Ergebnisbericht gemäß § 42b Abs. 2 AMG, revidierte Version

1	Name of Sponsor	University Heidelberg
2	Name of Finished Product	Vasovist®
3	Name of Active Substance	Gadofosveset
4	Individual Study Table	Does not apply
5	Title of Study	Determination of Diagnostic Accuracy and Added Value of Vasovist-Enhanced Peripheral MRA in Comparison to Intra-arterial Digital Subtraction Angiography (i.a. DSA) in Patients with Peripheral Artery Disease
6	Investigators	Prof. Stefan Schönberg, Mannheim Prof. Henrik Michaely, Mannheim Prof. Winfried Willinek, Bonn PD Dr. Kai Wilhelm, Bonn PD Dr. Dariusch Hadizade, Bonn Dr. Guido Kukuk, Bonn Prof. Ulrich Kramer, Tübingen Prof. Karl-Friedrich Kreitner, Mainz Dr. Harald Kramer, München Prof. Konstantin Nikolaou, München Never initiated centers Prof. Dr. Georg Bongartz, Basel Tim Leiner, MD PhD, Leinen
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8	Publication	No published data
9	Studied period (years): date of first enrolment, date of last completed date of abortion	2008-2010 First patient recruited 24.06.2008 Last patient recruited 25.11.2010 Only three study centers effectively recruited patients. Within the study period only 31 patients could be recruited. The study was

		aborted after 25.11.2010 due to lacking success of patient inclusion. A minimum number of 145 patients was aimed for statistical analysis at based on the power estimation per protocol. The reason for the lacking success was the low number of patients with peripheral arterial occlusive disease stage III or IV whose renal function was not impaired (i.e. eGFR > 30ml/min).
10	Phase of development	Phase IV study
11	Objectives	To determine the accuracy of Vasovist® enhanced MRA of the leg with regard to quantitative grading of stenosis (<50%, >=50%) compared to digital subtraction angiography (DSA, standard of reference (SOR)) Secondary objectives – to determine: • Accurateness of description of the inflow, target, outflow of Vasovist® enhanced MRA compared to DSA • Change of therapeutic approach after reviewing - Vasovist® enhanced MRA compared to initial non-invasive angiography (MRA, CTA, US). • Correctness of description of stenotic lesion character (fatty plaque, inflammatory plaque etc.) for interventional therapy • Evaluation of diagnostic value of time-resolved first pass MRA in comparison to high-spatial resolution steady state MRA • Safety of Vasovist®-enhanced MRA
12	Methodology	MRA and DSA images were be evaluated in a blinded read by two readers. Efficacy analyses were to be performed in the per protocol set; the full analysis set was analyzed for safety
13	Number of patients (planned and analysed)	31 patients out of 145 planned patients could be included. All 31 included patients were analyzed.
14	Diagnosis and main criteria for inclusion	Peripheral arterial occlusive disease stage III or IV confirmed by MRA, CTA, non-selective DSA, DUS) and have an indication for the evaluation of the entire lower leg axis down to the feet (common femoral artery to the arteries of the foot) by therapeutic digital subtraction angiography (DSA).
15	Test product, dose and mode of administration,	Vasovist® solution for injection; intravenous (IV), 0.03 mmol/kg body weight injected as a single IV bolus with a flow rate of 1.5 mL/sec followed by a saline flush of at least 30 mL with the same injection rate, batch number 73013C
16	Duration of treatment	Vasovist® was injected only once for the contrast-enhanced MRA.
17	Reference therapy, dose and mode of administration, batch number	The standard of reference was intra-arterial digital subtraction angiography which was conducted as part of the standard clinical therapeutic approach. The contrast agent used for this angiography differed from site to site and was not part of this study.
18	Criteria for evaluation: Efficacy, Safety	Efficacy: Accuracy of quantitative stenosis grading (<50%, >=50%) of Vasovist® enhanced MRA with regard to intra-arterial DSA based on a blinded off-site assessment only. Safety: Continuous monitoring of AEs from the beginning of the Vasovist injection up to the end of the follow-up period of 12 hours after the Vasovist® MRA examination (end of the study)
19	Statistical methods	The grade of stenosis was assessed in six target segments by two blinded readers for the Vasovist®-enhanced MR images. The number of true positive and negative results as well as false positive and negative gradings will be assessed with regard to the DSA. Accuracy will be calculated as the number of correctly graded segments divided by the number of all visible segments (in the SOR).

20	Summary – Conclusions: Efficacy Results, Safety Results, Conclusion	Within the study period only 31 patients could be recruited. The study was aborted after 25.11.2010 due to lacking success of patient inclusion. The study protocol was not changed during the course of the study. Efficacy: Primary objective (Determination of the accuracy of Vasovist® enhanced MRA of the leg with regard to quantitative grading of stenosis (<50%, >=50%) compared to digital subtraction angiography (DSA, standard of reference (SOR)): 31 patients (23male/8female) were included. Despite the fact that the study recruited only a fourth of the aimed target study population an offside assessment of the data was performed. The limited number of data sets and different image assessment of the two independent readers did not provide a homogeneous data matrix which would have allowed further assessing the accuracy of quantitative stenosis grading (<50%, >=50%) of Vasovist® enhanced MRA with regard to intra-arterial DSA based. Based on these limited data the required power of the study to reach the efficacy aim was not achieved. Of the 31 patients included, both readers could assess 29 patients. 2 were excluded for non-diagnostic image quality. The diagnostic confidence for the MRA was evaluated as very confident (n=24, 82.8%), confident (n=5, 17.2%), not confident (n=0, 0%) or not confident at all (n=0, 0%). Secondary objectives: • Accurateness of description of the inflow, target, outflow of Vasovist® enhanced MRA compared to DSA: In the limited available data set a high concordance of the description of inflow, target and outflow was seen, yet no statistical test was applied as the number of included patients did not suffice to reach the needed statistical power. • Change of therapeutic approach after reviewing - Vasovist® enhanced MRA compared to initial non-invasive angiography (MRA, CTA, US): In the limited available data set a change in therapeutic approach based on the MRA data was recommended in 2/31 patients. No statistical test was applied as the number of included patients did not suffice to reach the needed statistical power. • Correctness of description of stenotic lesion character (fatty plaque, inflammatory plaque etc.) for interventional therapy: In the limited available data set no conclusive data could be obtained. • Evaluation of diagnostic value of time-resolved first pass MRA in comparison to high-spatial resolution steady state MRA: In the limited available data set the steady state MRA showed a higher assessability for both readers compared to the time-resolved MRA. The stenosis quantification of the steady-state MRA yielded similar results to DSA whilst the time-resolved MRA showed a lower concurrence. A target lesion for intervention was detected in 27/29 (93.1%) patients in DSA, in 5/29 (17.2%) patients in the first pass MRA and in 25/29 (86.2%) patients in the steady state MRA. A tabulated overview of the results is attached to this report.No in depth statistical test was applied as the number of included patients did not suffice to reach the needed statistical power. • Safety of Vasovist®-enhanced MRA: Within the study period no adverse events occurred.

		Conclusion: This study did not include a sufficient number of patients to yield statistically reliable and/or significant results. The accuracy of Vasovist®-enhanced MRA compared to DSA for the determination of the degree of stenosis (<50% vs. >=50%) could not be reliably determined.
21	Date of report	22.10.2020

Tables:

Assessibility					
	DSA	**MRA**			
		Steady State		**First Pass**	
		Reader 1	**Reader 2**	**Reader 1**	**Reader 2**
SFA	30/31 (96.8%	30/31 (96.8%)	30/31 (96.8%)		
PA	31/31 (100%	30/31 (96.8%)	30/31 (96.8%)	31/31 (100%)	20/31 (64.5%)
TFT	31/31 (100%	31/31 (100%)	30/31 (96.8%)	28/31 (90.3%)	25/31 (80.6%)
ATA	31/31 (100%	30/31 (96.8%)	30/31 (96.8%)	29/31 (93.5%)	28/31 (90.3%)
PTA	30/31 (96.8%	31/31 (100%)	30/31 (96.8%)	29/31 (93.5%)	28/31 (90.3%)
PA	31/31 (100%	31/31 (100%)	30/31 (96.8%)	29/31 (93.5%)	27/31 (87.0%)
DPA	31/31 (100%	29/31 (93.5%)	17/31(54.8%)	27/31 (87.0%)	19/31 (61.3%)

DSA digital subtraction angiography, MRA magnetic resonance angiography, SFA superficial femoral artery, PA popliteal artery, TFT tibiofibular trunc, ATA anterior tibial artery, PTA posterior tibial artery, PA peroneal artery, DPA dorsal pedal artery.

Stenosis Quantification															
	DSA					**MRA Steady State**					**MRA First Pass**				
	<50%	50-99%	occlusion	non assess	total	<50%	50-99%	occlusion	non assess	total	<50%	50-99%	occlusion	non assess	total
SFA	10 (34.5%)	19 (65.5%)	0 (0%)	0 (0%)	29 (100%)	11 (37.9%)	18 (62.1%)	0 (0%)	0 (0%)	29 (100%)	-	-	-	-	-
PA	22 (75.9%)	7 (24.1%)	0 (0%)	0 (0%)	29 (100%)	22 (75.9%)	7 (24.1%)	0 (0%)	0 (0%)	29 (100%)	2 (6.9%)	2 (6.9%)	0 (0%)	25 (86.2%)	29 (100%)
TFT	25 (86.2%)	4 (13.8%)	0 (0%)	0 (0%)	29 (100%)	25 (86.2%)	4 (13.8%)	0 (0%)	0 (0%)	29 (100%)	23 (79.3%)	4 (13.8%)	0 (0%)	2 (6.9%)	29 (100%)
ATA	20 (69.0%)	9 (31.0%)	0 (0%)	0 (0%)	29 (100%)	20 (69.0%)	9 (31.0%)	0 (0%)	0 (0%)	29 (100%)	19 (65.5%)	8 (27.6%)	0 (0%)	2 (6.9%)	29 (100%)
PTA	19 (65.5%)	10 (34.5%)	0 (0%)	0 (0%)	29 (100%)	19 (65.5%)	10 (34.5%)	0 (0%)	0 (0%)	29 (100%)	18 (62.1%)	9 (31.0%)	0 (0%)	2 (6.9%)	29 (100%)
PA	24 (82.8%)	5 (17.2%)	0 (0%)	0 (0%)	29 (100%)	25 (86.2%)	4 (13.8%)	0 (0%)	0 (0%)	29 (100%)	23 (79.3%)	5 (17.2%)	0 (0%)	1 (3.4%)	29 (100%)
DPA	29 (100%)	0 (0%)	0 (0%)	0 (0%)	29 (100%)	28 (96.6%)	1 (3.4%)	0 (0%)	0 (0%)	29 (100%)	25 (86.2%)	1 (3.4%)	0 (0%)	3 (10.3%)	29 (100%)

DSA digital subtraction angiography, MRA magnetic resonance angiography, SFA superficial femoral artery, PA popliteal artery, TFT tibiofibular trunc, ATA anterior tibial artery, PTA posterior tibial artery, PA peroneal artery, DPA dorsal pedal artery.