Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of report:	03 Apr 2014
Study title:	Open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infants to 23 months of age) undergoing a contrast-enhanced MRI with an intravenous injection of 0.1 mmol/kg body weight (BW) gadobutrol 1.0 M (Gadovist® 1.0)
Sponsor's study number:	91741
NCT number:	National Clinical Trial (NCT) number: 01544166
EudraCT number:	2010-023003-96
Sponsor:	Bayer
Clinical phase:	I
Study objectives:	The primary objective of the study was • To evaluate the pharmacokinetics (PK) of gadobutrol in plasma at the standard dose of 0.1 mmol/kg BW in pediatric subjects from birth to less than 2 years of age (term newborn infants to toddlers 23 months of age inclusive) The secondary objectives of the study were • To evaluate safety and tolerability of gadobutrol at the standard dose of 0.1 mmol/kg BW in pediatric subjects aged < 2 years • To evaluate qualitatively gadobutrol-enhanced images at the standard dose of 0.1 mmol/kg BW in pediatric subjects following magnetic resonance imaging (MRI) for any indication as exploit for contrast enhanced MRI by extracellular contrast agents • To estimate the glomerular filtration rate (GFR) prior to injection of gadobutrol, based on the Schwartz formula

Test drug:	Gadobutrol (Gadovist/Gadavist®, BAY 86-4875)
Batch Number:	00014271
Name of active ingredient:	Gadobutrol
Dose:	0.1 mmol/kg BW
Route of administration:	Intravenous injection
Duration of treatment:	1 single injection
Reference drug:	Not Applicable
Indication:	Gadolinium-enhanced MRI
Diagnosis and main criteria for inclusion:	Pediatric subjects (male and female children) from birth to less than 2 years of age (term newborn infants to toddlers 23 months of age inclusive), who are referred to a routine gadobutrol contrast-enhanced MRI of any body region Able to comply with the following study procedures • Availability for 8 hours post-injection for PK blood sampling and for the safety follow-up assessments at 24 ± 4 hours post-injection • Provide contact information for a safety follow-up assessment (telephone call at 7 ± 1 days post-injection)
Study design:	Open-label, multicenter, prospective study with randomized blood sampling schedule for the evaluation of gadobutrol PK

Methodology	Pediatric subjects who fulfilled all inclusion and none of the exclusion criteria received a standard dose of 0.1 mmol/kg BW gadobutrol. Within 8 hours after the gadobutrol injection, 3 blood samples for the evaluation of gadobutrol PK were to be drawn from each subject, i.e. 1 sample per time window (sparse sampling approach). The time windows were 15 to 60 min, 2 to 4 hours, and 6 to 8 hours post-injection, respectively. Each time window was subdivided into 4 sampling time intervals. Pediatric subjects were randomized to 1 sampling time interval for each of the 3 time windows. The exact time points of sampling were documented. Safety was assessed by physical examination, physical checks, vital signs, pulse oximetry, cardiac rhythm, and laboratory parameters at different time points starting at baseline and within 24±4 hours post gadobutrol injection. In addition, eGFR was obtained prior to gadobutrol injection. At 7 ± 1 days post-injection, a follow-up telephone call was performed to collect safety information. Adverse events were monitored continuously from enrolment up to the end of the study. The safety follow-up assessment ended with adverse event recording 7 ± 1 days after the gadobutrol injection (study duration for each individual subject was 7 ± 1 day). Magnetic resonance unenhanced images and combined (unenhanced and contrast-enhanced) image sets were assessed qualitatively by the investigator or his / her designee.
Study center(s):	9 recruiting study centers in 3 countries: Canada (1), Germany (3), and United States of America (5).
Publication(s) based on the study (references):	None at the time of report creation
Study period:	First subject, first visit: 16 May 2012 Last subject, last visit: 28 Nov 2013
Early termination	Not Applicable

Number of subjects:	Planned:	A maximum of 50 pediatric subjects was to be enrolled with at least 40 pediatric subjects with valid blood samples for evaluation of gadobutrol PK drawn during the randomly allocated sampling time intervals. At least 40 children evaluable for the primary endpoint from birth to 2 years of age from which at least 5 children from birth to 2 months of age must be evaluated. At least 43 children evaluable for safety assessment from birth to less than 2 years of age from which at least 9 subjects aged from birth to less than 2 months of age must be evaluated.
	Analyzed:	47 subjects enrolled, 44 subjects analyzed (43 subjects for PK and 44 subjects for efficacy/safety); 9 subjects were less than 2 months of age in PK, safety and efficacy population
Criteria for evaluation ***Efficacy / clinical pharmacology:***	**Pharmacokinetics (primary variables)** Primary endpoint(s) with time point(s) of assessment: Evaluation of the pharmacokinetics of gadobutrol in plasma: typical and individual area under the curve (AUC), Total body clearance (CL), volume of distribution at steady state (V_{ss}), Terminal elimination half-life ($t_{1/2}$) and Mean residence time (MRT), Simulation of C_{20} (Gadobutrol plasma concentration at 20 min post-injection) In addition, C_{30} (Gadobutrol plasma concentration at 30 min post-injection) was evaluated. **Efficacy (secondary variables)** Qualitative evaluation of gadobutrol enhanced images: The following efficacy variables were assessed and summarized for the unenhanced image set and the combined (unenhanced and contrast-enhanced) image set: • anatomical area evaluated • technical adequacy for diagnosis • contrast quality (only for combined image set) • presence of pathology, if yes number of lesions • degree of contrast enhancement in lesion or vessel	

	• border delineation of lesion or vessel • visualization of lesion-internal morphology or homogeneity of vessel enhancement • diagnosis • additional diagnostic gain by the contrast-enhanced image set (only for combined image set) • confidence in diagnosis • subject management
Safety:	Safety and tolerability (assessed by Adverse Event (AE) collection, physical examination, physical checks, vital signs, and laboratory parameters at different time points, starting at baseline and within 24 hours [plus/minus 4 hours] post gadobutrol injection) Further criteria for safety evaluation: Estimated glomerular filtration rate (eGFR), determined prior to gadobutrol injection, based on the Schwartz formula
Other:	Not applicable.
Statistical methods:	Plasma PK parameters were evaluated as primary variables of this study. Gadobutrol plasma concentrations were analyzed using a population-based PK approach. Median, minimum and maximum of estimated individual PK parameters and geometric mean values were generated and confidence intervals for these estimates based on population PK method are provided. Efficacy and safety parameters as well as eGFR were evaluated descriptively as secondary variables. Medical history and AE findings were summarized using Medical Dictionary for Regulatory Activities (MedDRA version 16.1) terms.
Substantial protocol changes:	The study was performed according to 91741 study clinical protocol v1.0 dated 22 September 2011. There were no amendments to this protocol (minor or substantial)

Study subjects

This study was an open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infants to 23 months of age) undergoing a contrast-enhanced MRI with an intravenous injection of 0.1 mmol/kg body weight (BW) gadobutrol 1.0 M.

Of the 47 enrolled subjects, 3 subjects failed screening because they did not meet the eligibility criteria. They did not receive the study drug and did not complete the study. A total of 44/47 subjects (93.6%) received the study drug, completed the study medication and were valid for the full analysis set (FAS) and safety analysis set (SAF). One subject had to be excluded from the per-protocol set (PPS) due to a major protocol deviation. The analysis of PK variables (primary endpoint) was based on the PPS (43 subjects).

Of the 44 subjects treated, 26 subjects were males and 18 were females. The mean age was 8.8 months ranging from 0.2 to 23 months.

Pharmacokinetic evaluation

Gadobutrol PK in pediatric subjects aged 0 - < 2 years were adequately described by a linear 2-compartmental model with elimination from the central compartment.

Values of the median, minimum and maximum of the individual key PK parameters CL, CL/kg, V_{ss}, V_{ss}/kg, AUC, $t_{1/2}$, and MRT are presented in Table 1.

Table 1: Summary of individual posthoc estimates and derived PK parameters of all pediatric subjects based on the final population PK model (PPS, N=43)

Parameter	Median	Minimum	Maximum
CL [L/h]	0.981	0.263	2.10
CL/kg [L/h/kg]	0.128	0.0666	0.184
V_{ss} [L]	1.99	1.14	3.34
V_{ss}/kg [L/kg]	0.277	0.236	0.409
AUC [µmol*h/L]	776	544	1470
$t_{1/2}$ [h]	1.62	1.16	3.37
MRT [h]	2.18	1.57	4.68

Simulations of gadolinium plasma concentrations

Plasma concentrations of gadobutrol at 20 min and 30 min after injection (C_{20}, C_{30}) were simulated for a total number of 2400 virtual pediatric subjects with homogeneous distribution over age. The inter-individual variability of CL as well as the residual error of the final population PK model were taken into account. The results of the simulations are summarized in Table 2.

Table 2: Simulated gadolinium plasma concentrations (µmol/L) at 20 min and 30 min after injection of 0.1 mmol/kg gadobutrol based on the final population PK model

Number of subjects	Parameter[a]	Median	5th percentile	95th percentile
2400 subjects	C_{20}	339	230	456
	C_{30}	292	194	394

[a] Gd plasma concentration at time=20 min and time=30 min after drug application

Simulated median (5th and 95th percentile in parenthesis) gadolinium plasma concentrations for a dose of 0.1 mmol/kg body weight were 339 (230, 456) µmol/L at 20 min post injection and 292 (194, 394) µmol/L at 30 min post injection for all simulated subjects.

The pharmacokinetics is very similar to pediatric subjects aged 2 – 17 years and adults.

Efficacy evaluation

Efficacy was evaluated for 44 subjects in the FAS as a secondary analysis following the administration of gadobutrol at the standard dose of 0.1 mmol/kg BW. The investigators qualitatively assessed the unenhanced image sets and the combined image sets separately.

Diagnoses in unenhanced and in combined MRI as well the final diagnosis were reported as "other" and further specified by the investigator if no pre-specified diagnosis was applicable.

The primary anatomical areas (body regions, target organs) evaluated for MRI were brain (n=21 subjects), retroperitoneal area (n=7), head/neck (n=5), spinal cord (n=5), chest/thorax (n=2), pelvic area (n=2), abdomen, and lymphatic system (each n=1).

The basic technical adequacy of the images was "excellent" in the vast majority of subjects (i.e. clearly visualized regions) in both unenhanced MRI (40/44 subjects, 90.91%) and combined MRI (41/44 subjects, 93.18%).

Overall contrast quality was assessed as "good" or "excellent" in all but one subjects (43/44, 97.72%) in combined MRI independent of the body region.

Lesions were detected in 33/44 subjects (75.00%) in both unenhanced and combined MRI. In the majority of subjects (29/44, 65.91%), 1 lesion was detected in both image sets; in 2/44 (4.55%) subjects, 2 lesions were detected in both image sets. In 1 subject with metastases of a left adrenal neuroblastoma, the number of lesions was not visualized with unenhanced MRI, but combined MRI showed 10 lesions.

The degree of contrast-enhancement in the combined MRI was "good" or "excellent" in 41/44 subjects (93.19%). In 3/44 subjects (6.82%), lesions/vessels were not enhanced (subjects were diagnosed with a structural malformation in the lung, a congenital disease/syndrome in the kidney, with metastases of a thoracic neuroblastoma in the liver).

Border delineation of the lesions/vessels showed higher ratings of "good" and "excellent" (43/44, 97.72%) in the combined MRI set compared to unenhanced MRI (33/44, 75.00%). At combined MRI, 1/44 (2.27%) subjects each was rated with "good" and "no" border delineation compared to 6/44 (13.64%) subjects with "moderate" and 5/44 (11.36%) with "no" in unenhanced MRI.

Lesion characterization evaluated as “good” was higher at combined MRI (43/44, 97.73%) compared to unenhanced MRI (27/44, 61.63%). At combined MRI, there were no subjects with “moderate” and 1/44 (2.27%) with “poor” lesion characterization assessed compared to 11/44 (25.00%) subjects with “moderate” and 6/44 (13.64%) subjects with a “poor” assessment in unenhanced MRI.

Diagnoses reported for unenhanced MRI and combined MRI diagnoses were mainly no lesions/normal (unenhanced: 10/44, 22.73%; combined: 11/44, 25.00%), congenital disease/syndrome (unenhanced: 6/44, 13.64%; combined: 8/44, 18.18%), and other diagnoses (unenhanced: 18/44, 40.91%; combined: 13/44, 29.55%). Almost each subject had an individual diagnosis specified by the investigator.

In the majority of subjects (24/44, 54.55%), the combined image set allowed an additional diagnostic gain, i.e. the initial diagnosis was changed to an improved diagnosis. In 1 subject, the diagnosis changed to a new diagnosis. In 19/44 subjects (43.18%), the diagnosis remained unchanged.

Overall, the confidence in diagnosis assessed as confident and very confident was higher in the combined MRI (43/44 subjects, 97.73%) compared to unenhanced MRI (38/33 subjects, 86.37%). The diagnosis was rated as “not confident” in 1 subject in the combined MRI and compared to 6/44 (13.64%) subjects in unenhanced MRI. The one subject with the “not confident” finding had this assessment in both the unenhanced and the combined MRI, while 5 subjects had an improved confidence in combined MRI.

A change in subject management was reported for 8/44 subjects (18.18%), whereas in 36/44 subjects (81.82%) the management remained unchanged from unenhanced MRI to combined MRI. The change in subject management was observed in the body regions retroperitoneal, brain, and pelvic area.

The most common reported final diagnoses were “congenital disease/syndrome”, “no lesions/ normal” (each 6/44, 13.6%), “malignant” lesions (4/44, 9.1%), and “other “(24/44, 54.5%).

A change in the diagnosis from unenhanced to combined MRI was reported in 5/44 subjects (11.36%). A change in the diagnosis from unenhanced MRI to final diagnosis was reported in 11/44 subjects (25.00%). A change in the diagnosis from combined MRI to final diagnosis was reported in 12/44 subjects (27.27%).

The efficacy evaluation is consistent with the known efficacy data of gadobutrol.**Safety evaluation**

Gadobutrol administered intravenously at a standard dose of 0.1 mmol/kg body weight was well tolerated. No deaths were reported and no subject discontinued the study drug prematurely due to adverse events (AEs) or serious adverse events (SAEs).

In 20/44 subjects (45.5%), at least one AE was reported during the study. Treatment-emergent AEs (TEAEs) were reported in 18/44 subjects (40.9%) in the SAF. The most common TEAEs were *cough*, *nasopharyngitis*, *rhinitis*, *pyrexia*, and *vomiting*. One subject had a TEAE of *vomiting* of mild intensity assessed as drug-related. In 5/44 (11.4%) subjects, TEAEs related to procedures required by the protocol were documented.

In 3/44 subjects (6.8%), SAEs (*subdural empyema, respiratory failure*, and *infected cyst*) were reported. All SAEs reported during this study were treatment-emergent; none of these were study drug-related. One SAE was reported to be related to procedures required by the protocol, the other two were related to underlying disease.

There were no clinically relevant changes in laboratory investigations and vital signs observed.

The safety data is consistent with the known safety profile of gadobutrol.

Overall conclusions

The pharmacokinetics of gadobutrol were adequately described in the pediatric population aged 0 – < 2 years based on population PK analysis using sparse plasma sampling data.

The pharmacokinetics of gadobutrol with regard to systemic exposure (AUC, the main safety parameter) and early plasma concentrations (the relevant parameter for efficacy) in the pediatric population aged 0 – < 2 years are very similar to pediatric subjects aged 2 – 17 years and adults.

The efficacy expected from the early gadobutrol (C_{20}) plasma concentrations was confirmed by the results of the efficacy analysis in this study. Consistent with efficacy established in adults and pediatric subjects 2 years of age and older, there was improved detection and characterization of regions of interest in all indications and body regions imaged as well as increased confidence in the diagnosis leading to optimized subject management.

The estimated AUC values in the young pediatric population aged 0 – < 2 years were in good agreement with the safety assessment of the study. With a similar safety profile as in pediatric subjects older than 2 years and adults, the positive benefit risk profile of gadobutrol (1.0 M) was confirmed in the pediatric population < 2 years including term newborns.

Based on the pharmacokinetic results of this study, supported by the favorable safety and efficacy results in the pediatric population 0 – < 2 years of age, an extrapolation of efficacy data from adults and older pediatric subjects to younger pediatric subjects according to ICH E11 is justified. No dose adjustment is required and the recommended standard dose of 0.1 mmol/kg body weight in pediatric subjects aged 2 – 17 years and adults is also appropriate for pediatric subjects aged 0 – < 2 years including term newborns. The dose recommendation based on PK comparison is consistent with the efficacy observed in the present study.

Investigational Site List

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Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Gadavist
Brand/Trade Name(s) ex-US	Gadovist
Generic Name	Gadobutrol
Main Product Company Code	BAY86-4875
Other Company Code(s)	ZK 135079
Chemical Description	10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10–tetraazacyclododecane–1,4,7–triacetic acid, gadolinium complex
Other Product Aliases	

Date of last Update/Change: 28 May 2013