Study Report

Intra-individual cross-over comparison of MultiHance® and Vasovist® enhanced MRA of the Carotids

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Clinical study phase: III b

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Summary

Vasovist® is the first intravascular contrast agent approved for use with MRA in the European Union, Switzerland, Turkey, Canada, Australia and the United States. The agent reversibly binds to albumin providing extended intravascular enhancement, which should overcome the limitations of conventional contrast agents in MRA. The long residence time in the blood, combined with the highest available T1 relaxivity of all approved agents enables to image with the highest spatial resolution. This allows not only to assess the filling of the vessel itself, but to image the carotid vessel walls which then enabels a combined morphological and functional information with a single contrat media bolus injection.

The optimum dose, clinical efficacy, and safety of gadofosveset trisodium have been evaluated in several clinical trials, the optimum dose was found to be 0.03 mmol/kg and an injection time of 2–3 ml/s is recommended for first-pass imaging.

Initial clinical experience proved that the overall accuracy of gadofosveset trisodium-enhanced MRA was similar to that of catheter-based DSA, as determined by blinded readings, however, no intraindividual comparative studies are available so far.

The excellent performance of the agent in MR angiographic studies is based on the two mechanisms: first the agent binds reversibly and non-covalently to albumin, allowing a half-life of approximately 15 hours. The protein binding also reduces the tumbling rate of the molecule resulting in a up to six times higher relaxivity and an extended imaging time of at least 30–60 minutes compared with other contrast agents.

Correct bolus timing for the first-pass imaging is along routine lines with either a test bolus of gadofosveset trisodium 1 ml injected at 2 ml/s followed by a 20 ml saline bolus injected at the same rate or preferably by using MR fluoroscopy . With exact timing, first-pass imaging shows excellent image quality, which is comparable to high performing extracellular contrast agents.

After reaching the equilibrium phase, gadofosveset trisodium enables to repeatedly image at a high or ultrahigh spatial resolution. Even using low-level systems, steady-state acquisition of isotropic voxels of <1 mm^3 is possible, with acquisition times ≤1 minute. As well as determining high resolution, this allows for reformatting of the data into any projection without compromising image quality.
In this first intraindividual comparative study Vasovist® was compared with MultiHance® in the assessment of high grade carotid artery disease. Although only a limited number of patients could be recruited, Vasovist provided a significant improved SNR and CNR which could also be confirmed with an significant improved visual impression of the vessel contrast.
As a safe contrast agent it also presented with an improved but not significant better stenosis assessment and overall diagnostic confidence.

Background

Besides conventional x-ray angiography (digital subtraction angiography – DSA), magnetic resonance angiography (MRA) is becoming the method of choice for the diagnostic work-up of cervical vessels. However, for an exact assessment of vascular diseases, image quality has to be optimal for stenosis grading and should allow for a description of the angio-architecture of vascular malformations or tumors.
Imaging of the carotid arteries using MRA is a great challenge. Contrast-enhanced MRA has considerable advantages over non-enhanced MR techniques, especially with regard to the speed of examination, anatomical coverage, and the contrast of vascular structures. Using conventional extracellular contrast agents, like Magnevist® or the higher relaxivity agent MultiHance®, MRA can only be performed in a first pass examination when the bolus passes the area of interest. Due to the fast elimination of theses agents from the vascular space, imaging at steady state is not possible (which would allow to image at a very high spatial resolution). Gadofosvest trisodium (Vasovist®) represents a new class of intravascular MR contrast agents. The compound was just recently approved for MRA of the abdominal and peripheral vessels in the European Union. Vasovist is the first intravascular contrast agent approved for the use with MRA in the European Union, Switzerland, Turkey, Canada, Australia and the United States. The complex binds to serum albumin (non covalent), thus changing the relaxivity and half-life of the complex. It is a gadolinium-based contrast agent and the first representative in this new class of blood-pool contrast agents for MRA. Besides the long

lasting presence in the intravascular space, its binding affinity to serum albumin leads to a significant increase of T1- and T2-relaxivities and, hence, to changes in MR contrasting. The increase in T1-relaxivity, a measure of the paramagnetic property, causes a rise in enhancement with a direct influence on the vascular signal in MRA and makes it comparable to other high relaxivity (but extracellular) agents like MultiHance®; however, at a substantially lower Gd concentration. With the prolonged intravascular presence of the agent, the optimal imaging window for vascular structures is widened to about 60 minutes which permits steady state imaging with very high spatial resolution.
Further details about Vasovist® and Multihance® can be found in the respective SmPC, which contains comprehensive information on the study drugs.

Study Rationale and Objectives

Although multiple studies exist about the use of Vasovist® in different areas of the vascular system, there is only limited evidence about the performance of the agent in imaging of the cervical vessels (mainly the carotids).
The ideal way to assess the performance of a contrast agent is the intraindividual cross-over comparison with an already approved and well perfoming agent in the area of interest. For Vasovist, the comparative agent of choice is the higher relaxivity agent Gadobenate Dimeglumine (MultiHance®) which has been recently approved for MR angiography. MultiHance® is a weakly protein interacting agent with increased relaxivity which has proved to be a well performing contrast agent in MRA.
In this study, Vasovist® and MultiHance® should be compared intra-individually at an estimated number of 67 patients (60 valid patients required) using i.a. DSA as the standard of reference if available (i.a. DSA performed for clinical reasons, not part of the study procedures). The study had a multicenter design (2 centers) and was performed on standard clinical 1.5T MR systems.
The acquired MRI data will be assessed in an independent off-site assessment. In a qualitative blinded read an independent radiologist will assess the visibility of vessel segments, the degree of stenoses, and judge on diagnostic confidence. The quantitative assessment will be based on a region of interest (ROI) analysis quantifying and comparing signal-to-noise and contrast-to-noise ratios.

Primary objective

• To prove the superiority of 0.03 mmol/kg of Vasovist® over 0.1 mmol/kg of MultiHance® in the depictive representation of the supraaortic vessel segments

Secondary objectives

• To assess the accuracy of Vasovist® in comparison to MultiHance® for determination of the degree of stenosis using DSA as the standard of reference (analysis of 17 vessel segments)

• To assess the length of the stenosis in Vasovist® and MultiHance® enhanced MRA in cmparison to i.a. DAS

• To assess SNR and CNR in first pass MRA (pre- and post-stenotic segment of the high degree stenosis leading to inclusion; and A. cerebri media)

• To assess the diagnostic confidence of the combined assessment of first pass and steady state vs. first pass alone of Vasovist® enhanced MRA in patients with carotid artery disease (per vessel segment and overall)

Methods

Analysis of the primary and secundary efficacy variables are achieved by a blinded read analysis performed at the MIH office in Heidelberg.

Primary efficacy variable

The primary target variable is the overall assessment of the visibility of supra-aortic vessel segments (visual assessment score). Basis for evaluation is the overall patient.

Analysis of primary efficacy variable

The primary efficacy variable will be analyzed using a repeated measurement analysis of variance with reader nested within patient. A 19-point visual analogue scale is used. It is assumed that the assessment is normally distributed and that a 19-point scale is sufficiently close to continuous data.
Positive scores indicate an advantage of Vasovist®-enhanced MRA whereas negative scores indicate an advantage of Multihance®-enhanced MRA.
Following hypotheses will be tested
Ho: The average visual assessment score of the comparison of Vasovist®- and MultiHance®-enhanced MRA is below or equal to zero will be tested with an one-sided alpha of 2.5% against
H1: The average visual assessment score of the comparison of Vasovist®- and MultiHance®-enhanced MRA is above zero.
The hypotheses will be tested with a t-test within a repeated measurement analysis of variance with reader nested within patient. As secondary analysis the analysis will be performed for each reader's assessment.

Analysis of the secondary efficacy variables

The secondary efficacy variables will be analyzed descriptively only; no hypothesis testing will be performed.
Degree of stenosis as assessed in each of the predefined 17 vessel segments
Degree of stenosis as continuous variable, analysis: provision of summary statistics
Degree of stenosis on a two point scale (<50%, >= 50%), analysis: sensitivity, specificity and accuracy calculation

Length of stenosis, measured by both MRA procedures and DSA.
Analysis: Descriptive statistics.

SNR and CNR (internal carotid artery, external carotid artery, medial cerebral artery, circle of Willis
Analysis: Summary statistics

Diagnostic confidence (per segment and overall) on a four-point scale (very confident/ confident/not confident/not confident at all)
Analysis: Frequency tables

Blinded Read

Primary target variables

Subjective overall (per patient) preference for Vasovist® vs. MultiHance® regarding visibility of vessel segments (visual analog 19-point scale from -9 to 9 with 0 = both procedures are equal)

-9 9
|__|__|__|__|__|__|__|__||__|__|__|__|__|__|__|__|
1st MR better 2nd MR better

Secondary target variables

• Degree of stenosis as assessed in each of the predefined 17 vessel segments (<75%, 75% to <90%, 90-99%, 100%); maximal stenosis to be assessed in case of 2 stenoses in the same segments; sensitivity, specificity, accuracy of Vasovist® vs. MultiHance® with DSA as the SOR

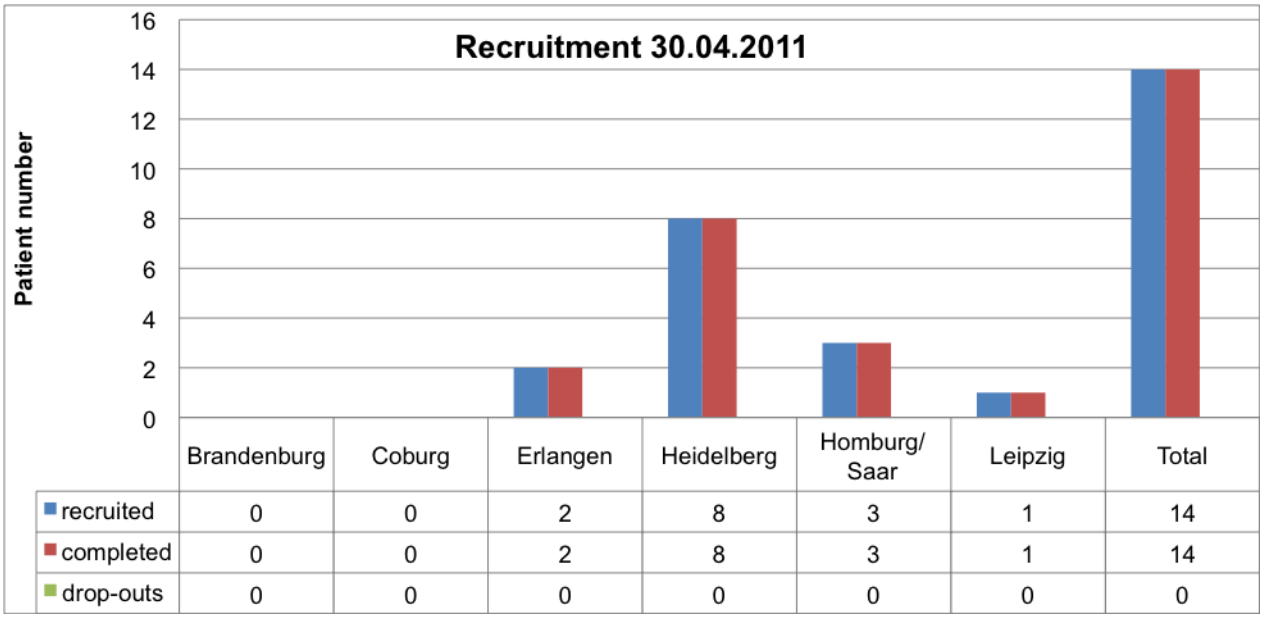
• Length of stenosis, measured by both MRA procedures and DSA.

• SNR and CNR (internal carotid artery, external carotid artery, medial cerebral artery, circle of Willis, stenosis leading to study inclusion)

• Diagnostic confidence (per segment and overall); 4 point scale (very confident, confident, not confident, not confident at all)

Results

A total of 14 Patients could be recruited for the study – the majority (8 subjects) in Heidelberg. Out of these patients 12 could be evaluated by the blinded read analysis. 2 Patients had insufficient or incomplete imaging data. DSA was available in only a very limited number of patients (2 subjects) because DSA is not anymore the standard of reference in carotid artery disease and not ordered by the referring physicians (vascular surgery or angiology).



	Brandenburg	Coburg	Erlangen	Heidelberg	Homburg/ Saar	Leipzig	Total
recruited	0	0	2	8	3	1	14
completed	0	0	2	8	3	1	14
drop-outs	0	0	0	0	0	0	0

Safety Assessment

There were no severe adverse events (SAE) reported in the study.

Efficacy Assessment (Blinded Read Results)

1. Available images

Vasovist images

n	%	Random number
12	100.0	1,4,7,10,13,16,19,22,25,28,31,45

MultiHance images

n	%	Random number
12	100.0	2,5,8,11,14,17,20,23,26,29,32,46

2. Evaluable images

Vasovist images

n	%	Random number
12	100.0	1,4,7,10,13,16,19,22,25,28,31,45

MultiHance images

n	%	Random number
12	100.0	2,5,8,11,14,17,20,23,26,29,32,46

3. Stenoses

3.1 Degree

Pat. ID	CM	int. carotid a. left	int. car. a. right	ext. car. a. left	vertebr. a. right
01-001	Vasovist	-	-	90% - 99%	-
	MultiHance	90% - 99%	-	-	< 75%
01-002	Vasovist	90% - 99%	-	-	-
	MultiHance	90% - 99%	-	-	-
01-003	Vasovist	-	90% - 99%	-	-
	MultiHance	-	75% - <90%	-	-
01-004	Vasovist	< 75%	< 75%	-	-
	MultiHance	< 75%	< 75%	-	-
01-005	MultiHance	75% - <90%	-	-	-
	Vasovist	75% - <90%	-	-	-
01-007	Vasovist	100%	-	-	-
	MultiHance	100%	-	-	-
01-008	Vasovist	-	100%	-	-
	MultiHance	-	100%	-	-
02-002	Vasovist	90% - 99%	75% - <90%	-	-
	MultiHance	90% - 99%	not evaluable*	-	-
02-003	MultiHance	100%	-	-	not evaluable**
	Vasovist	100%	< 75%	-	-
05-001	MultiHance	-	-	-	100%
	Vasovist	-	-	-	100%
05-002	Vasovist	100%	100%	-	-
	MultiHance	100%	100%	-	-
04-001	Vasovist	100%	75% - <90%	-	-
	MultiHance	not evaluable***	75% - <90%	-	-

* very bad image quality
** not in FOV
*** complete occlusion

3.2 Lenght (mm)

Pat. ID	CM	int. carotid a. left	int. car. a. right	ext. car. a. left	vertebr. a. right
01-001	Vasovist	.	12		.
	MultiHance	12	.		3
01-002	Vasovist	10	.		.
	MultiHance	11	.		.
01-003	Vasovist	.	4		.
	MultiHance	.	3		.
01-004	Vasovist	2	8		.
	MultiHance	2	7		.
01-005	MultiHance	2	.		.
	Vasovist	2	.		.
01-007	Vasovist	.	.		.
	MultiHance	.	.		.
01-008	Vasovist	.	.		.
	MultiHance	.	.		.
02-002	Vasovist	5	.		.
	MultiHance	5	.		.
02-003	MultiHance	.	.		.
	Vasovist	.	2		.
05-001	MultiHance	.	.		.
	Vasovist	.	.		.
05-002	Vasovist	.	.		.
	MultiHance	.	.		.
04-001	Vasovist	4	.		.
	MultiHance	.	5		.

4. Signal intensity measurements

4.1 Examinations with Vasovist

Localization: Internal carotid artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	610.8	421.2	533.0	284	711	165	1784
Pre stenosis, SD	12	25.2	24.0	15.0	11	24	4	82
Post stenosis, mean	6	444.8	160.9	446.5	-	-	229	673
Post stenosis, SD	6	38.8	32.7	32.5	-	-	7	95

Localization: External carotid artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	639.8	433.9	467.0	348	600	246	1557
Pre stenosis, SD	12	56.3	60.4	33.5	19	61	5	222
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: Middle cerebral artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	458.1	326.9	347.5	261	546	112	1356
Pre stenosis, SD	12	61.1	41.4	42.0	31	67	21	145
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: Circle of Willis

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	539.0	344.2	459.0	358	544	175	1524
Pre stenosis, SD	12	63.9	64.2	35.5	22	78	12	219
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: Surrounding artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	56.5	28.7	55.0	33	69	26	111
Pre stenosis, SD	12	13.3	14.5	9.0	5	12	1	55
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: background noise example

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	21.9	14.8	15.0	11	28	8	49
Pre stenosis, SD	12	6.9	6.0	5.0	2	6	1	18
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

4.2 Examinations with MultiHance

Localization: Internal carotid artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	551.8	421.7	465.5	189	516	163	1665
Pre stenosis, SD	12	22.3	18.2	17.5	8	23	5	65
Post stenosis, mean	6	323.2	84.6	328.5	-	-	176	429
Post stenosis, SD	6	42.7	32.9	39.5	-	-	7	95

Localization: External carotid artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	532.3	407.4	401.5	206	540	204	1571
Pre stenosis, SD	12	60.2	65.1	55.0	16	65	4	251
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: Middle cerebral artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	458.0	331.9	320.0	243	360	186	1282
Pre stenosis, SD	12	58.7	48.1	49.0	17	74	12	189
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: Circle of Willis

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	566.1	362.7	463.5	376	530	159	1334
Pre stenosis, SD	12	54.3	54.2	40.0	23	54	13	215
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: Surrounding artery

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	51.1	22.1	47.0	35	55	19	91
Pre stenosis, SD	12	15.9	14.8	11.0	7	12	5	57
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

Localization: background noise example

Value	n	Mean	SD	Median	Q1	Q3	Min	Max
Pre stenosis, mean	12	25.2	16.7	19.5	14	27	9	62
Pre stenosis, SD	12	6.2	5.7	5.0	3	6	1	23
Post stenosis, mean	0	-	-	-	-	-	-	-
Post stenosis, SD	0	-	-	-	-	-	-	-

5. Diagnostic confidence (in segments with stenoses)

Pat. ID	CM	int. car. a. left	int. car. a. right	ext. car. a. left	vertebr. a. right
01-001	Vasovist	1	1	1	1
	MultiHance	1	2	1	1
01-002	Vasovist	1	1	1	1
	MultiHance	1	1	1	1
01-003	Vasovist	1	1	1	1
	MultiHance	1	1	1	1
01-004	Vasovist	2	2	2	2
	MultiHance	1	1	1	2
01-005	MultiHance	2	2	1	2
	Vasovist	1	1	1	1
01-007	Vasovist	1	1	1	1
	MultiHance	1	1	1	1
01-008	Vasovist	1	1	1	1
	MultiHance	1	1	1	1
02-002	Vasovist	2	3	2	2
	MultiHance	2	3	2	3
02-003	MultiHance	1	1	1	1
	Vasovist	1	1	1	2
05-001	MultiHance	1	1	1	1
	Vasovist	1	1	1	1
05-002	Vasovist	1	1	1	1
	MultiHance	2	2	2	2
04-001	Vasovist	1	1	1	1
	MultiHance	1	1	1	1

1 = very confident
2 = confident
3 = not confident
4 = not confident at all

Patient-related summary:
Vasovist-images more confident than MultiHance-images: 4x
MultiHance-images more confident than Vasovist-images: 2x
No difference: 6x

6. Assessment of the overall diagnostic confidence

Vasovist images

	n	%	Random number
very confident	9	75.0	1,4,7,16,19,25,28,31,45
confident	3	25.0	10,13,22
not confident	0	0.0	
not confident at all	0	0.0	
Total	12	100.0	

MultiHance images

	n	%	Random number
very confident	10	83.3	2,5,8,11,14,17,20,26,29,46
confident	1	8.3	32
not confident	1	8.3	23
not confident at all	0	0.0	
Total	12	100.0	

7. Comparison of images

Available settings:
2x comparison MRA1/MRA2/DSA
11x comparison MRA1/MRA2

7.1 Vasovist-MRA vs. MultiHance-MRA, visibility of vessels

	n	%	Random number
Vasovist better	7	63.6	35,36,37,40,41,43,44
no difference	1	9.1	39
MultiHance better	3	27.3	34,42,48
Total	11	100.0	

WILCOXON test for paired differences: n.s. ($p < 0.10$)

7.2 Vasovist-MRA vs. MultiHance-MRA, diagnostic confidence

	n	%	Random number
Vasovist better	5	45.5	35,36,40,41,43
no difference	5	45.5	34,37,39,42,44
MultiHance better	1	9.1	48
Total	11	100.0	

WILCOXON test for paired differences: n.s. ($p < 0.10$)

7.3 Vasovist-MRA vs. MultiHance-MRA, visual impression of contrast intensity

	n	%	Random number
Vasovist better	8	72.7	35,36,37,39,40,41,43,44
no difference	2	18.2	34,48
MultiHance better	1	9.1	42
Total	11	100.0	

WILCOXON test for paired differences: $p < 0.05$

7.4 Vasovist-MRA vs. MultiHance-MRA, assessment of stenoses

	n	%	Random number
Vasovist better	4	36.4	35,36,41,43
no difference	6	54.5	34,37,39,40,42,44
MultiHance better	1	9.1	48
Total	11	100.0	

WILCOXON test for paired differences: n.s. ($p < 0.10$)

7.5 Is there any additional diagnostic information visible in comparison of Vasovist-MRA and MultiHance-MRA

	n	%	Random number
Yes	0	0.0	
No	11	100.0	34,35,36,37,39,40,41,42,43,44,48
Total	11	100.0	

7.6 MRA vs. DSA, diagnostic confidence

	n	%	Random number
Vasov. better than DSA	0	0.0	
no difference	1	50.0	44
DSA better than Vasov.	1	50.0	48
Total	2	100.0	

	n	%	Random number
MultiH. better than DSA	0	0.0	
no difference	1	50.0	44
DSA better than MultiH.	1	50.0	48
Total	2	100.0	

7.7 MRA vs. DSA, assessment of stenoses

	n	%	Random number
Vasov. better than DSA	0	0.0	
no difference	1	50.0	44
DSA better than Vasov.	1	50.0	48
Total	2	100.0	

	n	%	Random number
MultiH. better than DSA	0	0.0	
no difference	1	50.0	44
DSA better than MultiH.	1	50.0	48
Total	2	100.0	

Conclusion

In this study a total of 12 patients could be completely assessed on the bases of an intraindividual comparision between Multihance® and Gadovist® for the evaluation of high grade carotid artery disease.

The patient recruitment for this study was prolonged because of the intraindividual comparative design and the fact that the two examinations should be close together in time but without a therapeutic intervention in between. As most of the patients with subtotal or ultrahigh stenoses present with acute clinical symptoms a second examination under these regulations are difficult to achieve.

With the expiration of the available drug the study was finalized in July 2011.

Based on the available imaging data (24 MRI studies and 2 DSA studies) a blinded read analysis was performed.

Even the number of subjects is small a significant better SNR and CNR for the Vasovist studies could be confirmed for the majority of assessed vessel segments.

Also the visual impression of the intensity of enhancement was superior for the Vasovist examinations.

In the assessment of stenoses there was an advantage for Vasovist® over Multihance®, however, due to the small number of subjects, the comparison was not significant.

The same was observed for the visibility of vessel segments and the diagnostic confidence of the MRA studies.

Both contrast media proved to be safe as during the study no SAE´s or any other side effects were observed.

In conclusion Vasovist proved to be a safe and effective contrast media for studies of the supraaotic vasculature. Even with a small number of subjects examined a superior vessel contrast and visual impression of the vascular contrast could be shown. There was a clear trend for a better visibility of vessel segments and an improved diagnostic confidence.