Pharmacokinetics, Safety, and Tolerability of the Novel Tetrameric, High-Relaxivity, Macrocyclic Gadolinium-based Contrast Agent Gadoquatrane in Healthy Adults

Supplemental digital content

Contents

Chapter 1: Inclusion/exclusion criteria

Inclusion criteria *Subjects had to fulfill all of the following criteria to be included in the study:*
1. Signed informed consent prior to any study specific tests or procedures
2. Ability and willingness to understand and follow study-related instructions
3. Aged 18 to 45 years (inclusive) at screening visit
4. Body mass index (BMI) 18.5 to 30 kg/m² (inclusive)
5. Body weight 45 kg to 90 kg (inclusive)
6. Female subjects of reproductive potential had to agree to use highly effective contraception when sexually active, men had to agree to use condoms. This applied for the time period from signing of the informed consent to the end of the study period.
7. Healthy, based on medical history, physical examination, electrocardiogram (ECG), and laboratory tests
8. Confirmation of the subject's health insurance coverage prior to the first screening examination/visit
Exclusion criteria *Subjects were excluded from the study if they met any of the following criteria:*
1. Use of systemic or topically active medication or herbal remedies, prescription or non-prescription, from screening to the first drug administration. Only use of contraceptives and occasional use of paracetamol, aspirin, or ibuprofen was permissible.
2. Any severe disease within the last 4 weeks prior to the first study drug administration
3. History of orthostatic hypotension, fainting spells and blackouts
4. Any malignant tumor and history thereof
5. Any other medical condition which, at the discretion of the investigator, would have made study participation unadvisable
6. Any clinically relevant finding at the physical examination
7. Blood donation or plasmapheresis within 4 weeks prior to screening
8. Any clinically relevant deviation from reference ranges of the laboratory parameters at screening, or alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin exceeding the upper limit of normal ranges (ULN) by more than 10%, or creatinine above the ULN, or hemoglobin below 12 g/dL
9. Female subjects: pregnancy, positive pregnancy test, or lactation
10. Positive human immunodeficiency virus antibodies (HIV-1/2 Ab), hepatitis B virus surface antigen (HBsAg) or hepatitis C virus antibody (HCV-Ab) tests
11. Clinically relevant ECG findings, eg, heart rate <50 or >90 beats/min, PQ >220 msec, QTc >450 msec, QRS >120 msec, branch bundle block, any sign of coronary heart disease
12. Abnormal vital signs, eg, heart rate <50 or >90 beats/min; systolic blood pressure <100 or >140 mmHg; diastolic blood pressure <60 or >90 mmHg
13. Any known disposition for allergic, anaphylactoid, hypersensitivity or idiosyncratic reactions, eg, any history of clinical signs of hypersensitivity reaction to any agent (including, but not limited to, any allergen, food, drug, chemical, or contrast agent)
14. Family history of hypersensitivity reaction to contrast agent
15. Regular alcohol consumption equivalent to >20 g alcohol per day
16. Current smoker, or has smoked within 3 months prior to screening
17. Urine screen positive for any drug or cotinine
18. Positive alcohol breath test
19. Previous assignment to treatment or randomization during this study
20. Exclusion periods from other studies or simultaneous participation in other clinical studies
21. Subject was in custody by order of an authority or a court of law.
22. Close affiliation with the investigational site; eg, a close relative of the investigator, dependent person (eg, employee or student of the investigational site)
23. Subject was an employee of Bayer AG.
24. Participation in another trial with an investigational drug within 2 months prior to administration or during the trial
25. Criteria which, in the opinion of the investigator, precluded participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety

Chapter 2: Bioanalytical methods

All bioanalytical data presented were obtained by inductively coupled plasma mass spectrometry (ICP-MS) of total gadolinium (Gd). Analyses and method validation were conducted in compliance with the relevant US and EU guidelines (1, 2).

The plasma, urine and feces samples collected were stored at or below -20 °C and analyzed within 16 days (plasma), 224 days (urine), and 237 days (feces) after sample collection. The stability data indicated that the analyte was stable for these time periods.

The performance parameters for the bioanalytical methods used are shown in Table S2-1 (total Gd in human plasma), Table S2-2 (total Gd in human urine samples), and Table S2-3 (total Gd in human feces samples).

As the results of the metabolite profiling show no metabolic degradation of gadoquatrane (see Chapter 3), total Gd concentrations represent unchanged gadoquatrane concentrations.

Table S2-1: Performance of the ICP-MS method for the quantification of gadolinium in human plasma samples

Calibration standards	
Calibration range (LLOQ to ULOQ)	0.0318 to 47.7 µmol Gd/L
Mean inter-assay accuracy of back-calculated concentrations (except LLOQ)	-2.3% to 2.3%
Precision (except LLOQ)	≤3.8%
Accuracy at the LLOQ	-1.4%
Precision at the LLOQ	3.3%
Quality control samples	
Concentration range	0.0954 to 38.2 µmol Gd/L
Accuracy	-3.5% to 0.6%
Precision	3.6% to 7.6%

Abbreviations: ICP-MS, inductively coupled plasma mass spectrometry; LLOQ, lower limit of quantitation; ULOQ, upper limit of quantitation.

Table S2-2: Performance of the ICP-MS method for the quantification of gadolinium in human urine samples

Calibration standards	
Calibration range (LLOQ to ULOQ)	0.0636 to 47.7 µmol Gd/L
Mean inter-assay accuracy of back-calculated concentrations (except LLOQ)	-0.9% to 1.3%
Precision (except LLOQ)	≤2.9%
Accuracy at the LLOQ	0.4%
Precision at the LLOQ	2.7%
Quality control samples	
Concentration range	0.191 to 38.2 µmol Gd/L
Accuracy	-4.1% to 0.2%
Precision	5.5% to 9.4%

Abbreviations: ICP-MS, inductively coupled plasma mass spectrometry; LLOQ, lower limit of quantitation; ULOQ, upper limit of quantitation.

Table S2-3: Performance of the ICP-MS method for the quantification of gadolinium in human feces samples

Calibration standards	
Calibration range (LLOQ to ULOQ)	0.191 to 47.7 µmol Gd/kg
Mean inter-assay accuracy of back-calculated concentrations (except LLOQ)	-2.2% to 4.9%
Precision (except LLOQ)	≤1.8%
Accuracy at the LLOQ	-1.6%
Precision at the LLOQ	1.5%
Quality control samples	
Concentration range	0.572 to 38.2 µmol Gd/kg
Accuracy	-7.3% to -2.7%
Precision	3.2% to 7.0%

Abbreviations: ICP-MS, inductively coupled plasma mass spectrometry; LLOQ, lower limit of quantitation; ULOQ, upper limit of quantitation.

References

(1) European Parliament and Council. Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances: Current consolidated version: 20/04/2009. Accessed September 8, 2023. https://eur-lex.europa.eu/eli/dir/2004/10/oj

(2) U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine. Guidance for Industry: Bioanalytical Method Validation: May 2001.

Chapter 3: Metabolite profiling

All plasma and urine samples from participants in Cohorts 4, 5 and 6 treated with gadoquatrane were investigated for metabolite profiles. A chromatographic method was developed to separate gadoquatrane from free gadolinium (Gd) and from two known potential degradation products. Plasma samples were precipitated with methanol while urine samples were diluted with water. The supernatants from plasma and urine were injected onto the high-performance liquid chromatography (HPLC) column to separate possible degradation product peaks including free Gd from the parent. The HPLC system was coupled to an inductively coupled plasma-mass-spectrometry detector (ICP-MS detector) for detection and quantification of each peak containing Gd by comparison to calibration samples prepared by spiking of known reference compounds (see Table S3 - 1) to empty human plasma and urine.

Table S3 - 1: Sensitivity of the method in plasma and urine

Analyte	Limit of quantitation
Unchanged gadoquatrane	0.1 µM
Two Monomeric Gd-complexes (potential degradation products of gadoquatrane)	0.005 µM
Free gadolinium	0.004 µM [a]

[a] detection limit

To confirm the identity of unchanged gadoquatrane and potential degradation products, selected plasma and urine samples were analyzed by HPLC coupled to high-resolution mass spectrometry to determine the molecular formula based on exact mass detection as well as isotope distribution pattern.

The area-under-the concentration-time-curve (AUC) and the maximum concentration (C_{max}) of total Gd, unchanged gadoquatrane in plasma were calculated by non-compartmental analysis using the software ToxKin (Entimo).

The ratio of exposure (AUC) unchanged gadoquatrane to total Gd was determined to be approximately 1 in plasma of all participants investigated, indicating no formation of degradation products in human plasma.

Furthermore, metabolite profiling in human urine revealed predominantly unchanged gadoquatrane in urine samples from all study participants investigated. Very minor amount of gadolinium containing components were detected in urine (< 2%), which were also present and detected in in the formulation applied in this early clinical study. Based on the metabolite profiles in urine and plasma there was no degradation in vivo or release of free gadolinium.

Metabolite profiles were not investigated in feces because the amount of total Gd detected in feces was considerably less than 1% of the dose administered.

Chapter 4: Overview of the pharmacokinetics-related details of the first-in-human study of gadoquatrane and of three other phase 1 studies of gadoquatrane referenced in the present paper

	First-in-human study in mostly White men and women	**Study in Chinese men**	**Study in Japanese men**	**Dose-response study in mostly White men and women**
Study participants who received gadoquatrane [a] **(PK analysis set)**	36 healthy men and women (50% men; 94% White); aged 34 ± 5.8 years; body weight: 70 ± 9.6 kg; BMI: 23 ± 2.5 kg/m²	17 healthy Chinese men; aged 31 ± 8.0 years; body weight: 67 ± 7.9 kg; BMI: 24 ± 2.4 kg/m²	18 healthy Japanese men; aged 26 ± 5.8 years; body weight: 62 ± 9.1 kg; BMI: 22 ± 2.3 kg/m²	43 healthy men and women (51% men; 95% White); aged 40 ± 9.1 years; body weight: 74 ± 10.3 kg; BMI: 25 ± 2.3 kg/m²
Study design	Randomized, single-blind, placebo-controlled, escalating single-dose study with six consecutive dose cohorts	Randomized, single-blind, placebo-controlled, parallel-group, escalating single-dose study with two consecutive dose cohorts	Randomized, single-blind, placebo-controlled, parallel-group, escalating single-dose study with 3 consecutive dose cohorts	Randomized, single-blind, 4 x 4 cross-over with single intravenous injections of three different doses of gadoquatrane and a standard dose of gadobutrol.
Dose levels gadoquatrane [and comparator, if applicable]	0.025, 0.05, or 0.1 mmol Gd/kg bw by 5-minute iv infusion or 0.03, 0.1, or 0.2 mmol Gd/kg by iv injection (2 mL/s)	0.03 or 0.1 mmol Gd/kg bw by iv injection (2 mL/s)	0.01, 0.03, or 0.1 mmol Gd/kg bw by iv injection (2 mL/s)	0.01, 0.03, and 0.06 mmol Gd/kg bw by iv injection (1 mL/s) [and gadobutrol: 0.1 mmol Gd/kg bw by iv injection (1 mL/s)]
Blood sampling for PK analyses	Predose, 2, 5, 7[b], 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after the start of the administration	Predose, 2, 5, 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after the injection.	Predose, 2, 5, 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after the injection.	Sampling time windows: 20 min to 1 hour, 2 to 4 hours, and 6 to 8 hours after injection
Bioanalysis of PK plasma samples	Inductively coupled plasma mass spectrometry Lower limit of quantitation: 0.0318 µmol Gd/L			
PK-relevant safety findings	None.	None (internal data, Bayer)	None (internal data, Bayer)	None (internal data, Bayer).
Study center	CRS Clinical Research Services Berlin GmbH, Berlin, Germany	Beijing Hospital Clinical Research Center in China	SOUSEIKAI Fukuoka Mirai Hospital, Fukuoka, Japan	CRS Clinical Research Services Berlin GmbH, Berlin, Germany
Study dates	JUL 2018 (first participant, first visit) – FEB 2019 (last participant, last visit)	AUG 2020 (first participant, first visit) – FEB 2021 (last participant, last visit)	APR 2019 (first participant, first visit) – JUN 2019 (last participant, last visit)	MAY 2019 (first participant, first visit) – AUG 2019 (last participant, last visit)
Trial registration	EudraCT 2017-004756-32	chinadrugtrials.org.cn reg. no.: CTR20191598	---	EudraCT 2018-002426-23

[a] Data are arithmetic mean ± standard deviation unless indicated otherwise; [b] only after administration by infusion.
bw, body weight; Gd, gadolinium; PK, pharmacokinetics; SD, standard deviation
The methods used in the studies in Chinese and Japanese men were essentially identical with the methods used in the first-in-human study described in the present publication in detail.
The bioanalytical method used in the dose-response study was also the same, but only sparse blood samples were taken.

Chapter 5: Population pharmacokinetic methods

Densely sampled pharmacokinetic (PK) data from the present study and a phase 1 study in healthy Japanese men (see Chapter 4) as well as sparsely collected PK data from a phase 1 dose-response study in healthy, mostly White men (see Chapter 4) were pooled for population PK analysis in order to (i) characterize the variability in plasma, (ii) explore the influence of potential covariates on variability, and (iii) to compare the results with those for gadobutrol. The following key PK parameters were derived from the final population PK model: area under the concentration-time curve (AUC), total clearance from plasma (CL), volume of distribution at steady state (V_{ss}), and half-life ($t_{1/2}$).

Parameters were normalized to the body weight of the subject by dividing the individual PK parameter by the individual body weight of the subject. In addition, Gd plasma concentrations at 10 minutes and 20 minutes after gadoquatrane injection (C_{10} and C_{20}, respectively) were predicted for each subject for the 0.1 mmol Gd/kg dose.

The first-order conditional estimation method with interaction was used for model development. Post-processing of NONMEM-analysis results was carried out in R, v3.5.2.

Models were selected on the basis of the following criteria: (i) successful minimization and covariance step, (ii) number of significant digits, (iii) standard error of estimates, (iv) acceptable gradients at the last iteration, (v) correlation between model parameters, (vi) objective function value, (vii) physiological plausibility of parameter values, (viii) visual inspection of diagnostic plots (1).

In general, models were developed in order of increasing complexity, beginning with very simple model structures and proceeding until further improvement in fit was not supported by the data. This principle was applied to (i) the search for structural model components (characterizing elements such as the number of apparent distribution compartments) and variability components (characterizing elements such as individual and residual variability structure) yielding the base model, and to (ii) the evaluation of subject covariate effects ending up in the final model.

The following covariates at baseline were pre-selected based on prior knowledge and biological plausibility: age, sex, racial subgroup (Caucasian, Asian, African American), estimated glomerular filtration rate, and body weight and other body size parameters. Thereof, either all covariates with a graphical indication of a parameter-covariate relation or, in case of shrinkage in a random effect, all pre-selected covariates were further tested following the forward inclusion/backward elimination procedure (2).

The level of significance was P <0.01 for an effect to be included in the base model development and forward inclusion of covariates. For retention of a covariate relation during backward elimination P <0.001 was used.

Model development was guided by the previously developed adult population PK model for gadobutrol (3), an established extracellular GBCA with physico-chemical, pharmacological, and pharmacokinetic properties very similar to those of gadoquatrane.

The parameter estimates of the final model are given in Table S5 - 1. All parameters were estimated with high to moderate precision (ie, relative standard error (RSE) of <36%, based on $COV step in NONMEM). The model fulfilled successful numerical convergence and the condition number was low (86.8).

According to the above criteria, the fit of a 3-compartment model was adequate without any relevant bias in goodness-of-fit plots and superior compared to less or more complex model structures.

Table S5 - 1: Parameter estimates obtained from the final population PK model

Parameter	Unit	Estimate	RSE [%]	Description
Fixed effects (THETA)				
CL	L/h	7.42	1.4	Clearance
V1	L	7.46	5.1	Central volume of distribution
Q2	L/h	8.35	9.5	First intercompartmental clearance
V2	L	7.50	4.4	First peripheral volume of distribution
Q3	L/h	0.0474	7.3	Second intercompartmental clearance
V3	L	1.31	7.1	Second peripheral volume of distribution
eGFR on CL	%	0.471	20.7	Percent change in CL per one eGFR unit from the median eGFR of 110 mL/min/1.73 m^2
Random effects [a]				
Inter-individual variability (OMEGA)				
CL (ω^2)	-	0.0131	15.5	IIV in clearance
CL (CV)	%	17.9		
CL (η-shrinkage)	%	6.52		
V1 (ω^2)	-	0.0317	19.5	IIV in first peripheral volume of distribution
V1 (CV)	%	10.6		
V1 (η-shrinkage)	%	25.1		
V2 (ω^2)	-	0.0110	35.8	
V2 (CV)	%	11.5		
V2 (η-shrinkage)	%	31.6		
Residual error of gadolinium (SIGMA)				
prop_1 (σ^2)	-	0.0330	9.4	Proportional residual error
prop_1 (CV)	%	18.1		
prop_1 (ε-shrinkage)	%	6.56		

IIV: inter-individual variability; RSE: residual standard error; eGFR: estimated glomerular filtration rate

All clearance and volume parameters were normalized to a body weight of 69 kg, which was the median body weight of the analysis population.

[a] The coefficient of variation (CV%) is calculated by SQRT(EXP(OMEGA^2)-1) x 100 and SQRT(SIGMA2) x 100; RSE refers to estimates of ω2 and σ2.

References

(1) Byon W, Smith MK, Chan P, et al. Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. CPT: pharmacometrics & systems pharmacology 2013;2(7):e51. doi:10.1038/psp.2013.26.

(2) Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. Pharmaceutical research 1998;15(9):1463–1468. doi:10.1023/a:1011970125687.

(3) Reif S, Schultze-Mosgau M, Sutter G. From adults to children: simulation-based choice of an appropriate sparse-sampling schedule. Paediatric drugs 2012;14(3):189–200. doi:10.2165/11595430-000000000-00000.

Chapter 6: Analysis of the Gd concentration-QTc interval relationship

The relationship between gadolinium (Gd) concentration and length of the (ECG) QT interval corrected for heart rate (QTc) was analyzed applying the pre-defined linear concentration-QTc effect model described by Garnett et al. (1, 2), after it had been confirmed that all criteria for applying this model were met. According to Garnett et al., the QT response is to be evaluated at a sufficiently high multiple of the clinically expected exposure (at least a multiple of two) to waive the need for assessing assay sensitivity with a positive control.

The analysis data set covered gadoquatrane doses between 0.025 and 0.2 mmol Gd/kg body weight given as single iv infusions or injections. As the highest tested dose of 0.2 mmol Gd/kg bw is 5 times higher than the anticipated diagnostic dose of 0.04 mmol Gd/kg bw, the analysis did not require a positive control (1, 2).

For each relevant time point, three representative ECG tracings of 10-second duration each were selected from continuous ECG recordings. PK sampling was performed immediately after the last ECG recording of each triplicate. Arithmetic means of ECG parameters including QT and QTc were calculated for each set of triplicate ECGs per subject and time point.

A total of 415 paired Gd concentration-QTcF values[1] from 49 participants (36 participants on active and 13 participants on placebo treatment), with 7 to 9 measurements per participant, were analyzed. The Gd plasma concentration ranged from a minimum of 0.577 µmol/L to a maximum of 2782 µmol/L (arithmetic mean: 353 µmol/L; 5th and 95th percentiles: 1.10 µmol/L and 1326 µmol, respectively).

References

(1) Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn 2018;45(3):383–397. doi:10.1007/s10928-017-9558-5.

(2) Garnett C, Bonate PL, Dang Q, et al. Correction to: Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn 2018;45(3):399. doi:10.1007/s10928-017-9565-6.

[1] QT_{cF} = QT interval corrected for heart rate according to Fridericia formula

Chapter 7: Non-compartmental pharmacokinetic analysis: supplemental figures and tables

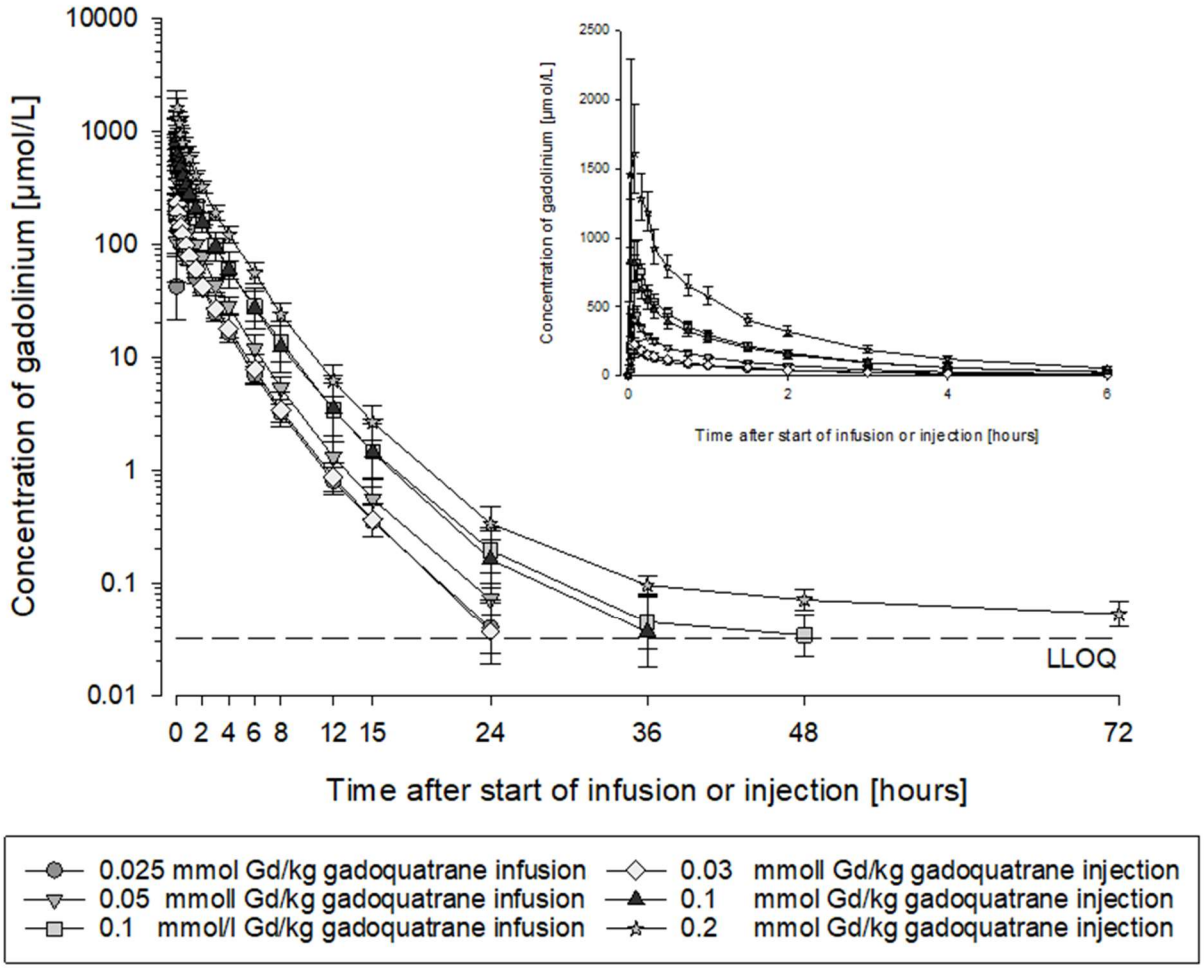

Figure S7 - 1: Geometric mean concentrations (± SD) of gadolinium in plasma after single intravenous administration of different doses of gadoquatrane to healthy male and female study participants

Gd, gadolinium; LLOQ, limit of quantitation; SD, standard deviation.
Infusions were given over 5 minutes.

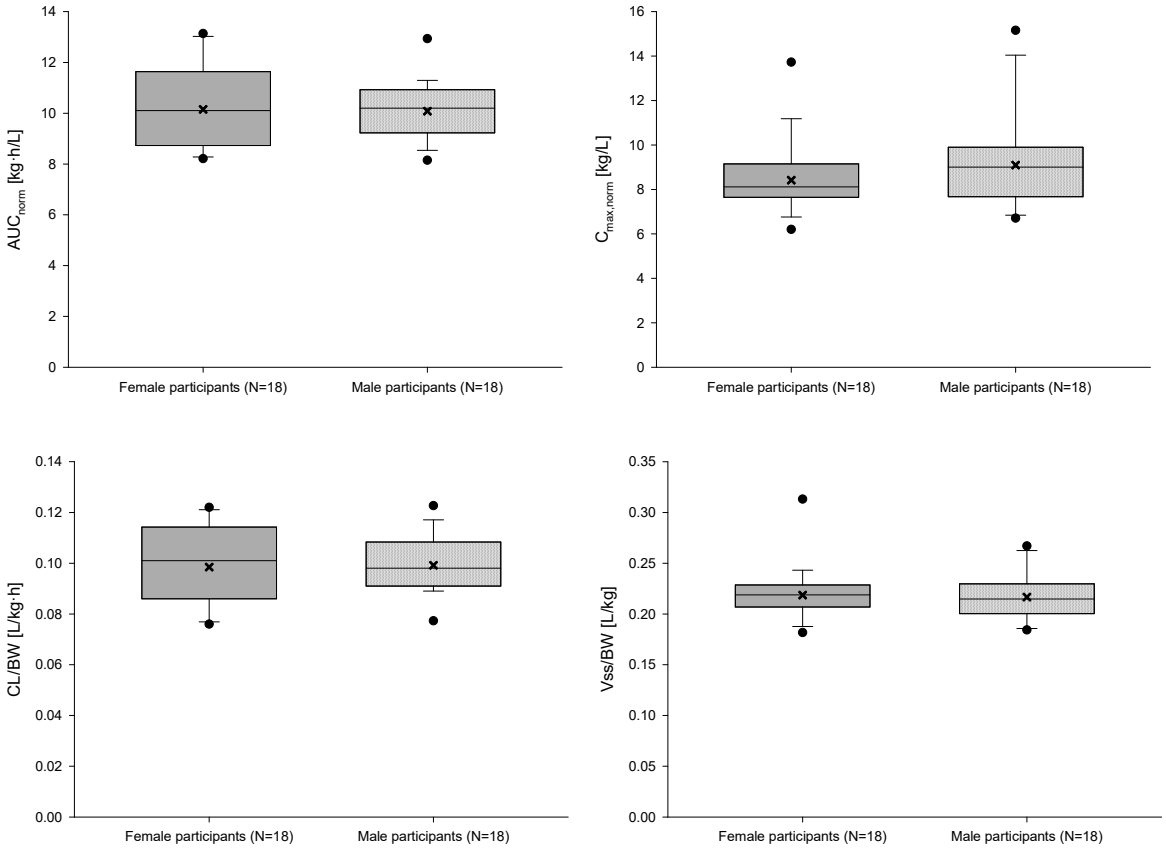

Figure S7 - 2: Pharmacokinetic parameters normalized to body weight obtained in study participants of different sex after single intravenous administration of different doses of gadoquatrane

Boxes: 25th to 75th percentile; horizontal lines: medians; crosses: geometric means; whiskers (error bars): 10th to 90th percentile; any value more extreme is plotted separately.

AUC_{norm}, area under the concentration-time curve from zero to infinity divided by dose/kg body weight; CL/BW, total body clearance of drug per kg body weight; $C_{max,norm}$, maximum observed drug concentration divided by dose/kg body weight; N, number of evaluable study participants; V_{ss}/BW, apparent volume of distribution at steady state per kg body weight.

Table S7 - 1: Pharmacokinetic parameters obtained after single intravenous administration of different doses of gadoquatrane

Parameter [unit]	0.025 mmol Gd/kg infusion	0.05 mmol Gd/kg infusion	0.1 mmol Gd/kg infusion	0.03 mmol Gd/kg injection	0.1 mmol Gd/kg injection	0.2 mmol Gd/kg injection
	N=6	N=6	N=6	N=6	N=6	N=6
C_{max} [µmol/L]	209 (16.4)	464 (21.2)	827 (17.3)	250 (11.8)	948 (34.3)	1780 (25.6)
$C_{max,norm}$ [kg/L]	8.36 (16.5)	9.28 (21.2)	8.28 (17.3)	8.28 (12.1)	9.48 (34.4)	8.92 (25.6)
AUC [µmol·h/L]	254 (8.57)	489 (8.61)	1070 (11.4)	293 (16.9)	1020 (22.1)	2050 (12.0)
AUC_{norm} [kg·h/L]	10.2 (8.23)	9.78 (8.51)	10.7 (11.4)	9.73 (17.2)	10.2 (22.1)	10.2 (12.0)
AUC(0-t_{last}) [µmol·h/L]	254 (8.60)	489 (8.61)	1070 (11.4)	293 (17.0)	1020 (22.1)	2040 (12.1)
AUC(0-t_{last})$_{norm}$ [kg·h/L]	10.1 (8.26)	9.78 (8.50)	10.7 (11.4)	9.71 (17.3)	10.2 (22.1)	10.2 (12.1)
CL [L/h]	7.25 (20.4)	6.88 (14.3)	6.67 (17.4)	7.23 (14.3)	6.60 (16.8)	6.58 (10.7)
CL/BW [L/h/kg]	0.0985 (8.23)	0.102 (8.51)	0.0936 (11.4)	0.103 (17.2)	0.0984 (22.1)	0.0978 (12.0)
CL_R/BW [L/h/kg]	0.0879 (10.2)	0.0917 (14.0)	0.0779 (22.3)	0.105 (15.8)	0.0945 (23.4)	0.0715 (30.7)
t_{max} [hours] [a]	0.117 (0.115-0.167)	0.117 (0.0833-0.121)	0.117 (0.117-0.167)	0.0589 (0.0339-0.0847)	0.0583 (0.0333-0.0833)	0.0599 (0.0333-0.0847)
t_{last} [hours] [a]	24 (15-24)	24 (24-24)	48 (24-72)	24 (15-24)	42 (24-72)	72 (72-72)
$t_{1/2,eff}$ [h] [b]	1.51 (5.33)	1.39 (11.3)	1.53 (17.9)	1.46 (10.5)	1.54 (17.3)	1.73 (5.84)
MRT [h]	2.01 (5.33)	2.01 (11.3)	2.21 (17.9)	2.11 (10.5)	2.22 (17.3)	2.50 (5.84)
V_{ss}/BW [L/kg]	0.214 (4.54)	0.205 (6.81)	0.207 (10.1)	0.217 (13.5)	0.219 (7.91)	0.244 (14.0)

AUC, area under the concentration-time curve from zero to infinity after single dose; AUC(0-t_{last}), AUC from time 0 to the last concentration data point >LLOQ; AUC_{norm}, AUC divided by dose/kg body weight; AUC(0-t_{last})$_{norm}$, AUC(0-t_{last}) divided by dose/kg body weight; CL, total body clearance of drug; CL/BW, total body clearance of drug per kg body weight; CL_R/BW, renal body clearance of drug per kg body weight; C_{max}, maximum observed drug concentration after single dose administration; $C_{max,\ norm}$, C_{max} divided by dose per kg body weight; LLOQ, lower limit of quantitation; MRT, mean residence time; N, number of (evaluable) participants; t_{last}, time of last observed concentration value above LLOQ; $t_{1/2,eff}$, effective half-life calculated based on the MRT, which was multiplied by the logarithm of 2. This half-life describes the overall effective elimination of the drug. t_{max}, time to reach C_{max} (in case of two identical C_{max} values, the first was used). V_{ss}/BW, apparent volume of distribution at steady state per kg body weight.

[a] Data are medians followed by ranges in parentheses.

[b] The effective half-life was chosen over the terminal elimination half-life, as it takes both into account, distribution and elimination, and is therefore less dependent of how long samples were taken than the terminal elimination half-life. The latter changes considerably based on sampling time and sensitivity of the bioanalytical method and covers only a very small fraction of the systemic exposure.

All data are geometric means followed by coefficients of variation (%) in parentheses unless indicated otherwise.
Drug concentrations in plasma are based on Gd concentration.

Table S7 - 2: Investigation of dose-proportionality for two different modes of gadoquatrane administration (ANOVAs on log data)

Mode of administration	Parameter	Unit	DF	Mean sum of squares	F value	*P* value
IV infusion	AUC_{norm}	L·h/kg	2	0.0116	1.30	0.3023
	$C_{max,norm}$	L/kg	2	0.0239	0.71	0.5055
IV bolus injection	AUC_{norm}	L·h/kg	2	0.00442	0.15	0.8662
	$C_{max,norm}$	L/kg	2	0.0272	0.43	0.6580

ANOVA, analysis of variance; AUC_{norm}, area under the concentration-time curve from zero to infinity divided by dose/kg body weight; $C_{max,norm}$, maximum observed drug concentration divided by dose per kg body weight; DF, degree of freedom; IV, intravenous.

Table S7 - 3: Key pharmacokinetic parameters obtained after single intravenous administration of different doses of gadoquatrane by sex

Parameter [unit]	N	0.025 mmol Gd/kg infusion	0.05 mmol Gd/kg infusion	0.1 mmol Gd/kg infusion	0.03 mmol Gd/kg infection	0.1 mmol Gd/kg injection	0.2 mmol Gd/kg injection
C_{max} (male) [µmol/L]	3	228 (9.13)	527 (19.8)	784 (16.9)	251 (16.8)	976 (39.7)	1840 (37.2)
C_{max} (female) [µmol/L]	3	192 (19.1)	408 (14.8)	871 (19.6)	248 (8.22)	920 (37.2)	1730 (16.2)
AUC (male) [µmol·h/L]	3	247 (4.84)	502 (10.2)	1060 (5.72)	299 (9.26)	967 (25.6)	2060 (9.21)
AUC (female) [µmol·h/L]	3	261 (11.8)	476 (7.77)	1070 (17.1)	288 (25.1)	1070 (22.1)	2030 (16.6)
CL/BW (male) [L/h/kg]	3	0.101 (5.12)	0.0996 (9.96)	0.0938 (5.67)	0.101 (9.56)	0.103 (25.7)	0.0970 (9.23)
CL/BW (female) [L/h/kg]	3	0.0962 (11.2)	0.105 (7.83)	0.0934 (17.2)	0.105 (25.5)	0.0937 (22.2)	0.0986 (16.6)
CL_R/BW (male) [L/h/kg]	3	0.0891 (3.61)	0.0925 (7.72)	0.0838 (13.1)	0.102 (6.12)	0.101 (25.2)	0.0854 (5.80)
CL_R/BW (female) [L/h/kg]	3	0.0867 (15.5)	0.0908 (20.8)	0.0725 (30.5)	0.108 (23.9)	0.0880 (24.0)	0.0598 (36.6)
$t_{1/2,eff}$ (male) [h]	3	1.48 (5.58)	1.40 (13.8)	1.52 (6.41)	1.53 (6.87)	1.49 (15.8)	1.67 (1.20)
$t_{1/2,eff}$ (female) [h]	3	1.53 (5.47)	1.39 (11.4)	1.54 (27.8)	1.39 (12.4)	1.60 (21.5)	1.79 (7.14)
V_{ss}/BW (male) [L/kg]	3	0.215 (3.27)	0.200 (7.70)	0.206 (11.8)	0.223 16.4	0.222 (12.0)	0.234 (10.2)
V_{ss}/BW (female) [L/kg]	3	0.213 (6.32)	0.211 (6.20)	0.208 (10.7)	0.210 (12.8)	0.216 (2.50)	0.254 (18.3)

AUC, area under the concentration-time curve from zero to infinity after single dose; CL/BW, total body clearance of drug per kg body weight; CL_R/BW, renal body clearance of drug per kg body weight; C_{max}, maximum observed drug concentration after single dose administration; N, number of evaluable study participants; $t_{1/2,eff}$, effective half-life calculated based on the mean residence time, which was multiplied by the logarithm of 2. This half-life describes the overall effective elimination of the drug. V_{ss}/BW, apparent volume of distribution at steady state per kg body weight.

All data are geometric means followed by coefficients of variation (%) in parentheses.
Drug concentrations in plasma are based on Gd concentration.

Table S7 - 4: Total amount of gadolinium detected in urine and feces within 72 h after single intravenous administration of different doses of gadoquatrane

Parameter [unit]	0.025 mmol Gd/kg infusion	0.05 mmol Gd/kg infusion	0.1 mmol Gd/kg infusion	0.03 mmol Gd/kg injection	0.1 mmol Gd/kg injection	0.2 mmol Gd/kg injection
	N=6	N=6	N=6	N=6	N=6	N=6[c]
$A_{E,urine}$(0-12h) [% of dose]	88.4 ± 4.81 (5.44%)	89.0 ± 7.87 (8.85%)	84.1 ± 17.3 (20.6%)	101 ± 5.24 (5.17%)	94.4 ± 3.64 (3.85%)	74.2 ± 18.0 (24.2%)
$A_{E,urine}$(0-24h) [% of dose]	89.0 ± 4.77 (5.36%)	89.7 ± 8.00 (8.91%)	84.9 ± 17.5 (20.6%)	102 ± 5.16 (5.06%)	95.6 ± 3.32 (3.47%)	74.9 ± 18.1 (24.1%)
$A_{E,urine}$(0-72h) [% of dose]	89.3 ± 4.77 (5.34)	90.0 ± 8.00 (8.89)	85.1 ± 17.5 (20.6)	102 ± 5.15 (5.04)	96.0 ± 3.33 (3.46)	75.2 ± 18.1 (24.1)
$A_{E,feces}$(0-72h) [% of dose]	0.0370 ± 0.0268 (72.5) [a]	0.0264 ± 0.0225 (85.2) [b]	0.0295 ± 0.0245 (83.1) [b]	0.0418 ± 0.0281 (67.2)	0.0538 ± 0.0427 (79.3) [b]	0.0610 ± 0.0478 (78.4) [b]

$A_{E,urine}$, amount of Gd excreted into urine in percent of the administered dose; $A_{E,feces}$, amount of Gd excreted via feces in percent of the administered dose; Gd, gadolinium; N, number of evaluable study participants.

[a] N = 4; [b] N = 5. (Note: A few participants had no bowel movements during the sampling interval.)

[c] One participant had an exceptionally low urinary recovery within the first 4 hours post dose, most likely due to procedural difficulties. Thus, the cumulated amounts are lower in this group than in the other dose cohorts.

Data are arithmetic mean ± standard deviation followed by coefficient of variation [%] in parentheses.