Observational Study / Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	Safety profile of Ultravist in children and elderly (UV Age)
Protocol version and date	v 2.0 /28 Jan 2021
Report version and date	V1.0 /2nd February 2022
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS37597
IMPACT number	21494
Active substance	Radiological / Low Osmolar non-ionic Contrast Medium (LOCM), (V08AB05) Iopromide
Medicinal product	Ultravist
Study Initiator and Funder	Bayer AG
Research question and objectives	To describe the risk of hypersensitivity reactions to Ultravist specifically in children (< 18 years of age) and elderly patients (≥65 years), compared to those in the middle age group (≥ 18 to < 65 years).
Country(-ies) of study	37 countries including Europe (mostly Germany and Spain), Asia (mostly China and South Korea) and USA.
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG

Confidentiality statement:

1. Abstract

Acronym/Title	Safety profile of Ultravist in children and elderly (UV Age)
Report version and date **Author**	2021 PPD Bayer AG
Keywords	Contrast Medium, Radiology, Iopromide, anaphylactoid reactions
Rationale and background	The safety profile of Iopromide and all other iodinated contrast media is well understood, there is a continuous discussion pertaining to the nature of hypersensitivity reactions (HSRs). One open question is a potential age relation, which would be ascribed to a the immune system status. Exploring this question furthers the understanding of the pathomechanisms of HSR to Iopromide and thus to ICM in general.
Research question and objectives	Evaluate the potential age dependence of HSRs to Iopromide.
Study design	The study was designed to investigate the risk of HSR in three age groups, comparing children and elderly patients to an adult reference group.
Setting	In this integrated analysis the data of four company sponsored non-interventional studies 'PMS I', 'Ultravist in CT', 'IMAGE' and 'TRUST' were pooled and analyzed.
Subjects and study size, including dropouts	About 132,000 records of patients were expected for evaluation.
Variables and data sources	The primary variables to answer the study objectives were the number and percentage of HSRs per defined age group.
Results	A total of 132,850 patients were included (2978 children, 43,209 elderly, and 86,663 adults). Hypersensitivity reactions were significantly less frequent in children (0.47%) and elderly (0.38%) compared with adults (0.74%). The adjusted odds ratio (vs adults) for children was 0.58 (95% confidence interval, 0.34–0.98; $P < 0.043$), and that for the elderly was 0.51 (95% confidence interval, 0.43–0.61; $P < 0.001$),

	indicating a lower risk for both subpopulations as compared with adults.
Discussion	This study analyzed the risk of HSRs to iopromide in children (<18 years) and elderly patients (≥65 years) compared with adults (≥18 to <65 years) and revealed substantial evidence for a lower risk of HSRs in children and elderly. A previous evaluation of the observational studies showed a number of parameters impacting the risk of HSRs: route of administration, sex, history of diabetes mellitus, allergy, asthma, and previous contrast media reaction. This set of confounders was prespecified, and the statistical model was adjusted accordingly to demonstrate the effect of age. As expected, the number of patients in the 3 age groups was not evenly distributed. The majority of administrations were performed in adults (65%) followed by elderly (32.5%). Less than 2.3% of the study population were children. This is easily explainable by the different number of years summarized in the age brackets of the groups (children, 18 years; adults, 43 years) and the number of indications for contrast enhanced imaging. In both analyses, HSRs were significantly less frequent in children or elderly compared with adults. 0.47% of children and 0.38% of elderly experienced HSRs compared with 0.74% of adults. The adjusted ORs (vs adults) for children (0.58) and elderly (0.51) were significant ($P < 0.043$ and $P < 0.001$, respectively). Many authors support the general notion that ADRs and specifically HSRs after iodine CM administration are lower in children than in adults. To the best of our knowledge, this study is the first systematic analysis of HSRs in these 2 age groups, thus providing new and relevant information on safety of LOCMs. Getting a better understanding of the age dependency of the HSR is of clinical importance. We hypothesize that the pathophysiological reason for the lower HSR incidence in children and elderly is that in children the immune system gradually matures during infancy and in elderly the immune system deteriorates with age. Thus, the present study improves knowledge on nature of HSR and enables user to even better understand the risk for any

	patient in need of imaging.
Marketing Authorization Holder(s)	Bayer AG

2. List of abbreviations

AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	European Commission
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
GPV	Global Pharmacovigilance
GSL	Global Safety Leader
HEOR	Health Economics and Outcomes Research
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
OS	Observational Study
OSP	Observational Study Protocol
OSR	Observational Study Report
PASS	Post-Authorization Safety Study
PBRER	Periodic benefit-risk evaluation report
PMCF study	Post Market Clinical Follow-up study
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

3. Investigators

Not applicable for retrospective pooled integrated analysis of four non-interventional studies.

4. Other responsible parties

The study was run internally, without the help of a CRO, but built on a previous similar investigation (UVIA), which was supported by the CRO Parexel.

5. Milestones

Table 1: Milestones

Milestone	Actual date	Comments
Start of study preparation	1H-2020	Study was conceptualized and refined after publication of UVIA
CSP/Statistical Analysis Plan	28 JAN 2021	
Registration in the EU PASS register	23-Oct-2020	
Final TLFs	31 March 2021	As a database analysis this constitutes the actual backbone of the study – basis for the manuscript
Results reported as a part of manuscript	First submission: August 17, 2021; Accepted for publication, after revision, October 1, 2021. Online first: December 6th 2021	
Results reported at Congress	RSNA 2021 December 1st, 2021	
CSR draft	Dec 2021	

6. Rationale and background

The purpose of the study was to investigate a potential age dependence of the risk of hypersensitivity to Iopromide based on the assumption that due to the allergic nature of the HSRs an

immune system status/age dependence is detectable. With this assumption on the pathomechanisms of HSR one would expect a lower rate of HSR in elderly (less active immune system), and children (not yet fully matured immune system) compared to a reference adult population.

7. Research question and objectives

Can an age dependence be detected and confirmed in our observational trial data, which has been used in a previous investigation to detect a different rate of HSRs depending on route of administration?

The primary objective:
To describe the risk of hypersensitivity reactions to Ultravist in children (< 18 years of age) and elderly patients (≥ 65 years) compared to middle-age adults (≥ 18 to < 65 years)

The secondary objectives:

1. Assess the rate of HSR of three age groups (adults, children, elderly), and compared the HSR rate of the children and the elderly in comparison to the adult population.
2. To describe the general reported ADR profile in the three age groups

8. Amendments and updates

The amendment 1 (protocol version 2.0) is based on recently collected information on Best Practices in Pharmacovigilance in defining age groups differently to the definition in V1 of the protocol, such as:

- Children: < 18 years (old value ≤19 years)
- Elderly patients: ≥65 years (old value ≥60years)

Middle age group: ≥ 18 to < 65 years (old value 20-59)

9. Research methods

9.1 Study design

Pooled analysis of four observational studies with descriptive statistics and logistical regression.

9.2 Setting

UV Age used the same data as a starting point as UVIA (see CSR 19677).

In this integrated analysis the data of four company sponsored non-interventional studies with Iopromide in contrast-enhanced X-ray examination were pooled (for publications on these studies

please refer to 'source studies' in reference list). The pool consisted of studies 'PMS I', 'Ultravist in CT', 'IMAGE', and 'TRUST'. In the year 2010, the three studies 'PMS I', 'Ultravist in CT' and 'IMAGE' were pooled and the general ADR profile was analyzed. The 'TRUST' study conducted purely in catheter labs in China enriches the intra-arterial administration group.

The four studies were all sponsored by Bayer or Schering. They comprise all available prospective observational studies with primary data collection performed with Iopromide.

These were:

- 'PMS I' was conducted in contrast-enhanced X-ray examination between June 1999 and November 2003 in 27 countries in Europe, Africa and Asia and comprised 74,717 patients (Kopp 2008) of which 65,452 patients received intra-venous and 8,368 patients intra-arterial administration.
- 'Ultravist in CT' was performed with focus on contrast-enhanced CT examination (intra-venous application) between November 2006 and December 2008 and included 15,168 patients in Germany, Iran, Romania and Saudi Arabia (Palkowitsch 2014).
- 'IMAGE' consists of 44,835 patients with contrast-enhanced X-ray examination and was conducted in 21 European and Asian countries from February 2008 to September 2009 (Palkowitsch 2012), 41,703 patients received intra-venous administration, and 2,782 patients with intra-arterial administration.
- 'TRUST' assessed the safety and tolerability of Iopromide in patients undergoing cardiac catheterization (intra-arterial administration). It was conducted from August 2010 to September 2011 in China and included 17,513 patients (Chen 2015).

The pooled integrated analysis was performed by Bayer statistics and data management.

9.3 Subjects

Four company-sponsored observational studies on Iopromide were pooled and analyzed comprising a total of 152,233 patients. PMS I (n=74,717), IMAGE (n=44,835), TRUST (n=17,513) and Ultravist in CT (n=15,168). While PMS I and IMAGE included patients with i.v. and i.a. injection, TRUST only included i.a. patients and Ultravist in CT only i.v. patients (Table 2).

For these studies Institutional Review Board / Ethics Committee approvals and patient informed consents were obtained from participating countries. This voluntary Post-Authorization Safety Study (PASS) was registered at ClinicalTrials.gov (NCT04605471) and at ENCePP (EUPAS37597).

For the purpose of study pooling the data anonymization was increased to eliminate all potential links to patient charts. For example, the original site and patient identifiers were replaced by random numbers and all free text was eliminated. For adverse events, only MedDRA coded terms were stored.

Table 2: Essentials of pooled studies

Study name	Countries	Study Duration	Intravenous Injection (N=105,460)	Intra-arterial Injection (N=27,871)	Cases (N=822)	Controls (N=132,509)	Total (N=133,331)
PMS I	27 countries in Europe, Africa and Asia	6/1999 – 11/2003	55,470 (52.6%)	7,581 (27.2%)	353 (42.9%)	62,698 (47.3%)	63,051 (47.3%)
IMAGE	21 countries in Europe and Asia	2/2008 - 11/2009	35,903 (34.0%)	3,016 (10.8%)	343 (41.7%)	38,576 (29.1%)	38,919 (29.2%)
TRUST	China	8/2010- 11/2011	---	17,274 (62.0%)	16 (1.9%)	17,258 (13.0%)	17,274 (13.0%)
Ultravist in CT	Germany, Iran, Romania, Saudi Arabia	11/2006 – 12/2008	14,087 (13.4%)	---	110 (13.4%)	13,977 (10.5%)	14,087 (10.6%)

9.4 Variables

Cases were defined as patients reports with a typical and unequivocal HSR as defined by the ACR Committee on Drugs and Contrast Media 2018, Version 10.3.26 Irrespective of the investigators' assessment, all cases were categorized as drug related, that is, always the most conservative approach for drug relationship was chosen.

Controls were defined as subjects in whom no adverse event was reported. Unspecific reactions (eg, headache, nausea) and possibly procedure-related reactions (eg, drop in blood pressure, bradycardia, tachycardia) were excluded from the cases and from the controls, to avoid misclassification and confounding by the procedure performed.

Adverse event data are coded by MedDRAversion 21.0.

9.4.1 Target variables

Risk of Hypersensitivity Reactions of the three predefined groups and adjusted odds ratios of significant covariates with the covariant of interest being age.

9.5 Data sources and measurement

The study was conducted by pooling data of four company sponsored non-interventional studies with Iopromide.

For details of the preparation of the data pool please refer to CSR 19677 (UVIA).

9.6 Bias

This was an integrated analysis on pooled data from four non-controlled, multi-center, observational cohort studies. The four studies were conducted in different years and in different countries and geographic regions all over the world. Nearly 45% of the pooled patients were enrolled in Europe and a group of 45% of the observed patients were enrolled in China. Geographical and cultural differences in the reporting of adverse events were possible.

Since the observation time of the patients in the observational studies used in this analysis was 30-60 minutes after the procedure, late-onset anaphylactoid reactions occurring hours or days after injection were not captured.

9.7 Study size

Given the previous extensive analysis of the data pool, the sample size of about 130.000 patients was known upfront.

9.8 Data transformation

During the mapping of the four studies, categories of variables were harmonized. For example, categories which described the same concomitant disease but with different terms were mapped to the same category. All data transformations were described in the Data Management Report.

9.9 Statistical methods

All variables were analyzed descriptively: categorical variables by absolute and relative frequencies and continuous variables by the mean, standard deviation, minimum, median, quantiles, and maximum. Logistic regression was used to estimate odds ratios (ORs) for HSRs in children or elderly compared with adults. A set of possible confounders was prespecified similar to the previous publication of the same pooled database. Adjustment for possible confounders related to age was performed by backward selection using a P value <0.10 as important to keep for further adjustments. At the final step, all possible risk factors and confounders found to be important earlier were fitted simultaneously in a multivariable model, and those with P value <0.10 were retained. The results from the final model are presented. The analysis was of exploratory nature, without adjustment for multiplicity.

9.9.1 Main summary measures

All variables were analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables were described by absolute value and as change from baseline, if applicable. Results were presented by type of Iopromide administration (intra-arterially and intravenously).

Background data such as subject demographics, specific concomitant diseases, specific risk factors like previous moderate or severe acute reaction to an iodine-base contrast agent, unstable asthma, atopy requiring medical treatment, pre-medication, examination region, type of examination and indication for the application of Iopromide were described by means of summary statistics.

Concentration of Iopromide was summarized and total dose of Iopromide applied was calculated for each patient (ml and g iodine).

9.9.2 Main statistical methods

In order to address the primary objective, cases of anaphylactoid reactions and controls were identified as described in section 9.4.The exposure variable of interest is defined as i.a. administration vs. i.v. administration of Iopromide. A crude odds ratio with 95 % CI of the risk of anaphylactoid reactions for i.a. vs. i.v. administration was calculated in the case-control analysis.

Furthermore, unconditional, univariate logistic regression models were computed to identify relevant covariates (e.g. history of allergy, premedication etc.) and potential confounder. A covariate was considered as important when its effect, represented by a descriptive p-value, was below 0.1. Age and sex were always included as a covariate. Subsequently, the covariates identified in the univariate regression models were brought together in a multivariate logistic regression model in order to identify the individual effect on the occurrence of anaphylactoid reactions. No matching on confounders were performed in the case-control analysis.

The topics of the secondary objectives were evaluated by means of frequency and summary tables.

9.9.3 Missing values

In general, subjects with missing data in variables needed for a specific model for the analysis of the primary variable were excluded for this model only. Subjects with missing age or sex were exluded from all analyses. No imputation was done.

9.9.4 Sensitivity analyses

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

Data quality relied on the source data of the integrated observational studies. The data in these studies were captured by paper or electronic CRFs. No checks for multiple documented patients were done because multiple documentation was unlikely given the different years and regions where the studies were conducted.

CRO Parexel, who established the data pool, which was used for this study, was responsible for data integrity. Bayer statistics and data management were responsible for biometrical evaluation.

10. Results

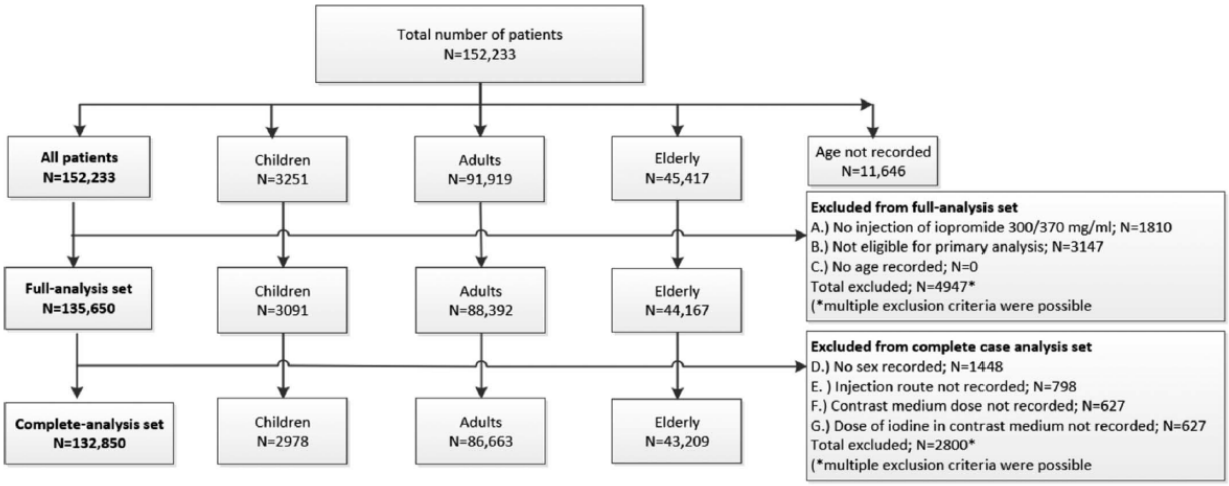
The main results of this investigation have also been summarized in a scientific manuscript (Endrikat et al. 2021).

10.1 Participants

All participants stem from Bayer sponsored observational trials (Table 3). The below diagram shows the patient data flow into the complete analysis set.

A total of 152,233 patients were pooled from four studies. After the documented exclusion steps, a total of 132,850 patients comprised the full analysis set. There were 86,663 adults as reference, 2978 children, and 43,209 elderly patients.

Table 3: Patient data flow in analysis



10.2 Descriptive data

10.2.1 Distribution across regions

The majority of the patients (47.9%) were recruited in Europe, about one quarter in China (27.7%) and one quarter in other Asian countries (excluding China) (24.2%). Very few patients came from Africa.

In all geographic regions, patients of all 3 age groups were recruited. Although 43.2% of children were recruited in other Asian countries (excluding China), 11.6% were from China. On the other hand, elderly were more frequently enrolled in China (25.5%) compared with other Asian countries (18.3%).

Iopromide concentration, sex, and race were comparably distributed within the 3 age groups. The incidence of concomitant disease was lowest in children (33.5%) and highest in elderly (52.3%). For premedication, injection route, examination region, and indication, no remarkable difference could

be stated. The iodine dose was lowest in children. Two thirds of adults and elderly received 20 to 40 g of iodine.

10.2.2 Characteristics of study population

Table 4. Baseline characteristics of patients

	Children, n = 2978 (2.24%)	Adults, n = 86,663 (65.23%)	Elderly, n = 43,209 (32.52%)	Total, n = 132,850 (100%)
Indication*				
Tumor/suspicion of tumor	476 (16.0%)	16,508 (19.0%)	8088 (18.7%)	25,072 (18.9%)
Pain	175 (5.9%)	5212 (6.0%)	1648 (3.8%)	7035 (5.3%)
Posttherapy control	117 (3.9%)	4509 (5.2%)	2341 (5.4%)	6967 (5.2%)
Staging	137 (4.6%)	3194 (3.7%)	1831 (4.2%)	5162 (3.9%)
Inflammatory diseases	214 (7.2%)	2766 (3.2%)	1011 (2.3%)	3991 (3.0%)
Infarct/suspicion of infarct	33 (1.1%)	2202 (2.5%)	1146 (2.7%)	3381 (2.5%)
Hemorrhage	23 (0.8%)	603 (0.7%)	209 (0.5%)	835 (0.6%)
Trauma	50 (1.7%)	428 (0.5%)	91 (0.2%)	5 (0.4%)
Other	291 (9.8%)	15,917 (18.4%)	7407 (17.1%)	23,615 (17.8%)
Not specified	13 (0.4%)	31 (<0.1%)	0 (<0.1%)	54 (<0.1%)
Missing	1616 (54.3%)	39,692 (45.8%)	21,713 (50.3%)	63,021 (47.4%)
Iodine dose				
≤20 g	2035 (68.3%)	14,825 (17.1%)	5957 (13.8%)	22,817 (17.2%)
>20–40 g	870 (29.2%)	56,930 (65.7%)	29,414 (68.1%)	87,214 (65.6%)
>40–60 g	70 (2.4%)	10,834 (12.5%)	5759 (13.3%)	16,663 (12.5%)
>60 g	3 (0.1%)	4074 (4.7%)	2079 (4.8%)	6156 (4.6%)
Type of examination				
CT	1297 (43.6%)	35,293 (40.7%)	20,898 (48.4%)	57,488 (43.3%)
CT (multislice)	730 (24.5%)	21,968 (25.3%)	8574 (19.8%)	31,272 (23.5%)
Angiocardiography	18 (0.6%)	8577 (9.9%)	3899 (9.0%)	12,494 (9.4%)
Urography	487 (16.4%)	6659 (7.7%)	2951 (6.8%)	10,097 (7.6%)
CT (single slice)	230 (7.7%)	2115 (2.4%)	670 (1.6%)	3015 (2.3%)
Angiography	25 (0.8%)	1099 (1.3%)	672 (1.6%)	1796 (1.4%)
Phlebography	10 (0.3%)	212 (0.2%)	74 (0.2%)	296 (0.2%)
DSA	9 (0.3%)	150 (0.2%)	62 (0.1%)	221 (0.2%)
PTCA	0	116 (0.1%)	49 (0.1%)	165 (0.1%)
PTA	0	35 (<0.1%)	43 (<0.1%)	78 (<0.1%)
Other	7 (0.2%)	4464 (5.2%)	2382 (5.5%)	6853 (5.2%)
Not specified	165 (5.5%)	5975 (6.9%)	2935 (6.8%)	9075 (6.8%)

*Multiple reasons possible.
CT, computed tomography; DSA, digital subtraction angiography; PTA, percutaneous transluminal angioplasty; PTCA, percutaneous coronary angioplasty.

(part I of Table 4)

	Children, n = 2978 (2.24%)	Adults, n = 86,663 (65.23%)	Elderly, n = 43,209 (32.52%)	Total, n = 132,850 (100%)
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Not specified	165 (5.5%)	5975 (6.9%)	2935 (6.8%)	9075 (6.8%)

*Multiple reasons possible.
CT, computed tomography; DSA, digital subtraction angiography; PTA, percutaneous transluminal angioplasty; PTCA, percutaneous coronary angioplasty.

(part II of Table 4)

10.3 Outcome data

The key results of the study are displayed in the Table 5.

Table 5. Risk of Hypersensitivity Reactions and Adjusted Odds Ratios of Significant Covariates

	Cases, n = 818 (%)	Controls, n = 132,032 (%)	Odds Ratio	95% CI	*P*
Age group (vs adults)	640 (78.2)	86,023 (65.2)			
Children	14 (1.7)	2964 (2.2)	0.58	0.34–0.98	0.043
Elderly	164 (20.0)	43,045 (32.6)	0.51	0.43–0.61	<0.001
Sex (vs male)	411 (50.2)	74,575(56.5)			
Female	407 (49.8)	57,457 (43.5)	1.16	1.01–1.34	0.032
Injection route (vs intravenous injection)	762 (93.2)	104,257 (79.0)			
Intra-arterial	56 (6.8)	27,775 (21.0)	0.49	0.35–0.70	<0.001
Diabetes mellitus (vs no)					
Yes	68 (8.3)	10,316 (7.8)	1.57	1.22–2.03	<0.001
Allergy (vs no)					
Yes	82 (10.0)	3477 (2.6)	3.73	2.93–4.74	<0.001
Asthma bronchial (vs no)					
Yes	15 (1.8)	805 (0.6)	2.14	1.26–3.63	0.005
Contrast media reaction (vs no)					
Yes	22 (2.7)	695 (0.5)	4.28	2.74–6.70	<0.001
Other (vs no)					
Yes	152 (18.6)	19,182 (14.5)	1.37	1.14–1.64	<0.001

95% Confidence intervals (CIs) are constructed using asymptotic Wald confidence limits without correction.
P value from Wald test.

10.4 Main results

10.4.1 Primary objective

The key results are summarized in Table 6. The majority of cases, that is, 640/818 (78.2%), were in the group of adults. Adults, however, comprised just 65.2% of the controls. Fourteen cases (1.7%) were in children and 164 (20%) in elderly. In the control group, these patient groups comprised 2.2% and 32.6%, respectively. Thus, the adjusted OR (vs adults) for children was 0.58 (95% confidence interval [CI], 0.34–0.98; $P < 0.043$), and that for the elderly was 0.51 (95% CI, 0.43–0.61; $P < 0.001$), indicating approximately half the risk.

10.4.2 Secondary objectives

Specific HSRs of the age groups

Overall, HSRs were significantly more frequently recorded in adults (0.74%) compared with children (0.47%) and elderly (0.38%) ($P < 0.05$) (Table 5). The most frequent HSRs were pruritus (0.22%), urticaria/rash/erythema (0.38%), and cough/sneezing (0.11%). It is always the adult group that showed the highest incidences (Table 6). The clinically most relevant severe adverse reactions, anaphylactic shock, laryngeal edema, and respiratory arrest, one of each, were recorded in the elderly cohort (Table 6).

Table 6. Risk of anaphylactoid reactions and odds ratios of significant covariates

	Children, n = 2978 (%)	Adults, n = 86,663 (%)	Elderly, n = 43,209 (%)	Total, n = 132,850 (%)
All patients with HSRs	14 (0.47%)	640 (0.74%)	164 (0.38%)	818 (0.62%)
Pruritus	8 (0.27)	232 (0.27)	53 (0.12)	293 (0.22)
Cough, sneezing*	2 (0.07%)	113 (0.13%)	34 (0.08%)	149 (0.11%)
Cough	2 (0.07%)	62 (0.07%)	20 (0.05%)	84 (0.06%)
Sneezing	0	55 (0.06%)	15 (0.03%)	70 (0.05%)
Urticaria, rash, erythema*	8 (0.27%)	411 (0.47%)	87 (0.20%)	506 (0.38%)
Urticaria	3 (0.10%)	203 (0.23%)	39 (0.09%)	245 (0.18%)
Rash	1 (0.03%)	158 (0.18%)	31 (0.07%)	190 (0.14%)
Erythema	4 (0.13%)	80 (0.09%)	21 (0.05%)	105 (0.08%)
Dyspnea	2 (<0.1)	66 (<0.1)	28 (<0.1)	96 (<0.1)
Bronchospasm	0	7 (<0.1)	2 (<0.1)	9 (<0.1)
Face edema	0	4 (<0.1)	0	4 (<0.1)
Throat irritation	0	4 (<0.1)	0	4 (<0.1)
Dysphagia	0	2 (<0.1)	1 (<0.1)	3 (<0.1)
Dysphonia	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Eye swelling	0	0	2 (<0.1)	2 (<0.1)
Nasal congestion	0	2 (<0.1)	0	2 (<0.1)
Anaphylactic shock	0	0	1 (<0.1)	1 (<0.1)
Lacrimation increased	0	1 (<0.1)	0	1 (<0.1%)
Laryngeal edema	0	0	1 (<0.1)	1 (<0.1%)
Respiratory arrest	0	0	1 (<0.1)	1 (<0.1%)
Rhinitis	0	1 (<0.1)	0	1 (<0.1%)

*Multiple HSRs per subject were possible.
HSRs, hypersensitivity reactions.

10.5 Adverse events/adverse reactions

No new AEs/ADRs where were found in UV Age study as the performed integrated analysis was based on already existing data pooled from four company sponsored non-interventional studies with Iopromide, which have been analyzed regarding this question several times previously.

11. Discussion

11.1 Key results

This study analyzed the risk of HSRs to Iopromide in children (<18 years) and elderly patients (≥65 years) compared with adults (≥18 to <65 years) and revealed substantial evidence for a lower risk of HSRs in children and elderly. The results are in line with the hypothesis on which this investigation has been based.

We hypothesize that the pathophysiological reason for the lower HSR incidence in children and elderly is that in children the immune system gradually matures during infancy and in elderly the immune system deteriorates with age. 38 We thus suggest that the documented age dependency of

HSRs is consistent with an allergy-type nature of the reactions and that the age dependency in fact reflects an immune system status effect on the likelihood of the occurrence of such reactions.

Age dependency is thus added to the risk factors for which in our view the evidence is consistent and convincing: Main risk factor: Previous reaction, especially previous reaction to a known culprit brand in case the same brand is planned for new imaging. Route of administration, related to earlier or later lung passage (UVIA results, Endrikat et al. 2019), and now age/immune status. All three factors are consistent with a allergic nature of the HSRs to Iopromide/ICMs.

We consider the results of this investigation to be not only applicable to Iopromide but regarding the principle effect to all ICM (class effect mechanism).

Clinical Impact

Getting a better understanding of the age dependency of the HSR is of clinical importance. As one key safety concern it is important that the users have a complete as possible picture of the pathomechanisms of HSR. As both children and elderly are seen as more vulnerable patient groups it is an important information that the HSR risk correlates with age/immune status, making it less likely that such reaction occurs if the patient are younger or older than the adult reference population, where those reactions are also not frequent.

Considerations to some detail of the study

A previous evaluation of the observational studies showed a number of parameters impacting the risk of HSRs: route of administration, sex, history of diabetes mellitus, allergy, asthma, and previous contrast media reaction.15 This set of confounders was prespecified, and the statistical model was adjusted accordingly to demonstrate the effect of age. As expected, the number of patients in the 3 age groups was not evenly distributed. The majority of administrations were performed in adults (65 and 58%in analysis I and II, respectively) followed by elderly (32.5% in analysis I and II). Less than 2.3% of the study population were children (Table 1, Table 2). This is easily explainable by the different number of years summarized in the age brackets of the groups (children, 18 years; adults, 43 years) and the number of indications for contrast enhanced imaging. Importantly, this age group distribution is fairly similar in both databases supporting the approach to commonly report on

both data sets.

Previously published data pointing in a similar direction.

The results of the detailed analysis performed here, was already noticeable in first pooled analysis of the four non-interventional studies as well as in the report on the biggest of the four contributing studies Kopp et al. 2008 and Palkowitsch et al. 2014

Likewise, Zhang et al. 2014 investigated the incidence of ADRs by age in 137,473 patients after LOCM administration. A total of 428 cases of ADRs (0.31%) were recorded. The incidence in

children was 0.23% to 0.32%; in adults (20–60 years), 0.3% to 0.43%; and in elderly (>60 years), 0.11% to 0.27%, confirming our results.

Callahan et al. 2009 focused on a pediatric population up to 21 years who got ioversol. Over a period of 7 years, they included 12,494 patients at a large urban children's hospital. The overall incidence of contrast media reactions was 0.46%. They conclude that ADRs in children are rare and mild but significantly increasing with advancing age.

A number of other publications also reported that the majority of ADRs happen in the adult age group, that is, less frequent in the pediatric, and older population e.g. An et al. 2019, Seong et al. 2013.

Ho et al. 2012 analyzed 29,962 patients in a tertiary Australian hospital who got intravenous Iopromide and identified 47 cases of immediate HSRs (0.16%). There were 2 cases in the age group younger than 20 years; the peak incidence was between 50 and 59 years (16 cases) and declined after the age of 60. These results strongly confirm our results. Ho et al. 2012 finally claimed age younger than 55 years to be a statistically significant risk factor.

The lower incidence of ADRs in the elderly Population was reported by Katayama et al 1990, but not focusing on HSRs.

Just recently, Voltolini et al. 2021 reported findings from 9 Italian allergy centers. A total of 407 patients with HSRs were compared with 152 controls. Interestingly, male sex and age older than 65 years were associated with lower incidences of HSRs,37 confirming what we report here.

Open questions

A lot of thinking has gone into the potential risk factors for HSRs and the exact pathomechanisms, see e.g. Bush et al. 1991 or Schild 2014. While many questions are now solved also with the help of analysis performed in the and the previous study UVIA, the question of whether gender or ethnicity are independent risk factors for HSRs does not seem to be satisfactorily cleared. This could potentially be addressed in a further dedicated analysis of this pooled dataset.

11.2 Limitations

Some limitations need to be addressed. A total of 11,646 patients without documented age had to be excluded upfront. Although the investigated a data pool consists of of 4 very similar studies, conducted by Bayer using the same case report forms. slight differences in reporting standards (time of conduct, country of conduct) cannot be completely excluded.

In observational studies an underreporting cannot be ruled out, although this likely does not play a major role here, as recording of acute reactions was the primary goal of the observational investigations. Care is, however, mandated when interpreting the absolute reporting figures. An age-specific underreporting. bias (e.g. for very young children or very diseased elderly) seems unlikely but cannot be completely excluded based on the available data.

Sixth, we did not analyze specifically HSRs that occurred after reexposure, a topic of current scientific discussion.

Seventh, we did not record the temperature of Iopromide before injection, a topic also in current scientific focus.

11.3 Interpretation

UVAg4e confirms, keeping in mind the limitations stated above, previous hypotheses about the nature of HSRs, previously call anaphylactoid reactions to Iopromide and ICM – an allergic nature of the HSRs is consistent with the documented age/immune system status dependence.

11.4 Generalizability

The study population was global and heterogeneous, so that generalizability of this results is assumed to be high to all patients world-wide, as well as to other ICM brands.

Experts assume to have fundamentally similar mechanism for the triggering of HSRs across the so-called LOCM class (the non-ionic monomers).

12. Other information

N/A

13. Conclusion

This study confirmed the long-standing presumption of a lower risk for anaphylactoid reactions after i.a. administration versus i.v. administration in a sufficiently large cohort of Ultravist observational study patients.

References

Publication of the study results

Endrikat J, Chernova, J, Gerlinger C., Pracz M, Lengsfeld, P., Bhatti, and Michel A. Risk of Hypersensitivity Reactions to Iopromide in Children and Elderly An Analysis of 132,850 Patients From 4 Observational Studies and Pharmacovigilance Covering >288 Million Administrations, 2021 Invest Radiol (online first)

Source Studies

PMS I

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IMAGE

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Additional publications related to research question

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Appendices

Annex 1: List of stand-alone documents

List of stand-alone documents

Document Name	Final version and date (if available)*
Protocol	v 2.0 /28 Jan 2021
SAP	V 1.0 /10 March 2021

Annex 2 Signature Pages

Signature Page

Acronym/Title	Safety profile of Ultravist in children and elderly (UV Age)
Protocol version and date	v 2.0 /28 Jan 2021
Report version and date	V1.0/2nd February 2022
Impact	21494
EU PAS register number	EUPAS37597
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
IMPACT number	21494
Active substance	Radiological / Low Osmolar non-ionic Contrast Medium (LOCM), (V08AB05) Iopromide
Medicinal product	Ultravist
Study Initiator and Funder	Bayer AG
Research question and objectives	To describe the risk of hypersensitivity reactions to Ultravist specifically in children (< 18 years of age) and elderly patients (≥65 years), compared to those in the middle age group (≥ 18 to < 65 years).
Country(-ies) of study	37 countries including Europe (mostly Germany and Spain), Asia (mostly China and South Korea) and USA.
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG

The signatories agree that the study will be conducted under the conditions described in the protocol.

Signatories

- PPD (Study Conduct Responsible)
- PPD (Study Medical Expert)
- PPD (Study Statistician)
- PPD (Study Data Manager)
- PPD (Study Epidemiologist)
- PPD (Study Safety Lead)