EUROPEAN CLINICAL CONTROLLED TRIAL
Study Report (#2510) (PEDIATRIC EXCRETORY UROGRAPHY)
Protocol #DXV037 PIVOTAL 1

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Study Design - This was a phase-3, multicenter, double-blind, comparative, parallel group clinical trial in pediatric patients referred for excretory urography. This study report consists of one protocol (DXV037) with a three different clinical trials conducted under this protocol supported the safety & efficicay of the drug. The demographic characteristics are as follows:

Demographic Characteristics		VIS-270 mgI/mL			VIS-320 mgI/mL			OMN-300 mgI/mL		
Total Patients. (N=72)		<2 yrs (11)	>2 yrs (11)	Total (22)	<2 yrs (13)	>2 yrs (12)	Total (25)	<2 yrs (11)	>2 yrs (14)	Total (25)
Gender (m/f)	42/30	7/4	6/5	13/9	9/4	6/6	15/10	8/3	6/8	14/11
Age (months)										
Mean	51.4	7.7	91.4	49.5	7.8	85.6	45.1	6.0	101.2	59.3
Min/Max										
Weight (kg)										
Mean	17,46	8.35	24.37	16.36	7.22	27.29	16.86	7.26	28.29	19.04
Min/Max										
Height (cm)										
Mean	95.6	68.1	122.5	95.3	65.3	121	92.0	64.7	126.5	99.3
Min/Max										
Race										
Caucasian	68	10	11	21	13	12	25	8	14	22
Black	2	0	0	0	0	0	0	2	0	2
Oriental	1	1	0	1	0	0	0	0	0	0
Other	1	0	0	0	0	0	0	1	0	1
	72			22			25			25

Reviewer's Comment - There were no statistically significant differences in gender, age, weight or height between the two contrast agent groups. Race however, was unevenly distributed.

Medications - With respect to medication profiles were similar between the contrast groups. The number of patients who received medications other than contrast agents (see Table below):

Medication Received		VISIPAQUE 270 mgI/mL	VISIPAQUE 320 mgI/mL	OMNIPAQUE 300 mgI/mL
24 hrs prior to Exam.	Yes/No	12/10	8/17	7/18
Premedication	Yes/No	1/21	1/24	0/25
During Examination	Yes/No	0/22	0/25	0/25
Post-procedural	Yes/No	0/22	2/23	0/25

Patient withdrawal - No patients were withdrawn from the trial and the drug code was not broken for any of the patients.

History of Risk Factors - The family histories are tabulated below:

A Patient May Have More Than One Risk Factor

Relevant Family History	VISIPAQUE 270 mgI/mL	VISIPAQUE 320 mgI/mL	OMNIPAQUE 300 mgI/mL
Allergy/Hypersensitivity	3	5	1
Asthma	3	5	3
Diabetes Mellitus	0	1	0
None	18	15	22

Protocol Deviations - There were three patients (#211, 232 and 315), all in the VIS-270 group that had technical difficulties (vein disruption). Data from these patients were included in all analyses.

Injection Information - The total volume was given between 6 & 50 mL of contrast agents in all study groups. All pediatric patients received contrast agents only once. The mean volume of VIS-270 mgI/mL was 23.6 mL = 6.4 gI (0.43 gI/kg bw), and for VIS-320 mgI/mL was given 24.4 mL = 7.8 gI (0.56 gI/kg bw) and versus 27.7 mL = 8.3 gI (0.49 gI/kg bw) for the OMN-300 mgI/mL. The dosage of contrast agent administered was indicated by volume, total dose of iodine, and gI/kg bw as follows:

Drug & Weight Group	Total (N)	Total Volume(mL) Mean	Min	Max	(n)	Total Dose Iodine(gI) Mean	Min	Max	(n)	Body Weight(kg) Mean	Min	Max	(n)
VIS-270: 7-10 kg (2)	5	15.2			5	4.1			5	0.48			5
<7 " (1)	3	8.0			3	2.2			3	0.46			3
>20 " (4)	4	43.0			4	11.6			4	0.32			4
>10-20" (3)	10	24.7			10	6.7			10	0.44			10
Total	22	23.6			22	6.4			22	0.43			22
VIS-320: 7-10 kg (2)	7	15.3			7	4.9			7	0.61			7
<7 " (1)	5	11.0			5	3.5			5	0.73			5
>20 " (4)	8	42.9			8	13.7			8	0.43			8
>10-20 " (3)	5	21.2			5	6.8			5	0.51			5
Total	25	24.4			25	7.8			25	0.56			25
OMN-300: 7-10 kg (2)	3	16.7			3	5.0			3	0.58			3
<7 " (1)	6	11.0			6	3.3			6	0.60			6
>20 " (4)	9	46.2			9	13.9			9	0.41			9
>10-20 " (3)	7	23.0			7	6.9			7	0.47			7
Total	25	27.7			25	8.3			25	0.49			25

Reviewer's Comment - No disagreement with the sponsor's analysis. However, there is much confusion and disorderly arranged sequence of the weight group from 0 to 20 kg observed in the above tabulation (ref. Table 5a, p199).

Efficacy Results - Efficacy was assessed by evaluating the diagnostic data provided by the contrast-enhanced images for four different anatomical areas (renal parenchyma, calyces, pelvis and ureter) at four different time points. In addition, an overall diagnostic information was rated based on 4-point scale (excellent, good, poor and inadequate). The assessments of the quality of the overall diagnostic images for both right and left kidneys are as follows:

Diagnostic Information		VIS-270	VIS-320	OMN-300
Overall Lt Kidney	Excellent	10	13	8
	Good	8	12	13
	Poor & Inadequate	4	0	4
Overall Rt Kidney	Excellent	12	15	11
	Good	9	8	13
	Poor & Inadequate	1	2	1
Contrast enhancement confirm the diagnosis		22	23	24
Contrast enhancement ruled out the diagnosis		0	2	1

Reviewer's Comment - No disagreement with the sponsor's analysis. The overall image quality results showed no significant differences between the three drug groups.

Safety Results:

Vital Signs - Both systolic/diastolic blood pressure and pulse rate were measured immediately prior to and immediately after injection and at the end of the procedure. No significant change in mean values of vital signs was observed in either dose group. Only one patient (#317) in the VIS-320 group had vital signs changes (from baseline value of mmHg mmHg postcontrast administration) which lasted about 30 minutes. This patient also experienced periorbital edema of the left eye with severe intensity that lasted for ten hours. Medical attention was provided.

Laboratory Parameters - I noticed that none of the three study centers had any laboratory parameters evaluated.

Adverse Events - No serious adverse events were encountered in the patients studied. A total of five patients (#332 in the VIS-270 group, #11, #316, #317 in the VIS-320 group and #338 in the OMN-300 group) experienced adverse events from mild to severe intensity. There were three patients in the VIS-320 (higher concentration) group that had moderate-severe adverse events as compared to lower cencentration drug groups.

Number of Patient (5)	VIS-270 (N=1)			VIS-320 (N=3)			OMN-300 (N=1)		
Body As A Whole	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Fever	1			1					
Periorbital edema						1			
Erythema				1					
Pruritus								1	
Transient HTN					1				
	1			2	1	1		1	

Note: A patient may have had more than one kind of adverse event.

Reviewer's Comment:

Despite the lack of laboratory measurements, however, the overall results of this clinical trial, comparing VISIPAQUE versus OMNIPAQUE contrast agent during intravenous urography suggests that the effectiveness and general safety profile of Visipaque 270 and 320 mgI/mL appears comparable to Omnipaque 300 mgI/mL.

EUROPEAN CLINICAL CONTROLLED TRIAL
Study Report (#2513) (PEDIATRIC EXCRETORY UROGRAPHY)
Protocol #DXV041 PIVOTAL 2

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Study Design - This was a phase-3, randomized, parallel, double-blind comparison between VIS-270 mgI/mL, VIS-320, and OMN-300 mgI/mL; (including an open phase-2 pilot study with three VIS-320 patients). The objective of the study was to compare VISIPAQUE and OMNIPAQUE regarding safety and efficacy in pediatric patients requiring excretory urography. The demographic characteristics are as follows:

Demographic Characteristics		VIS-270 mgI/mL			VIS-320 mgI/mL			OMN-300 mgI/mL		
Total Patients. (N=75)		<2 yrs (9)	>2 yrs (16)	Total (25)	<2 yrs (6)	>2 yrs (19)	Total (25)	<2 yrs (8)	>2 yrs (17)	Total (25)
Gender (m/f)	34/41	3/6	7/9	10/15	4/2	9/10	13/12	4/4	7/17	11/14
Age (months) Mean	49.6	11.6	65.3	45.9	11.3	73.3	58.4	12.8	59.2	44.4
Min/Max										
Weight (kg) Mean	16,9	9.4	19.8	16.0	8.6	22.3	19.0	9.8	18.6	15.8
Min/Max										
Height (cm) Mean	103.5	76.3	116.1	101.8	70.6	119.8	108.6	77.4	111.6	100.7
Min/Max										
Race										
Caucasian	70	9	15	24	5	17	22	7	17	24
Black	3	0	0	0	0	2	2	1	0	1
Oriental	2	0	1	1	1	0	1	0	0	0
Total	75			25			25			25

Reviewer's Comment - There were no statistically significant differences in gender, age, weight or height between the contrast agent groups. However, race was unevenly distributed. Note: The three pilot patients were all Caucasian females. Their age varied between and their weight from One received VIS-270, whereas the other 2 received VIS-320.

Medication - Approximately one third of the patients had used medication prior to injection and the majority of these patients had received prophylactic medication for urinary tract infections.

Patient withdrawal - No patients were withdrawn from the trial and the drug code was not broken for any of the patients.

History of Risk Factors - In the pilot group, all of the three patients had a relevant family history of allergy and hypersensitivity. In the phase-3 group, the most high-risk factors are tabulated below:

A Patient May Have More Than One Risk Factor

Relevant Family History	VISIPAQUE 270 mgI/mL	VISIPAQUE 320 mgI/mL	OMNIPAQUE 300 mgI/mL
Allergy/Hypersensitivity	12	14	9
Asthma	3	5	2
Others	0	1	1
None	12	7	13

Injection Information - The total volume was given between mL of VIS-270 group, between mL of VIS-320 group, and between mL for the OMN-300 mgI/mL group. The dosage of contrast agent administered was indicated by volume, total dose of iodine, and gI/kg bw as follows:

Drug & Weight Group	Total (N)	Total Volume(mL) Mean	Min	Max	(n)	Total Dose Iodine(gI) Mean	Min	Max	(n)	Body Weight(kg) Mean	Min	Max	(n)
VIS-270: 7-10 kg (2)	5	18.0			5	4.9			5	0.55			5
<7 " (1)	1	10.0			1	2.7			1	0.84			1
>20 " (4)	5	40.0			5	10.8			5	0.44			5
>10-20" (3)	14	33.0			14	8.9			14	0.54			14
Total	25	30.5			25	8.2			25	0.53			25
VIS-320: 7-10 kg (2)	3	20.0			3	6.4			3	0.83			3
<7 " (1)	1	10.0			1	3.2			1	1.07			1
>20 " (4)	8	40.5			8	13.0			8	0.45			8
>10-20 " (3)	13	32.2			13	10.3			13	0.63			13
Total	25	32.5			25	10.4			25	0.61			25
OMN-300: 7-10 kg (2)	4	20.0			4	6.0			4	0.73			4
<7 " (1)	1	15.0			1	4.5			1	0.71			1
>20 " (4)	4	40.0			4	12.0			4	0.45			4
>10-20 " (3)	16	31.2			16	9.3			16	0.61			16
Total	25	30.1			25	9.0			25	0.61			25

Reviewer's Comment:

No disagreement with the sponsor's analysis. Again, there is much confusion and disorderly arranged sequence of the weight group from kg observed in the above tabulation (ref. Table 5a, p158). Note: Three phase-2 pilot patients were also included in the above tabulation. The volumes administered were similar for three groups. The mean dose of gI/kg bw, was lowest in the VIS-270 group, whereas the dose was the same in the VIS-320 as in the OMN-300 mgI/mL group. This was due to the higher mean body weight (19.0 kg) in the VIS-320 mgI/mL group as compared to 15.8 kg for the OMN-300 mgI/mL group.

Efficacy Results - Efficacy was assessed by evaluating the diagnostic data provided by the contrast-enhanced images for four different anatomical areas (renal parenchyma, calyces, pelvis and ureter) at four different time points. In addition, an overall diagnostic information was rated based on 4-point scale (excellent, good, poor and inadequate). The assessments of the quality of the overall diagnostic images for both left and right kidneys are as follows:

Diagnostic Information	VIS-270 Lt & Rt		VIS-320 Lt & Rt		OMN-300 Lt & Rt		Total (Left	Right)
Excellent	19	19	21	22	14	16	54	57
Good	6	6	1	1	9	8	16	15
Poor	0	0	2	2	1	1	3	3
Inadequate	0	0	1	0	1	0	2	0
	(100%)	(100%)	(88%)	(92%)	(92%)	(96%)	(93%)	(96%)

Contrast Enhacement	VIS-270	VIS-320	OMN-300
Contrast enhancement confirm the diagnosis	12	14	12
Contrast enhancement ruled out the diagnosis	11	10	12
CE confirmed another diagnosis	3	1	2
CE did not allow comparison /c the diagnosis	1	0	0

Reviewer's Comment:

No disagreement with the sponsor's analysis. The overall image quality results graded as diagnostic and only few were non-diagnostic both in the VIS-320 and OMN-300 drug groups. There were no statistically significant differences between the three drug groups.

Safety Results:

Vital Signs - There were no clinically significant changes or trends in change from baseline value in any of the vital signs parameters. Although some individual variation was noticed, none of the change in vital signs measurements was considered to be a clinically relevant change from baseline value.

Laboratory Parameters:

Again, the blood chemistry and hematology parameters were not measured.

Adverse Events:

There were no serious adverse effects encountered in the patients studied. Note: No adverse event was reported in the VIS-270 mgI/mL group. Adverse events other than injection-associated discomfort presented in the Table below:

Number of Patient (6)	VIS-270 (N=0)			VIS-320 (N=4)			OMN-300 (N=2)		
Body As a Whole	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Fever								1	
Pain				1					
Nausea				1					
Vertigo				1					
Exanthema								1	
Itching				1					
				4				2	

Note: A patient may have had more than one kind of adverse event.

Reviewer's Comment:

In the absence of laboratory parameter measurements, however, the overall results of this clinical trial, comparing VISIPAQUE versus OMNIPAQUE contrast agent during intravenous urography suggests that the effectiveness and general safety of VIS-270, 320 mgI/mL appears comparable to OMN-300 mgI/mL.

INTEGRATED SUMMARY OF SAFETY AND EFFICACY

This summary presents an overview of the safety and efficacy results from clinical trials conducted in pediatric patients (newborn to 18 years of age) with known or suspected diseases to evaluate the diagnostic utility and safety of an intravascular (IA & IV) administration of Visipaque contrast agents.

Cardioangiography - Three pediatric clinical trials (phase-1 & phase-3 combined):

A total of 246 (131 males and 115 females) patients were studied. Visipaque 320 mgI/mL was given to 161 patients (86 males and 75 females), aged . (mean 2.43 years) and weighing (mean 11.08 kg). Omnipaque 350 mgI/mL was given to 85 (45 males and 40 females), aged (mean 2.8 years) and weighing (mean 12.37 kg). The values for the demographic parameters were generally similar between the groups for the age-groups 0-<29 days and 29 days-<2 years. For the age-group 2-<12 years, the values for mean age, weight, and height were slightly higher in the 0MN-350 group than in the VIS-320 group. The volume of Visipaque administered was (mean 46.9 mL) = (mean 15.0 gI) or (mean 4.7 mL/kg), and Omnipaque was given a total of (mean 48.1 mL) = (mean 16.8 gI) or (mean 4.79 mL/kg) intraarterially.

The statistical analysis revealed that there was no significant difference for gender, age, and weight between study centers and drug groups, except race was unevenly distributed. No statistically significant differences were evident between the two drug groups relative to the mean total volume of contrast agent administered.

Intravenous indications are; CT scanning of the Head/Body and Excretory urography:

A total of 448 (231 males and 217 females) patients were enrolled in 6 phase-3 pivotal clinical trials across three intravenous indications. Three patients were randomized to the clinical trial but not dosed, therefore no safety analysis was considered.

A total of 298 patients (144 males and 154 females) were studied in the Visipaque 270 and Visipaque 320 mgI/mL contrast groups and 150 patients (81 males and 69 females) for Omnipaque 300 mgI/mL contrast group. Visipaque 270 mgI/mL was given to 144 patients (78 males and 66 females), aged (mean 5.38 years) and weighing (mean 21.18 kg). Visipaque 320 mgI/mL was given to 154 patients (88 males and 66 females), aged (mean 5.45 years) and weighing (mean 21.21 kg). Omnipaque 300 mgI/mL was given to 150 patients (81 males and 69 females), aged years (mean 5.56 years) and weighing , (mean 21.63 kg). No statistically significant differences with respect to overall males and females in each drug group. There were no statistically significant differences observed with regard to mean gender, age and weight across the 3 indications. The majority of the patients were Caucasian: 83% in the VIS-270 group, 79% in the VIS-320 group and 81% in the OMN-300 group. Race however, was unevenly distributed.

The volume of Visipaque 270 administered was (mean 43.7) = (mean 11.80 gI) or (mean 2.05 mL/kg), Visipaque 320 mgI/mL was given a total of mean 43.9 mL) = (mean 14.06 gI) or (mean 2.10 mL/kg) and Omnipaque 300 mgI/mL was given a total of (mean 44.7 mL) = (mean 13.42 gI) or (mean 2.08 mL/kg) intravenously. No statistically significant differences were observed among the groups for the overall distribution of total volume, total dose and mL/kg based on body weight.

Demographic information from all concentrations of both contrast media were combined (ref. Table 6.2A.Vol.27.p87 attached). There was a statistically significant difference in mean age between the 4 indications for both contrast media combined (p=0.0001). Angiocardiography patients (mean age 2.6 years) were much younger than any other indication, and CT scanning of the patients (mean 7.1 years) were older than the angiocardiography , CT scanning of the body (mean age 5.2 years) & excretory urography patients (mean age 4.2 years), respectively. These differences between the indications were consistent within all the Visipaque and Omnipaque groups. There was no statistically significant difference in gender between indication and drug groups. Race, however, were unevenly distributed across the indications.

Dose Information from all concentrations of both contrast media were combined (ref. Table 6.3. p95 attached). The mean total volume and mean total dose for both contrast media combined was statistically significantly different among the indications (p-0.0001). The mean total volume and mean total dose were significantly greater in the CT scanning of the head indication (65.3 mL or 19.44 gI) than for any other indication, and the mean total volume and mean total dose in the angiocardiography indication (47.3 mL or 15.65 gI) were greater than CT scanning of the body indication (37.9 mL or 11.22 gI) or excretory urography indication (28.8 mL or 8.56 gI), respectively. This was consistent within the all Visipaque and Omnipaque groups. The rate of injection of the contrast media was significantly faster in angiocardiography than for any other intravenous procedures (p-0.0001), as would be expected based on the nature of the procedure.

Safety Summary:

Safety was assessed by measuring vital signs, serum chemistry, urine laboratory parameters, ECG, neurological examinations and adverse events at varying time intervals up to 40-56 hours after the contrast administration.

STUDY SCHEMA

Intraarterial Angiocardiography	Pre-injection Baseline	Post-injection 30sec	60sec	120 sec	180sec	End of Procedure	16-32hr	40-56hr
Systolic/Diastolic BP	x	x	x	x	x	x	x	
Pulse Rate	x	x	x	x	x	x	x	
ECG (lead 11)	x	(continuously)						
Serum Measurements	x						x	
(Serum creatinine)	x							x
Urine Measurements	x						x	
Adverse Events	x					x	x	x
IV(CT Head/Body & EU)								
Systolic/Diastolic BP	x					x	x	
Pulse Rate	x					x	x	
Serum Measurements	x (P-9998-011 and -012 only)						x	
Neurological Exam.	x (P-9998-011 only)						x	
Adverse Events	x					x	x	x

Note: No laboratory work done in excretory urography (study #1 & #2) and CT scanning of the body (pivotal 2).

Hemodynamics (Angiocardiography only) - For each patient, hemodynamic changes from baseline were measured for systolic/diastolic blood pressure and heart rate data. The largest changes from baseline for each trial are summarized, by group and stratified by age-group (see Appendices 3.102 and 3.104). There were no major differences in the frequences of changes in hemodynamic measurements when analyzed, by group and stratified by age-group, although patients in the age-group 0-<29 days had fewer changes compared with patients in the age-groups 29 days-<2 years or 2-<12 years in both groups. Five patients in the 39998-013 clinical trial (001-0186, 003-0355 in the VIS-320 group, 002-0281, 003-0303, 003-0311 in the OMN-350 group) had clinically relevant changes in hemodynamic but no trends were observed.

Vital signs:

Angiocardiography - Overall, there were no clinically significant trends in the vital sign parameters with either contrast medium observed. Although, more increases than decreases of vital signs parameters in each drug group were observed, but there was no meaningful difference between the two contrast groups.

Intravenous Route - Across all three intravenous indications, a total of 18 patients had changes in vital sign parameters that were considered to be clinically significant. In trial DXV039, there were 17 patients underwent CT scanning of the head (6 in the VIS-270 group, 5 in the VIS-320 group and 6 in the OMN-300 group) and one patient (VIS-320 group) underwent excretory urography trial. Overall, there were no clinically relevant trends in vital signs changes observed in any group, between groups or among indications.

Electrocardiography (ECG)

ECG tracing was recorded for the phase-1 and phase-3 clinical trials. There were no clinically significant differences observed in either individual percent changes from baseline in PR, RR intervals, corrected QT, ST-segment or T-wave amplitude among injection sites within each group. In the (013) trial, there were four patients (002-0209, 003-0355 in the VIS-320 group, 003-0353, 003-0358 in the OMN-350 group) had post-injection ECG changes. Another two patients (1 in trial DXV036, 1 in trial 39998-018) also experienced a change in ECG measurements after the contrast administration. There were no ECG measurements performed in the intravenous indications.

Arrhythmias (Angiocardiography only) - The incidence of arrhythmia for each trial, and for all trials combined, by group and stratified by age-group, is presented in Appendices 3.11.1-4. In clinical trials 39998-013, and DXV036, twenty patients in the VIS-320 group & 8 patients in the OMN-350 group experienced at least one post-injection arrhythmia, occurring most frequently after LV injection. In both groups, the arrhythmias occurred most frequently in patients in the age-group 2 to <12 years. One post-injection arrhythmia was reported as an adverse event in trial 39998-018.

Laboratory Measurements:

Angiocardiography - The summary statistics for laboratory values and changes from baseline, shift tables and scatterplots of changes from baseline indicated no clinically significant trends for either contrast agent. Number of patients with increases and/or decreases from baseline values greater than 40% of the reference range at any post-injection time point is shown in Tables 7.5A, B, and C for the 2 US trials (#39998-013, #39998-018), the European trial (#DXV036) and all 3 clinical trials combined, respectively, by group. There were no trends observed within or across groups for any specific abnormal hematology, serum or urine chemistry parameters. In trial 39998-013, however, 2 patients (VIS-320 group) had post-injection increases in serum creatinine values that were greater than 80% of the reference range. In trial DXV036, one patient (OMN-350 group) had serum creatinine value changes with unknown etiology.

Intravenous indications - Laboratory measurements were taken for all patients in two clinical trials (p39998-011, and -012). Another trial (DXV038) in the CT scanning of the body, only a limited number of patients participated. No actual analysis was provided. Although, some individual variation was noticed, no clinically significant changes or trends were observed (See ref. Table 8.5A).

Neurologic examination was conducted for patients in trial p39998-011 (CT scanning of the head) only. Neurologic examinations were not performed in any of the other intravenous trials. There were no clinically significant changes from baseline observed in the neurologic examinations performed at any post-injection time point in any of the 3 contrast groups.

Deaths - Overall, six deaths have been reported (see Table below):

Group Trial No./ Patient ID	Adverse Event	(Onset)	Post-contrast Duration	Intensity	Relationship to Contrast Agent
Angiocardiography					
VIS-320					
39998-018/ (002-0005)	ARF	31 hours	25 days	Severe	Probably
39998-013/ (002-0209)	HF	2 days	10 hours	" "	Probably
39998-013/ (001-0181)	Sepsis	14 days	13 days	" "	Not related
39998-013/ (001-0184)	MI & Sepsis	4 days	1 day	" "	Not related
OMN-350					
39998-013/ (002-0210)	ARF, DIC, HF	1 day	3 days	" "	Probably
Intravenous indication					
VIS-270					
39998-012/ (003-0753)	Pul. edema	3 days	6 days	" "	Uncertain

De-note: MI=Myocardial infarction, ARF=Acute renal failure, DIC=Disseminated intravascular coagulation.

Reviewers Comment:

Death after angiocardiography procedure occurred in 5 (1.1%) of 446 Visipaque patients and one (0.5%) of 235 Omnipaque patients. Deaths within 10 hours to 24 days. It seems that few more deaths occurred in the Visipaque group than in the Omnipaque group. Acute renal failure patients; one in each drug group.

Adverse events other than deaths:

Incidence of individual adverse events reported after Visipaque and Omnipaque injection in controlled clinical trials (including phase-1 intraarterial injection) in pediatric intravascular indications.

All adverse events reported are included and are irrespective of drug relationship. If a patient had multiple occurrences of the same event, it is only counted once. If a patient had more than one different type of event, it is counted under each event type.

Intraarterial Injection - (including Phase-1 39998-018, Angiocardiography 39998-013/DXV036, 39998-011/DXV039) see Tables A & B below:

Table A: Summary of the incidence of individual adverse events reported after Visipaque and Omnipaque injection in United States and European clinical trials by centers

	Phase - 1	Phase - 3			
Protocol	(39998-018)	(39998-013 &DXV036)		(39998-011 & DXV039)	
No. of Pts (N=248)	43	117		88	
Contrast Agent	VIS-320	VIS-320(N58)	OMN-350(N59)	VIS-320(N62)	OMN-350(N26)
Adverse Events					
Vomiting	5 (12%)	2	2	7	3
Nausea	3 (7%)	1			
Anemia	4 (9%)			1	
Arrhythmia	3 (7%)	2	4	17	6
Apnea	1				
Asphyxia				1	
Cough				1	
Cardiac arrest	1				
Convulsion	1				
Cardiogenic shock		1	1		
Cyanosis				1	
DIC			1		
Flushing		1	1		
Fever	1	3	1	2	
Headache				1	
Hypotension				1	
Hypokalemia	2				
Hyponatremia	1				
Hypoxia	1				
Leukocytosis	1				
Lung Collapse	1				
Pain				1	1
Renal failure	1	1	1		
Rash	1	2			
Others				3	2
	27	13	11	36	12

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Table B: Summary of the incidence of individual adverse events reported after Visipaque and Omnipaque injection in United States and European clinical trials in Angiocardiography combined.

Contrast Agent No.of Pts (248) Adverse Events	Visipaque - 320 mgI/mL 163	Omnipaque - 350 mgI/mL 85
Vomiting	14 (8.6%)	5 (5.9%)
Nausea	4 (2.5%)	-
Anemia	5 (3.0%)	-
Arrhythmia	22 (13.5%)	10 (12%)
Fever	6 (3.6%)	1
Apnea	1	-
Asphyxia	1	-
Cough	1	-
Cardiac arrest	1	-
Convulsion	1	-
Cardiogenic shock	1	1
Cyanosis	-	1
DIC	-	1
Flushing	1	1
Headache	1	-
Hypotension	1	-
Hypokalemia	2	-
Hyponatremia	1	-
Hypoxia	1	-
Leukocytosis	1	-
Lung Collapse	1	-
Renal failure	2	1
Rash	3	-
Others	4	2
	76	23

Intravenous Indications - (Head CT 39998-011/DXV039, Body CT 39998-012/DXV038, EU DXV037/DXV041) see Tables C & D below:

Table C: Summary of the incidence of individual adverse events reported after Visipaque and Omnipaque injection in United States and European clinical trials by centers

Protocol	(39998-011 & DXV039)			(39998-012 & DXV039)			(DXV037 & DXV041)		
Total No./Pts (N=443)	150			146			147		
Contrast Agent	VIS-270	VIS-320	OMN-300	VIS-270	VIS-320	OMN-300	VIS-270	VIS-320	OMN-300
No. of Pts by Group	48	52	50	48	48	50	47	50	50
Adverse Events									
Vomiting	1		1		1	2			
Nausea	3		1		1	1		1	
Rash (maculopapular)		2							
Exanthema				1					1
Pruritus		2		1	1			1	1
Tiredness	1	1							
Transient hypertension								1	
Transient hypotension				1		1			
Shortness of breath				1					
Pulmonary edema				1					
Erythema		1						1	
Urticaria	1								
Muscle contractions				1					
Sweating					1				
Fever							1	1	1
Vertigo								1	
Periorbital edema								1	
Taste perversion				1					
Warmth feeling						1			
Others(Misc)			1					1	
	6	6	3	7	4	5	1	8	3

Table D: Summary of the incidence of individual adverse events reported after Visipaque and Omnipaque injection in United States and European clinical trials in three intravenous indications combined.

Total No. of Pts. (443)					
Contrast Agent	VIS - 270	VIS - 320	OMN - 300	VISIPAQUE	/ OMNIPAQUE
No. of Pts by Group	143	150	150	293	150
Adverse Events					
Vomiting	1	1	3	2	3
Nausea	3	2	2	5	2
Rash (maculopapular)		2		2	
Exanthema	1		1	1	1
Pruritus	1	4	1	5	1
Tiredness	1	1		2	
Transient hypertension		1		1	
Transient hypotension	1		1	1	1
Shortness of breath	1			1	
Pulmonary edema	1			1	
Erythema		2		2	
Urticaria	1			1	
Muscle contractions	1			1	
Sweating		1		1	
Fever	1	1	1	2	1
Vertigo		1		1	
Periorbital edema		1		1	
Taste perversion	1			1	
Warmth feeling			1		1
Others(Misc)		1	1	1	1
	14	18	11	32	11

Table E: Summary of the incidence of individual adverse events reported after Visipaque and Omnipaque injection in United States and European clinical trials by intravascular indications combined.

	INTRAARTERIAL TRIALS		INTRAVENOUS TRIALS		ALL TRIALS COMBINED	
Contrast Agent	VISIPAQUE	OMNIPAQUE	VISIPAQUE	OMNIPAQUE	VISIPAQUE /	OMNIPAQUE
No. of Pts by Group	163	85	293	150	456 (%)	235 (%)
Adverse Events						
Vomiting	14	5	2	3	16 (3.5%)	8 (3.4%)
Nausea	4	-	5	2	9 (2.0%)	7 (3.0%)
Anemia	5	-	-	-	5 (1.1%)	-
Arrhythmia	22	10	-	-	22 (4.8%)	10 (4.3%)
Fever	6	1	2	1	8 (1.8%)	2 (0.9%)
Rash (maculopapular)	3	-	2	-	5 (1.1%)	-
Exanthema	-	-	1	1	1	1
Pruritus	-	-	5	1	5 (1.1%)	1
Tiredness	-	-	2	-	2 (0.4%)	-
Transient hypertension	-	-	1	-	1	-
Transient hypotension	1	-	1	1	2	1
Hypokalemia	2	-	-	-	2	-
Hyponatremia	1	-	-	-	1	-
Hypoxia	1	-	-	-	1	-
Leukocytosis	1	-	-	-	1	-
Lung collapse	1	-	-	-	1	-
Shortness of breath	-	-	1	-	1	-
Pulmonary edema	-	-	1	-	1	-
Renal failure	2	1	-	-	2	1
Erythema	-	2	2	-	2	2
Urticaria	1	-	1	-	1	1
Apnea	1	-	-	-	1	-
Asphyxia	1	-	-	-	1	-
Cough	1	-	-	-	1	-
Cardiac arrest	1	-	-	-	1	-
Cardiogenic shock	1	1	-	-	1	1
Convulsion	1	-	-	-	1	-
Cyanosis	-	1	-	-	1	-
DIC	-	1	-	-	1	-
Flushing	1	1	-	-	1	1
Muscle contractions	-	-	1	-	1	-
Sweating	-	-	1	-	1	-
Headache	1	-	-	-	1	-
Vertigo	-	-	1	1	1	-
Periorbital edema	-	-	1	-	1	-
Taste perversion	-	-	1	-	1	-
Warmth feeling	-	-	-	1	-	1
Others(Misc)	4	2	1	1	5	3
	76	23	32	11	108	34

Reviewer's Comment:

The overall incidence of adverse events with Visipaque and Omnipaque in U. S. and European clinical trials in Tables A-E above. By comparison, the percentage of patients who reported adverse events after the administration of contrast agent was comparable between Visipaque and Omnipaque drug groups. However, a larger incidence of adverse events occurred in the Visipaque group (108) than in the Omnipaque group (34).

Table F: A summary of adverse events reported in all clinical trials combined, by Group and by Age-group presented by the sponsor below: Unfortunately, the adverse event information was incompletely tabulated.

Table F: Summary Of Adverse Events Reported In All Trials Combined, by Group and by Age-group

	All Visipaque Age-group				All Omnipaque Age-group			
Total No. Of Pts (N=694) Adverse Events	0-<29 days (26)	29D-<2 yrs (148)	2-<12 yrs (263)	12-<18 yrs (22)	0-<29 days (18)	29D-<2 yrs (72)	2-<12 yrs (129)	12-<18 yrs (16)
Vomiting	-	5 (3%)	11 (4%)	-	-	-	6 (5%)	1 (6%)
Nausea	-	1	6 (2%)	2 (9%)	-	-	2 (2%)	1 (6%)
Anemia	1 (4%)	3 (2%)	1	-	2 (11%)	-	-	-
Arrhythmia	-	1	-	-	-	-	1	-
Fever	1 (4%)	4 (3%)	3 (1%)	-	-	2 (3%)	-	-
Rash & (erythematousr)	2 (8%)	2 (1%)	3	-	-	.1	-	-
Renal failure	-	-	2 (1%)	-	-	1	-	-
Pruritus	-	-	5 (2%)	-	-	-	1	-
Tiredness	-	-	2	-	-	-	-	-
Hypokalemia	1 (4%)	1	-	-	1 (6%)	-	-	-
Hypoxia	1	-	-	-	-	1	-	-
Taste perversion	-	-	1	1	-	-	1	-
Somnolence	-	-	1	-	-	-	1	-

The sponsor failed to provide the following information?

Transient hypertension
Transient hypotension
Exanthema
Hyponatremia
Leukocytosis
Lung collapse
Shortness of breath
Pulmonary edema
Urticaria
Apnea
Asphyxia
Cough
Cardiac arrest
Cardiogenic shock
Convulsion
Cyanosis
DIC
Muscle contractions
Sweating
Headache
Vertigo
Periorbital edema
Warmth feeling (Flushing)
Others(Misc)

Efficacy Summary:

This summary presents an overview of the efficacy of Visipaque as an intravascular contrast agent for pediatric use. Eight (3 in the United States and 5 in the European trials) phase-3, double-blind, randomized, parallel-group clinical trials comparing the safety and efficacy of Visipaque to that of Omnipaque were studied in pediatric patients from newborn to 18 years of age. Another phase-1 trial was conducted in the U. S. but is not included in the efficacy analysis.

In each trial clinical, the contrast agent's contribution to making the radiographic diagnosis was documented. The quality of the contrast-enhanced radiographs was evaluated by both the investigator and, independently, by one additional board-certified or board eligible cardiologist/radiologist. The investigator and independent cardiologist/radiologist then met to reach a consensus and this consensus was recorded on the patient's case report form. The consensus radiographic diagnosis was recorded as both a code and a diagnosis name using the American College of Radiology's Index for Radiological Diagnosis.

A summary of the consensus ratings to the overall quality of enhancement (with 4-point scales) is tabulated in Tables below for both trials combined & each indication, respectively.

Angiocardiography - Two phase-3 randomized, parallel clinical trials were conducted in a total of 195 patients with ages ranging from for angiocardiography. The quality of the contrast-enhanced radiographs was evaluated by both on-site and off-site investigators. The rating scales for quality of visualization as used by the United States and European trials were identical.

Efficacy Results	Vis-320 mgI/mL (N=58)	Omn-350 mgI/,mL (N=59)
Angiocardiography		
Imaging Quality (good/excellent)	100%	98%
Increeased Confidence in diagnosis	48%	41%
Increased definition of vascular structure	78%	80%

CT Scanning of the Head - Two phase-3, clinical trials were conducted in a total of 150 pediatric patients with ages ranging from for contrast enhancement of the head. No statistically significant differences among contrast agent groups were observed for the analysis of imaging quality ratings.

Efficacy Results	Vis-270mgI/mL (N=48)	Vis-320mgI/mL (N=52)	Omn-350mgI/,mL (N=50)
Head CT			
Diagnostic (good/excellent)	100%	98%	98%

CT Scanning of the Body - Two phase-3, clinical trials were conducted in a total of 146 pediatric patients with ages ranging from for contrast enhancement of the body. No statistically significant differences between contrast groups were observed. The contrast agents provided good/excellent quality of visualization for 100% of the patients in Vis-270 group, 94% of the patients in Vis-320 group and 96% for the Omn-300 group.

Efficacy Results	Vis-270mgI/mL (N=48)	Vis-320mgI/mL (N=52)	Omn-350mgI/,mL (N=50)
Body CT			
Diagnostic (good/excellent)	100%	94%	96%

Excretory Urography - Two phase-3 (all from Europe) clinical trials were conducted in a total of 147 patients with ages ranging from for pediatric excretory urography. There were no statistically significant differences observed between the contrast agent groups or between the trials in the overall quality of visualization ratings for both right and left kidneys (see table below).

Efficacy Results	Vis-270mgI/mL (N=47)		Vis-320mgI/mL (N=50)		Omn-350mgI/,mL (N=50)	
Excretory Urography	Rt. K.	Lt. K.	Rt. K.	Lt. K.	Rt. K.	Lt. K.
Diagnostic (good/excellent)	100%	.96%	98%	100%	98%	98%

Reviewer's Comment:

The assessments of the quality of the overall diagnostic images for both intraarterial and intravenous indications are similar among the drug groups and centers. It is expected that imaging quality assessments were better graded for the on-site readers than with the off-site readers. A lower concentration of Visipaque-270 mgI/mL demonstrated imaging effectiveness similar to that of comparably higher concentrations of Visipaque-320 mgI/ml and Omnipaque-300 mgI/mL, respectively. With respect to dosage, however, children normally receive relatively higher doses of radio-contrast agent than adults (dose/kg bw), from a physiological and pathological standpoint.

ADDENDUM

An additional subset safety analysis was submitted by the Sponsor (see attachments):

A. Attachment 1 (p2-14) - Summary of the incidence of all individual adverse events reported after Visipaque and Omnipaque injection in U. S. & European studies combined.

B. Attachment 2 (p15-17) - Summary of adverse events reported in all clinical trials combined, by group and by age-group.

C. Attachment 3 (p18-25) - Identify statiscally significant different differences in all adverse event rates among the age groups (i.e. 0-<29 days, 29 days - <2 years, 2 years - <12 years and 12 years - <16 years).

D. Attachment 4 (p26-30) contains 3 items in response to our comment: A total of 113 of 296 patients (38%) were sedated prior to CT scanning. Please provide a subset analysis of adverse events for the patients who received pre procedure medication.

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
	TOTAL PATIENTS WITH NO ADVERSE EVENTS	169	83.25	98	88.29	224	87.50	112	90.32	393	85.62	210	89.36
	TOTAL PATIENTS WITH ADVERSE EVENTS	34	16.75	13	11.71	32	12.50	12	9.68	66	14.38	25	10.64
APPLICATION SITE DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	3	1.48							3	0.65		
	INJECTION SITE PAIN	2	0.99							2	0.44		
	INJECTION SITE REACTION	1	0.49							1	0.22		

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
BODY AS A WHOLE - GENERAL DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	4	1.97	1	0.90	8	3.13	4	3.23	12	2.61	5	2.13
	CRYING ABNORMAL							1	0.81			1	0.43
	FATIGUE					2	0.78			2	0.44		
	FEVER	4	1.97	1	0.90	4	1.56	1	0.81	8	1.74	2	0.85
	HOT FLUSHES							1	0.81			1	0.43
	PAIN					2	0.78	1	0.81	2	0.44	1	0.43

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)	N	%	N	%	N	%	N	%	N	%	N	%
CARDIOVASCULAR DISORDERS, GENERAL	TOTAL PATIENTS WITH ADVERSE EVENTS	1	0.49	1	0.90	1	0.39			2	0.44	1	0.43
	CARDIAC FAILURE	1	0.49							1	0.22		
	CYANOSIS					1	0.39			1	0.22		
	ECG ABNORMAL SPECIFIC			1	0.90							1	0.43
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	2	0.99			2	0.78			4	0.87		
	CONVULSIONS	1	0.49							1	0.22		

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	HEADACHE					1	0.39			1	0.22		
	MUSCLE CONTRACTIONS INVOLUNTARY	1	0.49							1	0.22		
	VERTIGO					1	0.39			1	0.22		
GASTRO-INTESTINAL SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	10	4.93	2	1.80	12	4.69	6	4.84	22	4.79	8	3.40
	ENTEROCOLITIS	1	0.49							1	0.22		
	MOUTH DRY					1	0.39			1	0.22		

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)	N	%	N	%	N	%	N	%	N	%	N	%
GASTRO-INTESTINAL SYSTEM DISORDERS	NAUSEA	5	2.46			4	1.56	3	2.42	9	1.96	3	1.28
	VOMITING	8	3.94	2	1.80	8	3.13	5	4.03	16	3.49	7	2.98
HEART RATE AND RHYTHM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	5	2.46	2	1.80					5	1.09	2	0.85
	ARRHYTHMIA	1	0.49							1	0.22		
	ARRHYTHMIA ATRIAL	1	0.49	1	0.90					1	0.22	1	0.43
	ARRHYTHMIA NODAL			1	0.90							1	0.43

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)	N	%	N	%	N	%	N	%	N	%	N	%
HEART RATE AND RHYTHM DISORDERS	ARRHYTHMIA VENTRICULAR	1	0.49							1	0.22		
	AV BLOCK	1	0.49							1	0.22		
	BUNDLE BRANCH BLOCK	1	0.49							1	0.22		
	TACHYCARDIA SUPRAVENTRICULAR	1	0.49							1	0.22		
METABOLIC AND NUTRITIONAL DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	2	0.99	2	1.80	1	0.39			3	0.65	2	0.85
	EDEMA PERIORBITAL					1	0.39			1	0.22		

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
METABOLIC AND NUTRITIONAL DISORDERS	HYPOGLYCEMIA	1	0.49							1	0.22		
	HYPOKALEMIA	2	0.99	1	0.90					2	0.44	1	0.43
	HYPONATREMIA	1	0.49	1	0.90					1	0.22	1	0.43
	HYPOPROTEINEMIA			1	0.90							1	0.43
PLATELET, BLEEDING & CLOTTING DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	2	0.99	2	1.80					2	0.44	2	0.85
	DIC			1	0.90							1	0.43

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
PLATELET, BLEEDING & CLOTTING DISORDERS	HEMORRHAGE NOS	1	0.49	1	0.90					1	0.22	1	0.43
	THROMBOSIS ARTERIAL LEG	1	0.49							1	0.22		
PSYCHIATRIC DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	1	0.49	1	0.90					1	0.22	1	0.43
	SOMNOLENCE	1	0.49	1	0.90					1	0.22	1	0.43
RED BLOOD CELL DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	4	1.97	2	1.80	1	0.39			5	1.09	2	0.85

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
RED BLOOD CELL DISORDERS	ANEMIA	4	1.97	2	1.80	1	0.39			5	1.09	2	0.85
RESISTANCE MECHANISM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	1	0.49							1	0.22		
	OTITIS MEDIA	1	0.49							1	0.22		
RESPIRATORY SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	5	2.46	1	0.90	1	0.39			6	1.31	1	0.43
	APNEA	1	0.49							1	0.22		
	ASPHYXIA					1	0.39			1	0.22		

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
RESPIRATORY SYSTEM DISORDERS	ATELECTASIS	3	1.48							3	0.65		
	COUGHING					1	0.39			1	0.22		
	DYSPNOEA	1	0.49							1	0.22		
	HYPOXIA	1	0.49	1	0.90					1	0.22	1	0.43
SKIN AND APPENDAGE DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	6	2.96			6	2.34	2	1.61	12	2.61	2	0.85
	PRURITUS	3	1.48			2	0.78	1	0.81	5	1.09	1	0.43

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
		N	%	N	%	N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)												
SKIN AND APPENDAGE DISORDERS	RASH	3	1.48							3	0.65		
	RASH ERYTHEMATOUS	1	0.49			3	1.17	1	0.81	4	0.87	1	0.43
	RASH MACULO-PAPULAR	1	0.49							1	0.22		
	SWEATING INCREASED					1	0.39			1	0.22		
	URTICARIA					1	0.39			1	0.22		
SPECIAL SENSES OTHER, DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS					3	1.17	1	0.81	3	0.65	1	0.43

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION									
		UNITED STATES				EUROPE				COMBINED	
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT	
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE	ALL OMNIPAQUE
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	TOTAL PATIENTS
		N=203		N=111		N=256		N=124		N=459	N=235
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)	N	%	N	%	N	%	N	%	N %	N %
SPECIAL SENSES OTHER, DISORDERS	PAROSMIA					1	0.39			1 0.22	
	TASTE PERVERSION					2	0.78	1	0.81	2 0.44	1 0.43
URINARY SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	2	0.99	1	0.90					2 0.44	1 0.43
	RENAL FAILURE ACUTE	2	0.99	1	0.90					2 0.44	1 0.43
VASCULAR (EXTRACARDIAC) DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	2	0.99							2 0.44	
	FLUSHING	1	0.49							1 0.22	

(CONTINUED)

INTRAVASCULAR TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR ALL FOUR INDICATIONS COMBINED, BY GEOGRAPHICAL LOCATION, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		GEOGRAPHICAL LOCATION											
		UNITED STATES				EUROPE				COMBINED			
		CONTRAST AGENT				CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=203		N=111		N=256		N=124		N=459		N=235	
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)	N	%	N	%	N	%	N	%	N	%	N	%
VASCULAR (EXTRACARDIAC) DISORDERS	PERIPHERAL ISCHAEMIA	1	0.49							1	0.22		
WHITE CELL AND RES DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	1	0.49							1	0.22		
	LEUKOCYTOSIS	1	0.49							1	0.22		

Intravascular: Summary of Adverse Events Reported for All Four Indications Combined, by Group and Stratified by Age-Group, N (%) [a]

	ALL VIS Age-Group				ALL OMN Age-Group			
Adverse Event	**0-<29 days**	**29 days-<2 years**	**2-<12 years**	**12-<18 years**	**0-<29 days**	**29 days-<2 years**	**2-<12 years**	**12-<18 years**
Total number of patients	26	148	263	22	18	72	129	16
Total number of patients with any adverse event	8 (31)	22 (15)	33 (13)	3 (14)	3 (17)	7 (10)	14 (11)	1 (6)
Adverse Event								
Vomiting	0	5 (3)	11 (4)	0	0	0	6 (5)	1 (6)
Nausea	0	1 (1)	6 (2)	2 (9)	0	0	2 (2)	1 (6)
Fever	1 (4)	4 (3)	3 (1)	0	0	2 (3)	0	0
Anemia	1 (4)	3 (2)	1 (<1)	0	2 (11)	0	0	0
Pruritus	0	0	5 (2)	0	0	0	1 (1)	0
Rash erythematous	1 (4)	2 (1)	1 (<1)	0	0	1 (1)	0	0
Hypokalemia	1 (4)	1 (1)	0	0	1 (6)	0	0	0
Atelectasis	1 (4)	1 (<1)	1 (<1)					
Rash	1 (4)	0	2 (1)	0	0	0	0	0
Pain	0	0	2 (1)	0	0	0	1 (1)	0
Renal failure acute	0	0	2 (1)	0	0	1 (1)	0	0
Taste perversion	0	0	1 (<1)	1 (5)	0	0	1 (1)	0
Arrhythmia atrial	0	1 (1)	0	0	0	0	1 (1)	0
Fatigue	0	0	2 (1)	0	0	0	0	0
Hemorrhage NOS	1 (4)	0	0	0	0	1 (1)	0	0
Hyponatremia		1 (<1)			1 (6)			

Intravascular: Summary of Adverse Events Reported for All Four Indications Combined, by Group and Stratified by Age-Group, N (%) [a]

	ALL VIS Age-Group				ALL OMN Age-Group			
Adverse Event	0-<29 days	29 days-<2 years	2-<12 years	12-<18 years	0-<29 days	29 days-<2 years	2-<12 years	12-<18 years
Hypoxia	1 (4)	0	0	0	0	1 (1)	0	0
Injection site pain	0	1 (1)	1 (<1)	0	0	0	0	0
Somnolence	0	0	1 (<1)	0	0	0	1 (1)	0
Injection site reaction			1 (<1)					
Crying abnormal						1 (1)		
Hot flushes							1 (<1)	
Cardiac failure	1 (4)							
Cyanosis		1 (<1)						
ECG abnormal specific							1 (<1)	
Convulsions	1 (4)							
Headache			1 (<1)					
Muscle contractions involuntary			1 (<1)					
Vertigo			1 (<1)					
Enterocolitis	1 (4)							
Mouth dry			1 (<1)					
Arrhythmia	1 (4)							
Arrhythmia nodal							1 (<1)	
Arrhythmia ventricular			1 (<1)					
AV block			1 (<1)					
Bundle branch block			1 (<1)					

Intravascular: Summary of Adverse Events Reported for All Four Indications Combined, by Group and Stratified by Age-Group, N (%) [a]

	ALL VIS Age-Group				ALL OMN Age-Group			
Adverse Event	0-<29 days	29 days-<2 years	2-<12 years	12-<18 years	0-<29 days	29 days-<2 years	2-<12 years	12-<18 years
Tachycardia supraventricular	1 (4)							
Edema periorbital		1 (<1)						
Hypoglycemia	1 (4)							
Hypoproteinemia						1 (1)		
DIC						1 (1)		
Thrombosis arterial leg		1 (<1)						
Otitis media		1 (<1)						
Apnea		1 (<1)						
Asphyxia			1 (<1)					
Coughing			1 (<1)					
Dyspnea			1 (<1)					
Rash maculo-papular			1 (<1)					
Sweating increased			1 (<1)					
Urticaria				1 (5)				
Parosmia			1 (<1)					
Flushing	1 (4)							
Peripheral ischemia		1 (<1)						
Leukocytosis			1 (<1)					

[a] Includes eight Phase III, double-blind, comparative trials and one Phase I, open-label, noncomparative trial.
NOS=not otherwise specified.
REF: Appendix 2.2.3

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

---------- NEWDOSE=ALL OMN ----------

CATMOD PROCEDURE

Response: DATA_YN		Response Levels (R)=	2
Weight Variable: None		Populations (S)=	13
Data Set: AEA		Total Frequency (N)=	235
Frequency Missing: 0		Observations (Obs)=	235

POPULATION PROFILES

Sample	AGE1	DRG_IND	Sample Size
1	0 - <29 DAYS	ANGIOCARDIOGRAPH	18
2	29 DAYS - <2 YEA	ANGIOCARDIOGRAPH	33
3	29 DAYS - <2 YEA	CT HEAD	10
4	29 DAYS - <2 YEA	CT BODY	11
5	29 DAYS - <2 YEA	UROGRAPHY	18
6	2 YEARS - <12 YE	ANGIOCARDIOGRAPH	33
7	2 YEARS - <12 YE	CT HEAD	31
8	2 YEARS - <12 YE	CT BODY	37
9	2 YEARS - <12 YE	UROGRAPHY	28
10	12 YEARS - <=18	ANGIOCARDIOGRAPH	1
11	12 YEARS - <=18	CT HEAD	9
12	12 YEARS - <=18	CT BODY	2
13	12 YEARS - <=18	UROGRAPHY	4

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

---------- NEWDOSE=ALL OMN ----------

RESPONSE PROFILES

Response	DATA_YN
1	N
2	Y

MAXIMUM-LIKELIHOOD ANALYSIS-OF-VARIANCE TABLE

Source	DF	Chi-Square	Prob
INTERCEPT	1	46.24	0.0000
AGE1	3	0.78	0.8542
DRG_IND	3	8.69	0.0337
LIKELIHOOD RATIO	6	3.16	0.7879

CONTRASTS OF MAXIMUM-LIKELIHOOD ESTIMATES

Contrast	DF	Chi-Square	Prob
Angio vs CT Head	1	2.90	0.0886
Angio vs CT Body	1	4.37	0.0365
Angio vs Urography	1	5.13	0.0235
CT Head vs CT Body	1	0.19	0.6659
CT Head vs Urography	1	0.62	0.4312

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

---------- NEWDOSE=ALL OMN ----------

CONTRASTS OF MAXIMUM-LIKELIHOOD ESTIMATES

Contrast	DF	Chi-Square	Prob
CT Body vs Urography	1	0.15	0.7019

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

---------- NEWDOSE=ALL VIS ----------

CATMOD PROCEDURE

Response: DATA_YN		Response Levels (R)=	2
Weight Variable: None		Populations (S)=	16
Data Set: AEA		Total Frequency (N)=	459
Frequency Missing: 0		Observations (Obs)=	459

POPULATION PROFILES

Sample	AGE1	DRG_IND	Sample Size
1	0 - <29 DAYS	ANGIOCARDIOGRAPH	22
2	0 - <29 DAYS	CT HEAD	1
3	0 - <29 DAYS	CT BODY	1
4	0 - <29 DAYS	UROGRAPHY	2
5	29 DAYS - <2 YEA	ANGIOCARDIOGRAPH	78
6	29 DAYS - <2 YEA	CT HEAD	15
7	29 DAYS - <2 YEA	CT BODY	20
8	29 DAYS - <2 YEA	UROGRAPHY	35
9	2 YEARS - <12 YE	ANGIOCARDIOGRAPH	60
10	2 YEARS - <12 YE	CT HEAD	72
11	2 YEARS - <12 YE	CT BODY	72
12	2 YEARS - <12 YE	UROGRAPHY	59
13	12 YEARS - <=18	ANGIOCARDIOGRAPH	1
14	12 YEARS - <=18	CT HEAD	14
15	12 YEARS - <=18	CT BODY	3
16	12 YEARS - <=18	UROGRAPHY	4

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

---------- NEWDOSE=ALL VIS ----------

RESPONSE PROFILES

Response	DATA_YN
1	N
2	Y

MAXIMUM-LIKELIHOOD ANALYSIS-OF-VARIANCE TABLE

Source	DF	Chi-Square	Prob
INTERCEPT	1	71.15	0.0000
AGE1	3	1.92	0.5897
DRG_IND	3	22.66	0.0000
LIKELIHOOD RATIO	9	6.68	0.6700

APPEARS THIS WAY
ON ORIGINAL

CONTRASTS OF MAXIMUM-LIKELIHOOD ESTIMATES

Contrast	DF	Chi-Square	Prob
Angio vs CT Head	1	8.17	0.0043
Angio vs CT Body	1	13.81	0.0002
Angio vs Urography	1	11.19	0.0008
CT Head vs CT Body	1	1.68	0.1946
CT Head vs Urography	1	0.25	0.6187

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

---------- NEWDOSE=ALL VIS ----------

CONTRASTS OF MAXIMUM-LIKELIHOOD ESTIMATES

Contrast	DF	Chi-Square	Prob
CT Body vs Urography	1	0.68	0.4095

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

TABLE 1 OF AGE1 BY DATA_YN
CONTROLLING FOR NEWDOSE=ALL OMN

AGE1(AGE GROUP) DATA_YN(ADVERSE EVENT)

Frequency Row Pct	N	Y	Total
0 - <29 DAYS	15 83.33	3 16.67	18
29 DAYS - <2 YEA	65 90.28	7 9.72	72
2 YEARS - <12 YE	115 89.15	14 10.85	129
12 YEARS - <=18	15 93.75	1 6.25	16
Total	210	25	235

INTRAVASCULAR TRIALS: ANALYSIS OF ADVERSE EVENTS
PATIENTS WITH ADVERSE EVENTS, BY AGE AND CONTRAST AGENT, FOR ALL FOUR INDICATIONS COMBINED
COMPARISON OF GROUPS (0 - <29 DAYS, 29 DAYS - <2 YEARS, 2 YEARS - <12 YEARS, AND 12 YEARS - <18 YEARS)

TABLE 2 OF AGE1 BY DATA_YN
CONTROLLING FOR NEWDOSE=ALL VIS

AGE1(AGE GROUP) DATA_YN(ADVERSE EVENT)

Frequency Row Pct	N	Y	Total
0 - <29 DAYS	18 69.23	8 30.77	26
29 DAYS - <2 YEA	126 85.14	22 14.86	148
2 YEARS - <12 YE	230 87.45	33 12.55	263
12 YEARS - <=18	19 86.36	3 13.64	22
Total	393	66	459

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

CT TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR CT INDICATIONS COMBINED, BY SEDATION STATUS, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

APPEARS THIS WAY
ON ORIGINAL

		SEDATED (N/Y)							
		N				Y			
		CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=128		N=64		N=70		N=36	
		N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)								
	TOTAL PATIENTS WITH NO ADVERSE EVENTS	113	88.28	59	92.19	69	98.57	34	94.44
	TOTAL PATIENTS WITH ADVERSE EVENTS	15	11.72	5	7.81	1	1.43	2	5.56
BODY AS A WHOLE - GENERAL DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	2	1.56	1	1.56				
	FATIGUE	2	1.56						
	HOT FLUSHES			1	1.56				

(CONTINUED)

CT TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR CT INDICATIONS COMBINED, BY SEDATION STATUS, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

		SEDATED (N/Y)							
		N				Y			
		CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=128		N=64		N=70		N=36	
		N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)								
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	1	0.78						
	MUSCLE CONTRACTIONS INVOLUNTARY	1	0.78						
GASTRO-INTESTINAL SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	5	3.91	3	4.69			1	2.78
	MOUTH DRY	1	0.78						
	NAUSEA	4	3.13	2	3.13			1	2.78

(CONTINUED)

CT TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR CT INDICATIONS COMBINED, BY SEDATION STATUS, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

APPEARS THIS WAY
ON ORIGINAL

		SEDATED (N/Y)							
		N				Y			
		CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=128		N=64		N=70		N=36	
		N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)								
GASTRO-INTESTINAL SYSTEM DISORDERS	VOMITING	2	1.56	3	4.69				
PLATELET, BLEEDING & CLOTTING DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS							1	2.78
	HEMORRHAGE NOS							1	2.78
RESPIRATORY SYSTEM DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	1	0.78						
	DYSPNOEA	1	0.78						

(CONTINUED)

CT TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR CT INDICATIONS COMBINED, BY SEDATION STATUS, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

APPEARS THIS WAY
ON ORIGINAL

		SEDATED (N/Y)							
		N				Y			
		CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=128		N=64		N=70		N=36	
		N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)								
SKIN AND APPENDAGE DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	6	4.69			1	1.43		
	PRURITUS	4	3.13						
	RASH	1	0.78						
	RASH ERYTHEMATOUS	1	0.78			1	1.43		
	RASH MACULO-PAPULAR	1	0.78						
	SWEATING INCREASED	1	0.78						

(CONTINUED)

CT TRIALS: SUMMARY OF ADVERSE EVENTS - NUMBER OF PATIENTS WITH ADVERSE EVENTS
FOR CT INDICATIONS COMBINED, BY SEDATION STATUS, CONTRAST AGENT, BODY SYSTEM AND ADVERSE EVENT

APPEARS THIS WAY
ON ORIGINAL

		SEDATED (N/Y)							
		N				Y			
		CONTRAST AGENT				CONTRAST AGENT			
		ALL VISIPAQUE		ALL OMNIPAQUE		ALL VISIPAQUE		ALL OMNIPAQUE	
		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS		TOTAL PATIENTS	
		N=128		N=64		N=70		N=36	
		N	%	N	%	N	%	N	%
BODY SYSTEM (WHO)	ADVERSE EVENT (WHO/PREF)								
SKIN AND APPENDAGE DISORDERS	URTICARIA	1	0.78						
SPECIAL SENSES OTHER, DISORDERS	TOTAL PATIENTS WITH ADVERSE EVENTS	3	2.34	1	1.56				
	PAROSMIA	1	0.78						
	TASTE PERVERSION	2	1.56	1	1.56				

TEAM LEADER REVIEW COMMENTS FOR VISIPAQUE PEDIATRIC SUPPLEMENT (IODIXANOL INJECTION)

NDA 20-531
Submitted: October 10, 1996
Sponsor: Nycomed Inc.
MOR Completed: May 22, 1997 by Silas Chow M.D.

Dr. Chow recommended that this supplement be approved.

This supplement is intended to provide support for the pediatric safety and effectiveness to match the claims for adults present in the current labeling.

The New Drug Application (NDA) for Visipaque was approved March 22, 1996 for the following indications for adults.

Approved Labeling

Indications	**Concentration Visipaque**
Angiocardiography	320 mgI/mL
CT Scanning of the Head	270 mgI/mL and 320 mgI/mL
CT Scanning of the Body	270 mgI/mL and 320 mgI/mL
Excretory Urography	270 mgI/mL and 320 mgI/mL

Pediatric Trials were conducted in the United States (US) and Europe (Euro) comparing Visipaque 270 and 320 mgI/mL with Omnipaque (iohexol) 300 and 350 as follows:

Indication	**Concentration (mgI/mL)**	
	Visipaque	Omnipaque
Angiocardiography	320	350
CT/Head	270, 320	300
CT/Body	270, 320	300
Urography	270, 320	300

A Phase 1 pharmacokinetic trial using Visipaque 320 mgI/mL for angiocardiography was conducted with 43 children (27M/16F) ages ranging from less than one day to 10 years. A Pharmacokinetics Review was completed by Young Moon Choi Ph.D. who recommended approval of this pediatric supplement.

Omnipaque is approved for pediatric use and the comparative concentrations chosen for this supplement are near those of

Visipaque. The physical characteristics of the two agents are compared below:

Physical Characteristics of Visipaque and Omnipaque

AGENT	mgI/mL	mOsm/Kg water	Viscosity @ 37C	Specific Gravity @ 37C
Visipaque	270	290	6.3	1.303
Visipaque	320	290	11.8	1.356
Omnipaque	300	672	6.3	1.349
Omnipaque	350	844	10.4	1.406

The following table is intended to show the indication, the trial report numbers for each study and number of patients exposed to Visipaque(both concentrations). Omnipaque was administered to about half as many children as Visipaque in each trial.

VISIPAQUE TRIAL REPORTS

INDICATION	US REPORT #	PATIENTS (NUMBER)	EUROPE REPORT#	PATIENTS (NUMBER)
PHASE 1	2493	43	---	---
ANGIOCARDIOGRAPHY	1968	58	2509 BELGIUM	62
CT/HEAD	1966	50	2512 SWEDEN	50
CT/BODY	1967	52	2511 NORWAY	40
UROGRAPHY	---	---	2510 FRANCE	50
UROGRAPHY	---	---	2513 SWEDEN	53

EFFICACY

The sponsor collected subjective (qualitative) evaluations of clinical efficacy which were presented in all study reports. The efficacy of Visipaque in children is not different from that for adults. The concentration of iodine is sufficient to render

the physical properties needed for radiographic procedures equivalent in both adults and children for the intended indications. **There is compliance with 21 CFR 201.57(f)(9)(iv) since "well controlled studies with adult subjects provided substantial evidence of effectiveness" for this pediatric population.**

SAFETY

The greatest risk with iodinated contrast use in the pediatric population (under 16 years) is in the age group under one year and especially the newborn (neonates <29 days). The most risk is associated with angiocardiography which is conducted on the arterial side. Contrast is delivered in greatest concentration to the heart and adjacent vessels through the carotid arteries to the brain and down the aorta to the kidneys and visceral organs.

The protocols for the studies called for serum creatinine levels to be measured at "16 to 32 hours". This is inadequate for assessment of renal function in adults where at least a 72 hour assessment of serum creatinine is routinely requested by FDA.

It is important to relate the dose of contrast to the body size/weight and check for a relationship with adverse events (ADEs) and altered renal function since Visipaque is eliminated from the body by the kidneys. It is impossible to adequately evaluate the effect of Visipaque on pediatric renal function because of the brevity of the time period of assessment "16 to 32 hours", however it is most probable that the pediatric kidney is mature enough to behave similarly to the adult kidney by at least one year of age.

The following comments address the results reported for Visipaque and do not deal with the comparator Omnipaque.

ANGIOCARDIOGRAPHY Visipaque 320 mgI/mL

Study Report 1968: U.S.A.

Sex:	M/F	30/28
Ethnicity:	Cauc.	44
	Black	6
	Other	8
Age:	<1 month (0.08 yr.)	17
ADEs	M/F	5/8(13)
Creatinine	increase	12 (5 <1 month & 8 >4mL/kg)

Pediatric labeling for Ultravist 300 mgI/mL, (for cardiac chambers and related major arteries) prescribes a maximum dose not to exceed 4mL/kg.

In this study report the majority of doses exceeded 4mL/kg with only 12 patients receiving 4mL/kg or less. It is recognized that this dose excess is highly related to the difficulties of the angiographic procedure and that the procedural risks due to Visipaque are confounded by the risks of catheterization. Of the 13 ADEs, 10 were in the patients that received doses >4mL/kg.

The protocol called for laboratory parameters within 24 hours before and at 16 to 32 hours post dose. BUN and creatinine at 64 to 80 hours when possible (very few were obtained). Table 4.3.5.4, Vol. 10/71, page 362 provides timing for pre and post dose with few laboratory values beyond 32 hours. Of the 17 neonates, 5(30%) had elevated creatinine values post Visipaque.

PLEASE SEE ATTACHED GRAPH #1: DOSE (mL) vs BODY WEIGHT (kg)

Study Report 2059: Belgium

Sex:	M/F	30/32
Ethnicity:	Cauc.	60
	Black	2
	Other	0
Age:	<1 month	13
ADEs	M/F	4/10
Creatinine	normal post dose	

The conventional pediatric iodine contrast dose e.g. Visipaque 300 mgI/mL, for visualizing the cardiac chambers and related major arteries is 4mL/kg. As with the U.S. trial there was a large variation, 25 patients above and 27 patients below 4mL/kg. Only 3 patients <1 month old received under 4mL/kg and only 2 of the patients <1 month old had ADEs recorded.

The protocol called for laboratory evaluations prior to dosing and at 16 to 24 hours post dose. The creatinine levels were mostly normal post dose and minimally elevated in patients #4 and #204. Few creatinine values were abnormal possibly due to the fact that they were collected at or before 24 hours and the abnormalities are more likely to be detected at 72 hours.

PLEASE SEE ATTACHED GRAPH #2: DOSE (mL) vs BODY WEIGHT (kg)

CT BODY **Visipaque 270 and 320 mgI/mL**

Study Report 1967: U.S.A.

270 mgI/mL	26 patients	
320 mgI/mL	26 patients	
Sex:	M/F	16/10 @ 270 mgI/mL
		14/12 @ 320 mgI/mL
Ethnicity:	Cauc.	34
	Black	11
	Oriental	2
	Other	5
Age:	<1 month (0.08 yr.)	0
ADEs:	M/F	1/2

Conventional pediatric labeling (Ultravist 300 mgI/mL) for contrast enhanced CT (CECT), prescribes a dose of 1 to 2mL/kg not to exceed 3mL/kg. Both concentrations of Visispaque were administered at the same volumes. It would have been more logical to require a smaller volume of the higher iodine contrast (Visipaque 320 mgI/mL) than was used for Visipaque 270 mgI/mL.

Approximately 20 doses exceeded 2mL/kg and one of the ADEs occurred in this higher dose group (shortness of breath and involuntary contractions).

There were no abnormal serum creatinine values reported for the 270 mgI/mL group of patients and only one in the 320mgI/mL group (patient #0657) with a rise in value post dose. The protocol required serum chemistry values prior to dosing and at 16 to 32 hours post dose with 60 to 80 hour assessments when possible. These latter time evaluations were either not collected or reported. The creatinine values were assessed too early to detect renal abnormalities as a delay of about 72 hours may occur before the test may become abnormal.

PLEASE SEE ATTACHED GRAPH #3: DOSE (mL) vs BODY WEIGHT (kg)

Study Report 2511: Norway

Sex:	M/F	14/8	@ 270 mgI/mL
		14/8	@ 320 mgI/mL
Ethnicity:	Cauc.	42	
	Oriental	1	
	Other	1	
Age:	<1 month (0.08 yr.)	9	
ADEs	M/F	2/1	
Creatinine	increase	1	@ 270 mgI/mL of 8 patients
		7	@ 320 mgI/mL of 9 patients

Pediatric labeling for Body CECT prescribes a dose of 1 to 2 mL/kg not to exceed 3mL/kg. This study was very precise in maintaining the dose level at 2mL/kg at both concentrations of Visipaque.

The laboratory values were collected on few patients, 7 at 270 mgI/mL and 9 at 320 mgI/mL.

PLEASE SEE ATTACHED GRAPH #4: DOSE (mL) vs BODY WEIGHT (kg)

CT HEAD **Visipaque 270 and 320 mgI/mL**

Study Report 1966: U.S.A.

Sex:	M/F	16/11	@ 270 mgI/mL
		14/9	@ 320 mgI/mL
Ethnicity:	Cauc.	23	
	Black	24	
	Other	3	
Age:	<1 month (0.08 yr.)	3	
ADEs	M/F	2/1	

As for Body CT, pediatric labeling (Ultravist 300 mgI/mL) recommends 1 to 2 mL/kg not to exceed 3 mL/kg. As with the trials for CT Head, the same volumes were administered for both concentrations of Visipaque 270 and 320 mgI/mL. There is no apparent reason for this dosing practice. Of the 50 patients studied only 12 exceeded the 2mL/kg dose recommendation.

Three patients had ADEs with patients 1153 and 1154 receiving near 3mL/kg body weight. The third patient received much less than 2mL/kg.

Creatinine values were obtained on 4 patients at baseline and post injection with no significant abnormality repported.
PLEASE SEE ATTACHED GRAPH #5: DOSE (mL) vs BODY WEIGHT (kg)

Study Report 2512: Sweden

Sex:	M/F	26/24
Ethnicity:	Cauc.	47
	Black	2
	Unknown	1
Age:	<1 month (0.08 yr.)	2
ADEs	M+F	8

There were no serum chemistries, only vital signs and ADEs.

The dosing was very exact providing a linear plot (mL vs kg body weight) with no deviations from a dose of exactly 3 mL/kg. The protocol required a dose of 2 mL/kg. As with all other trials there was no distinction made between Visipaque 270 and 320 mgI/mL in dosing the patients.

PLEASE SEE ATTACHED GRAPH #5: DOSE (mL) vs BODY WEIGHT (kg)

UROGRAPHY **Visipaque 270 and 320 mgI/mL**

Study Report 2510 (France) and Study Report 2513 studied safety by collecting vital signs and ADE data.

		Report 2510	Report 2513
Sex:	M/F	42/30	34/41
Ethnicity:	Cauc.	68	70
	Black	2	3
	Oriental	1	2
	Other	1	2
Age:	<2 years	11	9

No serum creatinine levels were obtained.

It is of interest that the dosing in Report 2513 (Sweden) is very conservative . The doses up to body weight of 20kg are near 2 mL/kg body weight. Over 20kg the doses did not increase for Visipaque 270 or 320 mgI/mL but remained at 40ml for patients up to a body weight of 36kg. The efficacy was adequate in spite of this reduced dose. It is suggested that a dose of 2mL/kg body weight should be the maximum dose recommended for pediatric urography and for that matter for all intravenous administrations, i.e., CT head and body. The maximum dose of 3 mL/kg is excessive for efficacy needs and the trials indicate a

higher incidence of ADEs when doses exceed 2mL/kg.

PLEASE SEE ATTACHED GRAPH #7: DOSE(mL) vs BODY WEIGHT (kg)

Adverse Events:
Patients in Phase 3 studies had a higher incidence of ADEs when administered Visipaque 320 mgI/mL (36/272, 13%) compared with 270 mgI/mL (12/144, 8%). The greatest incidence of any ADE following Visipaque 270 or 320 mgI/mL was in the neonate group <29 days old.

Of the 36 ADEs that occurred with the 320 mgI/mL preparation, 27 occurred during intra-arterial administration (angiocardiography) with 13/58 (22%) in Study Report 1968 and 14/62 (22%) in Study Report 2509.

CONCLUSIONS:

INTRA-ARTERIAL: Cardiac chambers and related major arteries.

Visipaque 270 mgI/mL was not evaluated. In view of the small size of the patients it might have been effective and had fewer side effects. There was no reason provided by the sponsor for not evaluating Visipaque 270 mgI/mL.

The studies did not identify a dose that could be related to body weight. The dosing was dictated by the procedure and where the dose exceeded 4 ml/kg the incidence of ADEs was increased.

The studies were inadequate to define the renal effects of Visipaque since serum creatinine was monitored mainly between 16 and 32 hours and creatinine values are likely to become abnormal beyond 48 hours. Of particular concern is the lack of renal data to assess what effect intra-arterial contrast has on the immature kidney. Pharmacokinetic data indicate that glomerular filtration in the newborn is about 30% of the adult level and that by 6 to 8 months it rises to near 90% of the adult level. The patients older than one year of age are of less concern because of the maturation of renal function.

When Visipaque 320 mgI/mL is used intra-arterially, there is a direct renal perfusion that is not encountered with an intravenous dose. This route of administration is more likely to produce renal damage than an intravenous dose.

The studies demonstrate that a dose of less than 2 mL/kg was not evaluated (see Graph #1 and #2, attached). The lowest range of known effective dose is between The incidence of

adverse events (related to both procedure and drug) is too great to recommend a dose higher than 4mL/kg.

INTRAVENOUS: CECT Body and Head; Urography:

All of the study reports for intravenous use, support a dose of 2 mL/kg as a maximum effective dose at all ages. The lack of renal data has not characterized the renal safety but there is no reason to believe that pediatric patients older than one year are at any greater risk than adult patients. There is a particular concern with the immature kidneys of patients less than six months of age.

The urography Study Report 2513 (Graph #7, attached) demonstrated efficacy at a dose of less than 2 mL/kg supporting the recommendation that the maximum intravenous dose of Visipaque 270 or 320 mgI/mL, should not exceed 2 mL/kg with a recommended intravenous dose between 1 and 2 mL/kg.

The study reports for the intravenous use of Visipaque demonstrated that 270 mgI/mL was equivalent to the efficacy of the 320 mgI/ml. There is a greater incidence of ADEs with the higher concentration and this increased risk should be noted in the labeling. Consideration should be given to advising against the use of Visipaque 320 mgI/kg in patients under 2 years.

RECOMMENDATIONS:

Intra-arterial use of Visipaque 270 and 320 mgI/mL may be approved for doses of 2mL/kg not to exceed 4mL/kg in patients one year of age or older.

Intravenous use of Visipaque 270 and 320 mgI/mL may be approved for doses of 1mL/kg not to exceed 2mL/kg in patients six months of age or older.

/S/

9/5/97

A. Eric Jones M.D.
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