relationship of the AE to study intervention include:

- The temporal sequence from study intervention administration: The event should occur after the study intervention is given. The length of time from study intervention exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- Concomitant medication or treatment: The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The assessment is not possible.

Causal relationship to protocol-required procedures

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a ‘reasonable causal relationship’ to protocol-required procedure(s).

- Possible answers are “yes” or “no”.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any *post mortem* findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 h of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the EDC tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 h.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in the investigators site file.

SAE Reporting to the sponsor via Paper CRF

- Facsimile transmission of the SAE paper CRF or provision of related PDF scans via email is the preferred method to transmit this information to the sponsor.
- In rare circumstances and in the absence of facsimile and PDF/email equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigators site file.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

In addition, male participants with partners of childbearing potential should use a condom from screening till end of study participation.

Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who received study intervention.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 h of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 h of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed ICF from both parents, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Abbreviations

2/3D	2/3 dimensional
AE	adverse event
AESI	adverse event of special safety interest
AUC	area under the concentration versus time curve from zero to infinity after single (first) dose
AUC_{norm}	AUC normalized for dose and body weight
BMI	body mass index
BP	blood pressure
bw	body weight
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	total body clearance of drug
CL/bw	total body clearance of drug normalized by body weight
C_{max}	maximum observed drug concentration in measured matrix after single dose administration

CNR	contrast to noise ratio
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CV	coefficient of variation
d	day(s)
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FiH	first-in-human
FLAIR	Fluid Attenuated Inversion Recovery
GBCA	gadolinium-based contrast agent
GCIS	General Clinical Imaging Services
GCP	Good Clinical Practice
Gd	gadolinium
GFR	glomerular filtration rate
GRE	gradient recalled echo
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IA	Interim analysis
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
IMP	investigational medicinal product
IR	inversion recovery
IRB	Institutional Review Boards
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MR	magnetic resonance

MRI	magnetic resonance imaging
NEX	number of excitations
NIMP	non-investigational medicinal product
NSA	number of acquisitions
NSF	Nephrogenic Systemic Fibrosis
PDF	Portable Document Format
pH	*pondus hydrogenii* (negative log of the ion concentration)
pi	post injection
PK	pharmacokinetic(s)
PR	PR interval
PT	preferred term
QA	quality assurance
QC	quality control
QRS	QRS interval in ECG
QT	QT interval in ECG, uncorrected
QTc	QT corrected by heart rate
ROI	region of interest
RSE	relative signal enhancement
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SE	spin echo
SI	signal intensity
SmPC	Summary of Product Characteristics
SNR	signal to noise ratio
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
$T1_W$	T1-weighted
TE	echo time
TEAE	treatment-emergent adverse event
TI	inversion time
TR	repetition time
V_{ss}	volume of distribution at steady state
V_{ss}/bw	V_{ss} normalized by body weight

10.6 Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 3 (29 JUL 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment was primarily implemented to incorporate an interim analysis to facilitate the planning of future phases of development and upcoming end of Phase 2 meetings /scientific advisory discussions with Health Authorities. The description of changes and a brief rationale for each change are as follows:

Section # and Name	Description of Change	Brief Rationale
Title Page	Update of medically responsible person for the study.	In order to maintain consistency with the updated internal clinical protocol template. The relevant contact name and role (PPD) for all relevant medically related queries and safety reporting requirements is maintained.
Title Page Document History Table Header throughout	The version number has been added to title page, Document History Table has been incorporated as an independent section, and the document header has been modified throughout to remove version number and include the version date.	Updated to reflect current internal processes and protocol template conventions.
1.3 Schedule of Activities **5.1** Inclusion Criteria	The SoA and inclusion criterion #6 were updated to further clarify that while baseline eGFR value ≥60 mL/min/1.73m^2 is required prior to administration of study intervention, the baseline eGFR assessment for period 1 can be derived from a serum creatinine result obtained within 4 weeks prior to the first MRI. As serum creatinine is an included parameter for safety laboratory assessments, the safety blood sample collected at baseline (within 48 hours prior to administration of study intervention), can also be utilized for determination of eGFR for either corresponding period.	Clarification of procedures pertaining to baseline eGFR assessments in the SoA and inclusion criterion #6.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criterion #12 was updated to include consideration of the half-life of any previous investigational drug and clarify eligibility of participants that would be in the follow-up period of another trial while not receiving investigational drug. Exclusion criterion #13 was updated to clarify that contraindications pertaining to the administration of gadobutrol will be interpreted based on the local product label.	Exclusion criterion #12 was updated in order to provide additional flexibility with prior clinical trial participation and with respect to facilitating recruitment of participants who are in the follow-up period of concurrent studies but are not receiving investigational drug. The local product label may vary depending on the location of the study site.
6.1 Study Interventions Administered	Table 6-1 was modified to reflect the addition of Bulgaria as a study country.	Study sites are currently being established in an additional country (Bulgaria), thus Bulgaria has been added to the protocol.
8.1.4.3 Number of Enhanced Lesions	Revised text to specify that the 3 blinded readers will record the total number of enhanced lesions for each enhanced (5 min pi) MR image set separately (no matched pairs approach).	Correction of previous error indicating 4 to 5 min pi for recorded number of enhanced lesions per MR image set.
8.2.6 Clinical Safety Laboratory Assessments **8.5.1** Drug Measurements	Specification of laboratory manual as primary guidance document for study samples. References to the sample handling sheets were removed.	Information about the collection, processing, storage and shipment of laboratory samples is provided in the laboratory manual.
9.4.2.2 Other Safety Examinations	The text pertaining to standard ECG data was revised to remove the requirement that they only be listed.	The requirement to only list standard ECG data was removed to provide greater flexibility with respect to the descriptive statistical output provided.
9.5 Interim Analyses **10.5** Abbreviations	Addition of an interim analysis. Abbreviations for interim analysis (IA) and Statistical Analysis Plan (SAP) were added accordingly.	An interim analysis of the dose investigated, as well as some selected efficacy and safety data will facilitate the planning of future phases of development and upcoming end of Phase 2 meetings /scientific advice with Health Authorities.

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