PASS Information

Title	Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions
Protocol version identifier	Version 1.1
Date of last version of protocol	04 May 2017
EU PAS Register number	Will be registered in the EU PAS Register following regulatory endorsement and prior to start of data collection
Active substance	Intravenous iron products (ATC code: B03AC, Iron, parenteral preparations): ▪ Iron(III)-hydroxide dextran complex ▪ Iron sucrose complex/iron(III)-hydroxide sucrose complex ▪ Ferric carboxymaltose complex ▪ Iron(III) isomaltoside complex ▪ Sodium ferric gluconate complex
Medicinal product	Medicinal products in the countries targeted in this study are listed by International Nonproprietary Names and Invented Names (Note: Invented names are those of medicinal products marketed by members of the IV Iron Consortium. The study will also include equivalent medicinal products of pharmaceutical companies that are not part of the IV Iron Consortium.) **Denmark:** ▪ Iron(III)-hydroxide dextran complex: CosmoFer ▪ Iron sucrose complex: Venofer ▪ Ferric carboxymaltose: Ferinject ▪ Iron(III) isomaltoside complex: Monofer **France:** ▪ Iron(III)-hydroxide dextran complex: Ferrisat ▪ Iron sucrose complex: Venofer, Fer Mylan, Fer Panpharma, Fer Arrow, Fer Sandoz ▪ Ferric carboxymaltose: Ferinject **Germany:** ▪ Iron(III)-hydroxide dextran complex: CosmoFer ▪ Iron sucrose complex: Venofer, FerMed ▪ Ferric carboxymaltose: Ferinject ▪ Iron(III) isomaltoside complex: Monofer ▪ Sodium ferric gluconate complex: Ferrlecit **The Netherlands:** ▪ Iron(III)-hydroxide dextran complex: CosmoFer ▪ Iron sucrose complex: Ferracin, Venofer, ferrihydroxide sucrose complex ▪ Ferric carboxymaltose: Ferinject ▪ Iron(III) isomaltoside complex: Monofer

	Sweden: ▪ Iron(III)-hydroxide dextran complex: CosmoFer ▪ Iron sucrose complex: Venofer ▪ Ferric carboxymaltose: Ferinject ▪ Iron(III) isomaltoside complex: Monofer/Diafer
Product reference	Note: Product references listed are those for products produced by members of the IV Iron Consortium. The study will also include exposure to equivalent medicinal products of pharmaceutical companies that are not part of the IV Iron Consortium. FerMed: 71610.00.00 (German authorisation number) Ferrovin: 96896/13/03-02-16, 78933/11/05-04-2013 (Greece authorisation number) Ferrovin: 021660/ 09-01-2013 (Cyprus authorisation number) Venofer: ▪ 31111 (Denmark authorisation number) ▪ 3400957128340 (France authorisation number) ▪ 6462062.00.00 (Germany authorisation number) ▪ RVG 20690 (The Netherlands authorisation number) ▪ 15754 (Sweden authorisation number) Ferinject: ▪ 39254 (Denmark authorisation number) ▪ 66227.00.00 (Germany authorisation number) ▪ 33865 (The Netherlands authorisation number) ▪ France authorisation numbers: – Ferinject 1 x 2 mL: 34009 386 812 4 6 – Ferinject 1 x 10 mL: 34009 386 924 7 1 – Ferinject 2 x 2 mL: 34009 219 393 1 6 – Ferinject 2 x 10 mL: 34009 219 394 8 4 – Ferinject 5 x 2 mL: 34009 386 823 6 6 – Ferinject 5 x 10 mL: 34009 386 933 6 2 – Ferinject 1 x 20 mL: 34009 585 988 5 2 ▪ 23738 (Sweden authorisation number) Monofer: ▪ 27791 (Sweden authorisation number) Cosmofer: ▪ 23462 (Sweden authorisation number) Fercayl: ▪ Fercayl 100mg/2ml: BE168497 (Belgian authorisation number) Ferrlecit: ▪ 638 5744.00.00, 644 1686.00.00 (German authorisation numbers)
Procedure number	VIFOR: EMEA/H/A-31/1322

Marketing authorisation holder(s)	IV Iron Marketing Authorisation Holders Consortium, comprising the following marketing authorisation holders (MAHs): Accord Healthcare Limited, Acino Pharma AG, Arrow Génériques, Claris Lifesciences (UK) Limited, Generis Farmacéutica S.A., Genfarma/G.E.S Genéricos Españoles S.A.U, Laboratoires Sterop S.A., Medice Arzneimittel Puetter GmbH & Co. KG, Mylan S.A.S, Orifarm Generics A/S, Panmedica (Panpharma S.A.), Pharmachemie BV (Teva), Pharmacosmos A/S, Rafarm S.A., Sandoz S.A.S, Sanofi Aventis Groupe, and Vifor Pharma LTD
Joint PASS	Yes
Research question and objectives	The goal of the study is to assess the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylactic reactions") on the day of or the day after the first IV iron use through the following parameters: ▪ Incidence proportion of anaphylactic reactions in patients first dispensed/administered IV iron (new users) overall, by group of IV iron product—iron(III)-hydroxide dextran complex versus non-dextran IV iron products—and by the individual IV iron types listed below: – Iron(III)-hydroxide dextran complex – Iron sucrose complex/iron(III)-hydroxide sucrose complex – Ferric carboxymaltose complex – Iron(III) isomaltoside complex – Sodium ferric gluconate complex ▪ Risk ratios of anaphylactic reactions in patients first dispensed/administered IV iron (new users), by group of IV iron product—iron(III)-hydroxide dextran complex versus non-dextran IV iron products, and by the individual IV iron types listed below using iron sucrose complex/iron(III)-hydroxide sucrose complex as the comparator: – Iron(III)-hydroxide dextran complex – Ferric carboxymaltose complex – Iron(III) isomaltoside complex – Sodium ferric gluconate complex
Countries of study	▪ Denmark ▪ France ▪ Germany ▪ The Netherlands ▪ Sweden
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	[redacted] on behalf of the IV Iron MAH Consortium. See the full list of MAHs and address/contact details in Table 3-1 in Annex 3. [redacted] Mesama Consulting Bangertenweg 460 CH-4252 Bärschwil, Switzerland Telephone: [redacted] E-Mail: [redacted]@mesama-consulting.com
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Approval Page: Research Partners

Project Title: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

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Version and Date:	Version 1.1, 04 May 2017

On behalf of the IV iron PASS Research team:

[redacted]

4 MAY 2017

Date

Approval Page: IV Iron Consortium

Project Title: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

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(Centre for Pharmacoepidemiology, Karolinska Institute)

Version and Date: Version 1.1, 04 May 2017

On behalf of the IV Iron MAH Consortium

[redacted]

04-May-2017

Date

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2 List of Abbreviations

ATC	Anatomical Therapeutic Chemical (classification system)
BIPS	Leibniz Institute for Prevention Research and Epidemiology - BIPS
CI	confidence interval
CNAM-TS	French health care insurance system for salary workers except civil servants and students
DIMDI- DaTraV	Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information
DNPR	Danish National Patient Registry
EBM	Einheitlicher Bewertungsmaßstab
EGB	a 1/97 permanent representative sample of SNIIRAM
EMA	European Medicines Agency
EMA-PRAC	European Medicines Agency Pharmacovigilance Risk Assessment Committee
EMR	electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Union electronic register of postauthorisation studies
EU	European Union
GePaRD	German Pharmacoepidemiological Research Database
GP	general practitioner
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ICD-10-GM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICPC	International Classification of Primary Care
IRB	institutional review board
RR	risk ratio
IM	intramuscular
ISPE	International Society for Pharmacoepidemiology
IV	intravenous
KfH QiN	KfH - Kuratorium für Dialyse und Nierentransplantation e.V. (Board of Trustees for Dialysis and Kidney Transplantation) and its Qualität in der Nephrologie (Quality in Nephrology) programme, Germany
KI CPE	Karolinska Institute, Centre for Pharmacoepidemiology
MAH	marketing authorisation holder
*n*Q	*n*th quarter of the year
PASS	postauthorisation safety study
PHARMO	PHARMO Database Network or PHARMO Institute for Drug Outcomes Research
PMSI	national hospital discharge summaries database system (France)

PPV	positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
RTI	RTI International
RTI-HS	RTI Health Solutions
SHI	German statutory health insurance provider
SNIIRAM	French National Health Insurance Inter Plans Information System Database
US	United States of America
WHO	World Health Organization

3 Responsible Parties

RTI Health Solutions—Coordinating Centre

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The KI CPE research team has confirmed participation starting in April 2017.

IV Iron Consortium
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For list of Marketing Authorisation Holders Consortium member names and contact details, see Table 3-1 in Annex 3

Study oversight will be conducted by a scientific steering committee, and an external scientific advisory board will be set up between the research partners, both data sources, the coordinating centre (RTI-HS), and the sponsor.

4 Abstract

Title: Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

Version 1.1, 04 May 2017

[redacted]; RTI Health Solutions on behalf of the IV iron PASS Research Team

Rationale and background: Hypersensitivity reactions in association with intravenous (IV) iron preparations have been reported in previous studies. The European Medicines Agency Pharmacovigilance Risk Assessment Committee (EMA-PRAC) recommended that marketing authorisation holders of IV iron compounds conduct a postauthorisation safety study (PASS) to further characterise the safety concerns regarding hypersensitivity reactions.

Research question and objectives: To evaluate the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylactic reactions") on the day of or the day after the first IV iron use by estimating the incidence proportions of anaphylactic reactions occurring on the day of or the day after in patients first dispensed/administered IV iron (new users), overall, by group of IV iron product [iron(III)-hydroxide dextran complex vs. other IV irons], and by type of IV iron product [iron(III)-hydroxide dextran complex, iron sucrose complex/iron(III)-hydroxide sucrose complex, ferric carboxymaltose complex, iron(III) isomaltoside complex, sodium ferric gluconate complex]. Risk ratios will be used to assess comparative risk of the outcome between IV iron groups and among the various IV iron types at the first exposure. The risk of anaphylactic reactions among new users of selected "anaphylaxis marker compounds" (that is, compounds for which anaphylaxis is a well-recognised effect), such as IV penicillin, will be calculated in general-population data sources to provide context for the risk in users of IV iron.

Study design: European multinational, longitudinal cohort study of new users of IV iron compounds conducted in populations covered through large electronic health databases and patient registries in Denmark, the Netherlands, France, Germany, and Sweden. The study period will vary across data sources and is defined as the time between the date of the first-available recorded code for dispensing/administration of IV iron and the latest date of data availability in each data source (ranging from as early as January 1998 through as late as December 2016). The start of the study will take into account the minimum 12-month lookback period required.

Population: The study cohort comprises adults from the source populations with at least 12 months of continuous enrolment in the data source who have a first-recorded code for dispensing or administration (hereafter, "dispensing/administration") of an IV iron compound or an IV anaphylaxis marker compound during the study period and had not received a dispensing/administration for the same study drug category within at least the prior 12 months. Patients will enter the cohort only once, and patients with concurrent use of IV iron and the anaphylaxis marker compound will not be included.

Variables: The main exposure of interest will be new use of selected IV iron products, which will be assessed through data for dispensed/administered medications as appropriate in each data source. New use of anaphylaxis marker compounds will be similarly assessed. The study outcome, anaphylactic reactions, will be defined according to a consensus clinical definition and identified through data source–specific algorithms. The outcome will be validated through direct source verification in the Central Denmark Region and in hospitals in the PHARMO Database Network in the Netherlands; indirect partial validation of the case-finding algorithm will be conducted in Germany and, if feasible, in France. Other variables of interest include medical conditions or medications that are indicators of a history of hypersensitivity reactions, indicators of severity of anaemia, conditions that are indicators of the indication for IV iron treatment and other relevant comorbidities and medications.

Data sources: Based on the results of feasibility evaluations in 2014 and 2016, the following data sources have been identified as the best candidate data sources in which to implement the study: the Health Services Database of the Central Denmark Region and national registries in Denmark; the PHARMO Database Network in the Netherlands; the French National Health Insurance Inter Plans Information System Database (SNIIRAM) in France; and in Germany, the German Pharmacoepidemiological Database (GePaRD), the registry of the KfH - Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN), the German Institute of Medical Documentation and Information (DIMDI)/Daten-transparenzverordnung] (DaTraV) database and hospitals in the Oldenburg area; and national registries in Sweden. All the research institutions have confirmed interest in participating in the study.*

Study size: The study will include all patients fulfilling the inclusion criteria and having none of the exclusion criteria. Based on the study feasibility assessments, approximately 250,000 to 300,000 patients with IV iron dispensings/administrations could be included. However, numbers may be small for the analysis of selected IV iron types.

Data analysis: Cohorts of new users of each IV iron type will be identified, and baseline characteristics of new users in each cohort will be assessed through descriptive analysis. Propensity scores that include other risk factors for anaphylaxis will be used to adjust for known confounders after trimming of the cohorts. If numbers are adequate, incidence proportions and risk ratios will be estimated individually in each data source, by IV iron group (dextrans, non-dextrans) and for each IV iron type using iron sucrose as the common comparator group. If the findings across data sources are homogeneous, pooled analysis will be conducted across data sources and countries with aggregate data based on event and patient numbers. Sensitivity analysis will include estimation of crude incidence proportions and risk ratios in the overall cohort, different time-at-risk windows for data sources with dispensed rather than administered IV medications, estimates for second and subsequent dispensings/administrations, and the impact of the regulatory referral in Europe and of the validation results. Incidence proportions of anaphylactic reactions will be estimated for patients with exposure to the anaphylaxis marker

* Participation of researchers at the Karolinska Institute using data from the Swedish national registers is planned to start in April 2017.

compounds. Researchers from each data source will conduct the data analysis according to the common protocol and a common statistical analysis plan, with documentation of data source–specific adaptations. Pooled analyses will be conducted at the coordinating centre.

Milestones[*]:

- Protocol submission to EMA-PRAC: 21 December 2016
- EMA-PRAC protocol endorsement: Anticipated 3Q 2017
- Registration in the EU PAS Register, including the protocol (following regulatory endorsement): 3Q 2017
- Ethics or other relevant approvals and data source–specific adaptation of study materials: 3Q-4Q 2017
- Start of data collection, i.e., retrieval (first data source): 1Q 2018
- Start of outcome validation studies: To be determined
- End of data collection, i.e., complete analytical data set (last data source for main analyses): 4Q 2018-1Q 2019
- Data source analysis: 1Q-2Q 2019
- Pooled analysis: 2Q-3Q 2019
- Final report of study results: 3Q 2019-1Q 2020 (an additional report may be needed for the re-analysis after source record validation has been completed)
- Final report of study results including DaTraV data: date to be determined

[*] Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

5 Amendments and Updates

The protocol version 1.1, dated 04 May 2017 is the amended protocol that incorporates modifications based on the comments made by the PRAC in the final protocol assessment report of 09 March 2017.

Summary of Amendments and Updates

Version Number	Date	Section(s) of Study Protocol	Amendment	Reason
1.1	04 May 2017	PASS Information, Annex 3, List of MAHs	Updated lists of medicinal products and marketing authorization holders; updated authors' contact information	Changes in MAHs consortium membership; updated contact details of authors
1.1	04 May 2017	Section 4, Abstract, Milestones; Section 6, Milestones and Timeline	Revised anticipated date of EMA protocol endorsement. New milestone for study report including DaTraV sensitivity analysis	Account for time required for PRAC's review and endorsement of amended protocol. Because of uncertainty around DaTraV study component timelines
1.1	04 May 2017	Section 9.1. Study Design	Added details on potential candidate products for IV anaphylaxis markers	Address PRAC's request
1.1	04 May 2017	Section 4, Abstract; Section 9.2.2, Study Period, Table 4	Revised timelines for expected study end date	Address PRAC's comment to use latest available data
1.1	04 May 2017	Section 9.2.3, Study Cohort	Clarified that selection of new users in each cohort will be done independently Clarified exclusion criteria and censoring events	Address PRAC's request
1.1	04 May 2017	Section 9.3.1, Exposures Section, Table 5	Streamlined table	To clarify that all types of compounds, regardless of brand/product name, are included in the study
1.1	04 May 2017	Section 9.3.1, Exposures Section Table 6	Added information on capture of intravenous versus intramuscular administration	Incorporate newly available information and address PRAC request
1.1	04 May 2017	Section 9.3.2 Outcomes Section	Updated codes for adrenaline (epinephrine)	Complete information

Version Number	Date	Section(s) of Study Protocol	Amendment	Reason
1.1	04 May 2017	Section 9.3.2.1, Outcomes Validation, Section 9.7.4.4, Adjustment of Incidence Estimates by Positive Predictive Value	Clarified indirect validation process	Address PRAC's request
1.1	04 May 2017	Section 9.3.3, Other Variables, Table 7	Modified evaluation period for confounding variables	Address PRAC's request
1.1	04 May 2017	Abstract, Section 9.7.3 Incidence Proportions and Comparative Analyses	Included subsequent dispensings/administrations in main analyses	Address PRAC's request
1.1	04 May 2017	Section 9.7.4.3, Impact of Referral Letter Assessment	Specified method to assess impact of referral letter	Address PRAC's request
1.1	04 May 2017	Section 9.7.5, Pooled Analysis	Revised text to clarify generation of pooled estimates and provided further details on methods used for pooling	Clarify plan for deriving pooled estimates Address PRAC's request

6 Milestones and Timeline

Milestone	Actual/Estimated Date
Protocol submission to EMA-PRAC: 3 months after receipt of the final assessment of the extended feasibility study report	21 December 2016
EMA-PRAC protocol endorsement	Anticipated by 3Q 2017
Registration in the EU PAS Register including the protocol (following regulatory endorsement)	3Q 2017
Ethics or other relevant approvals and data source–specific adaptation of study materials	3Q-4Q 2017
Start of data collection[a] i.e., retrieval (first data source)	1Q 2018
Start of outcome validation studies	To be determined
End of data collection[b] i.e., complete analytical data set (last data source for main analyses)	4Q 2018-1Q 2019
Data source analysis	1Q-2Q 2019
Pooled analysis	2Q-3Q 2019
Final report of study results	3Q 2019-1Q 2020 (an additional report may be needed for the re-analysis after source record validation has been completed)
Final report of study results including DaTraV data	TBD

EMA-PRAC = European Medicines Agency Pharmacovigilance Risk Assessment Committee; EU PAS Register = European Union electronic register of postauthorisation studies; *n*Q = *n*th quarter of the year.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts." (EMA, 2016)

[b] End of data collection is "the date from which the analytical data set is completely available." (EMA, 2016)

7 Rationale and Background

7.1 Rationale

Intravenous (IV) iron therapy was introduced in the 1950s for the treatment of severe anaemia (Auerbach and Ballard, 2010). In the last decades, the use of IV iron has been growing worldwide due to a better understanding of the management of moderate and severe anaemia related to numerous conditions such as chronic kidney disease, heavy uterine bleeding, pregnancy and postpartum anaemia, chemotherapy-induced anaemia, elective surgery, and chronic heart failure (Bailie and Verhoef, 2012). Studies evaluating hypersensitivity reactions in association with IV iron preparations have been previously

reported (Bailie et al., 2005; Bailie and Verhoef, 2012; Chertow et al., 2004; Chertow et al., 2006; Walsh et al., 2016; Wang et al., 2015).

The benefit-risk of iron-containing IV medicinal products was evaluated by the European Medicines Agency (EMA) in the context of a referral under Article 31 of Directive 2001/83/EC completed in September 2013. The iron complexes involved in the EMA's referral procedure were ferric carboxymaltose, iron dextran, sodium ferric gluconate, iron isomaltoside, and iron sucrose, which are authorised in European Union Member States (EMA, 2016).

As a result of this evaluation, the EMA imposed a labelling update reinforcing risk information on hypersensitivity reactions and formulated a series of "conditions to marketing authorisation," which included the recommendation by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) for the *"MAHs to conduct a post-authorisation safety study (PASS) to further characterise the safety concerns on the hypersensitivity reactions. The study will also have to be reflected in the updated/new RMP submission*" (EMA, 2016).

To address the EMA request, a consortium of IV iron manufacturers was created to conduct a non-interventional pharmacoepidemiology safety study in multiple European Union (EU) countries. This common protocol describes the study design, data sources, and analytical aspects and takes into account the results of the IV iron PASS feasibility evaluations performed in 2014 and 2016 (Gutierrez et al., 2014; Gutierrez et al., 2016) and the answers to questions submitted by the IV Iron Consortium to National Competent Authorities and the lead EMA-PRAC rapporteur in December 2014 and September 2015. It also takes into account comments from regulatory assessment reports from June 2016, July 2016, and October 2016. When different options for study design and analysis were available, our goal in making decisions was to align as much as possible with the recent studies in the United States of America (US) Medicare and Sentinel systems (see Background section).

7.2 Background

Hypersensitivity reactions in association with IV iron preparations have been reported in the scientific literature (Bailie et al., 2005; Bailie and Verhoef, 2012; Chertow et al., 2004; Chertow et al., 2006; Walsh et al., 2016; Wang et al., 2015).

Bailie and Verhoef (2012) conducted a study using data on adverse events reported to the World Health Organization (WHO) Uppsala Monitoring Centre in Sweden based on data collected from the first quarter of 2003 through the second quarter of 2009 from 16 European countries and North America. Serious allergic adverse events were defined as anaphylaxis plus other serious allergic reactions. Anaphylaxis was defined using the WHO's Adverse Reaction Terminology standardised coding system. Other serious allergic reactions were classified as any other events where the reports included any terms or codes for systemic allergy combined with any term for cutaneous evidence of bradykinin or histamine release. Reported rates of serious allergic reactions related to IV iron, per gram of iron used per million inhabitants, were between 1×10^{-3} and 90×10^{-3} events for sodium ferric gluconate, between 0.9×10^{-3} and 47×10^{-3} events for iron dextran, and

between 0.2 x 10^{-3} and 2.7 x 10^{-3} events for iron sucrose (Bailie and Verhoef, 2012). These findings suggest that the risk of anaphylaxis after IV iron administration is low.

Wang et al. (2015) conducted a cohort study of new users of IV iron products (n = 688,183) enrolled in the US fee-for-service Medicare programme from January 2003 through December 2013 and found that the risk for anaphylaxis assessed on the same date of a first exposure was 68 per 100,000 persons for iron dextran (95% confidence interval [CI], 57.8-78.7 per 100 000 persons) and 24 per 100,000 persons for all non-dextran IV iron products combined (iron sucrose, gluconate, and ferumoxytol) (95% CI, 20.0-29.5 per 100,000 persons), with an adjusted odds ratio of 2.6 (95% CI, 2.0-3.3). The estimated cumulative risk of anaphylaxis following total iron repletion of 1,000 mg administered over a 12-week period was highest with iron dextran (82 per 100,000 persons; 95% CI, 70.5- 93.1) and lowest with iron sucrose (21 per 100,000 persons; 95% CI, 15.3-26.4) (Wang et al., 2015). This study has been criticised on the basis of a potential misclassification of exposure due to the grouping of high- and low-molecular-weight dextrans together, as well as potential misclassification of the anaphylaxis outcome (DeLoughery and Auerbach, 2016). However, the authors have argued that the very low use of high-molecular-weight iron dextran ascertained during a study interval period suggest that results likely represent the risk of the low-molecular-weight dextran. Kalra and Bhandari (2016) recently reported on an estimate of the risk of death that they derived from Wang et al. supplemental data. According to their calculations, the risk of death was greater for the non-dextran IV iron group than for the IV iron dextrans (relative risk, 2.07; 95% CI, 0.99-4.78).

In the US, a large multisite database study was conducted under the Food and Drug Administration's Sentinel programme to evaluate the risk of anaphylactoid/anaphylaxis reactions on the day of or the day after exposure among IV iron users, in which health plan members with a first administration of a parenteral iron preparation were identified from January 2000 through June 2013 (Walsh et al., 2014; Walsh et al., 2013). Results from this study, based on a cohort of 70,866 new users of IV iron not undergoing dialysis, are consistent with those published in the Medicare study by Wang et al. (2015). The study reports crude incidence rates of 4 per 10,000 person-days (95% CI, 2-8) among iron dextran users and 2 per 10,000 person-days (95% CI, 1-3) for users of other iron products, with a 2.6-fold greater risk of anaphylaxis among IV iron dextran users than among users of non-dextran IV irons (Walsh et al., 2016). Walsh et al. (2013) had previously reported on the validation of an algorithm developed to identify anaphylaxis using health plan administrative and claims data within the Mini-Sentinel program. Using the clinical criteria by Sampson et al. (2006) as the gold standard, the positive predictive value for the algorithm based on ICD-9-CM codes was 63.1% (95%CI, 53.9%–71.7%).

8 Research Question and Objectives

The goal of the study is to assess the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylactic reactions"), overall and by groups and types, among patients with various indications for IV iron, including patients undergoing dialysis, in routine clinical practice in European populations.

The following parameters will be estimated:

- Incidence proportion (risk) of anaphylactic reactions occurring on the day of or the day after exposure to the first (new users), second, and subsequent, and overall dispensing/administration of any IV iron, by group of IV iron product (iron(III)-hydroxide dextran complex vs. other IV irons), and by the individual IV iron types listed below:
  - Iron(III)-hydroxide dextran complex
  - Iron sucrose complex/iron(III)-hydroxide sucrose complex
  - Ferric carboxymaltose complex
  - Iron(III) isomaltoside complex
  - Sodium ferric gluconate complex
- Risk ratios will be used to compare the risk of anaphylactic reactions between IV iron groups (i.e., dextrans vs. non-dextrans) and among the various IV iron types (iron sucrose, the IV iron type with longest time since marketing authorisation and the largest expected number of users), will be used as the comparison reference group) at the first exposure.
- The incidence proportion of anaphylactic reactions in patients first dispensed/administered selected anaphylaxis marker compounds will be calculated to provide context for the incidence of anaphylactic reactions from a medication group with a well-recognised risk of anaphylaxis.

9 Research Methods

9.1 Study Design

The study will be a European, multinational, multidatabase, retrospective cohort study of patients initiating IV iron treatment conducted in populations covered through large electronic health databases and patient registries in Europe. To obtain a sufficient number of IV iron new users to address the study objectives given the low frequency of anaphylactic reactions, multiple European data sources covering large populations will be used. According to the results of the study feasibility assessments conducted in 2014 and 2016, data sources that capture use of IV iron compounds include data sources in Denmark, the Netherlands, France, Germany, and Sweden. During the study feasibility assessment phase, capture of the exposure and outcome were assessed cross-sectionally.

The following research centres have confirmed their interest in participating in this PASS:

- Aarhus University, for the Health Services Database of the Central Denmark Region and Danish national registries, Denmark
- PHARMO Institute for Drug Outcomes Research, for the PHARMO Database Network (PHARMO), the Netherlands

- Bordeaux PharmacoEpi Research Unit CIC1401 of Bordeaux University (BPE), for the National Health Insurance Inter Plans Information System (SNIIRAM), France
- Leibniz Institute for Prevention Research and Epidemiology - BIPS (BIPS), for the German Pharmacoepidemiological Research Database (GePaRD)
- Oldenburg University, for hospitals in the Oldenburg area, Germany
- University of Cologne, for the registry of the KfH – Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN), Germany
- Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information (DIMDI-DaTraV), Germany. [Interest in participation was confirmed in November 2016, details in the protocol as available]
- Karolinska Institute, for the Swedish national registers starting in April 2017. [Interest in participation was confirmed in November 2016, details in the protocol as available]
- RTI Health Solutions as the coordinating centre

A detailed description of confirmed participating data sources is included in Section 9.4.

The purpose of the proposed study is to estimate the risk of anaphylactic reactions occurring on the day of or the day after a first dispensing/administration of an IV iron medication. Risk will be estimated using the incidence proportion among patients receiving any IV iron medication overall, by defined groups (i.e., IV iron dextrans vs. non-dextrans), and by individual types of IV iron products (i.e., iron dextrans, iron sucrose, ferric carboxymaltose, iron isomaltoside, and sodium ferric gluconate). Risk ratios and 95% confidence intervals (95% CI) will be used to compare the risk of anaphylactic reactions at the first (main analysis), second, and subsequent IV iron exposure overall and by the defined IV iron groups and individual types of IV iron. For comparisons between individual medication types, iron sucrose complex//iron(III)-hydroxide sucrose complex will be used as the comparator because it is the most frequently used type of IV iron, which will provide more robust estimates.

Anaphylaxis has not been studied in most of the data sources; therefore, in general-population data sources, to put into context the risk of anaphylactic reactions associated with exposure to IV iron and to have a marker with which to gauge the incidence estimates for the outcome of interest observed in each data source, the risk of anaphylactic reactions in patients initiating treatment with selected anaphylaxis marker compounds will also be assessed. These compounds will be selected in each data source based on the information available and on the characteristics of the population covered. Targeted compounds are intravenously administered products that are commonly used, have a well-characterised risk of anaphylaxis, and can be captured comprehensively in each data source.

In a preliminary assessment of possible candidate products, IV penicillins were selected as appropriate markers of anaphylaxis by the Health Services Database of the Central

Denmark Region, the PHARMO Database Network in the Netherlands, the French SNIIRAM database, and the GePaRD and DaTraV databases in Germany. The Danish National Patient Registry (DNPR), the KfH-QiN database in Germany, and the Swedish national registers will not be able to use any IV product as a marker of anaphylaxis due to limited or no coverage of in-hospital administered substances in the data sources. With rare exceptions (e.g., IV iron), IV products are administered only to hospitalised patients.

Preliminary counts of users of IV penicillins from data sources where preliminary counts were available are shown in Table 1, Table 2, and Table 3.

Table 1. Preliminary Counts of New Users of IV Penicillins in the Health Services Database of the Central Denmark Region in 2014

ATC Code	Type of IV Penicillin	Estimated New User Counts in 2014
J01CA01	Ampicillin	2,200
J01CA11	Mecillinam	1,200
J01CE01	Benzylpenicillin	4,800
J01CF01	Dicloxacillin	5,100
J01CF02	Cloxacillin	300
J01CF05	Flucloxacillin	< 10
J01CR02	Amoxicillin and enzyme inhibitor	< 10
J01CR05	Piperacillin and enzyme inhibitor	5,500

ATC = Anatomical Therapeutic Chemical; IV = intravenous.

Table 2. Preliminary Counts of New Users of IV Penicillins in the SNIIRAM Database in France. Period 2005-2014

ATC Code	Type of IV Penicillin	Estimated New User Counts 2005-2014
J01CA13	Ticarcillin	23,000
J01CR01	Ampicillin and enzyme inhibitor	
J01CR03	Ticarcillin and enzyme inhibitor	
J01CR05	Piperacillin and enzyme inhibitor	

ATC = Anatomical Therapeutic Chemical; IV = intravenous.

Table 3. Preliminary Counts of Unique Users of IV Penicillins in the PHARMO Database Network in the Netherlands. Period 2000-2015

ATC Code	Type of IV Penicillin	Estimated Unique User Counts 2000-2015
J01CA12	Piperacillin	4,400
J01CE01	Benzylpenicillin	26,000
J01CR05	Piperacillin and enzyme inhibitor	7,500

ATC = Anatomical Therapeutic Chemical; IV = intravenous.

The outcome of interest is anaphylactic reactions, which will be defined as a "serious allergic reaction that is rapid in onset and may cause death,'' according to the consensus definition of the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) (Sampson et al., 2006).

Given the nature of the anaphylactic reactions (i.e., the risk of anaphylaxis rapidly decreases after the first administration of the drug), the study will use a "new user" design (Ray, 2003). This approach will allow for more comparable study groups. New users will be defined as individuals starting treatment with IV iron without a recorded code for dispensing/administration of these drugs within at least 12 months prior to the cohort entry date.

Given the pathophysiological characteristics of anaphylactic reactions, subjects will be at risk for the outcome of interest only for a limited amount of time after an administration of IV iron or IV anaphylaxis marker compounds. The preferred exposure assessment would be through the date and time of administration of the medication. However, time of administration is not available in the data sources, and only date of dispensing is available in most data sources. For the main analyses in general-population data sources, the window of time at risk will be the day of and the day after the dispensing/administration of the drug. The date of administration will always be preferred if that date is available and reliable. For data sources relying only on drug dispensing codes, a sensitivity analysis exploring an alternative window of time at risk (i.e., 8-day risk window) will be conducted.

A number of demographic and medical and treatment history variables may act as confounders of the association of IV iron therapy and the risk of anaphylactic reactions. Given the small number of expected events, confounding by covariates at baseline will be addressed through propensity score methods (Cepeda et al., 2003; Perkins et al., 2000) (see Section 9.3.3). The main approach is to build independent propensity scores for each comparison of interest.

Two-phase methodological approaches have been used in epidemiology to address residual confounding due to missing information (Behr et al., 2012). Data on potential confounding factors are available. Case record evaluation will focus on the validation of cases and/or case-identification algorithms. Direct validation of the cases will be conducted in the Health Services Database of the Central Denmark Region for Danish data and hospitals in the PHARMO Database Network for the Netherlands. Indirect validation of case-identification algorithms will be conducted through hospitals in the

Oldenburg area in Germany for the GePaRD and DaTraV and may be performed through some hospitals in France for the SNIIRAM.

9.2 Setting

9.2.1 Source Population

The source population will comprise all individuals who have at least 12 months of registration during the study period (defined in Section 9.2.2) in each of the participating data sources.

9.2.2 Study Period

The study period is defined in each data source as the time between the date of the first-available recorded code for dispensing or administration of IV iron and the latest date of data availability (see Table 4). In each data source, the date for the start of the study will take into account the minimum 12-month lookback period required. Data availability in each data source depends on the frequency with which data are updated at each data source and on the approvals for obtaining the data.

Table 4. Estimated Study Period in Each Data Source

Data Source	Start Date[a]	Expected End Date
Denmark, DNPR	01 January 2005	30 June 2016
Denmark, Health Services Database of the Central Denmark Region, incl. EMR	01 January 2010	31 December 2016
The Netherlands, PHARMO Database Network	01 January 1998	31 December 2016
France, SNIIRAM	01 January 2008	31 December 2014[b]
Germany, GePaRD	01 January 2005	31 December 2015
Germany, KfH QiN	01 January 2008	31 December 2015
Germany, DIMDI-DaTraV	01 January 2009	31 December 2013
Germany, hospitals in the Oldenburg area	01 January 2005	31 December 2015
Sweden, national registers	01 January 2007	31 December 2016

DIMDI-DaTraV = Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information; DNPR = Danish National Patient Registry; EMR = electronic medical record; GePaRD = German Pharmacoepidemiological Research Database; SNIIRAM = National Health Insurance Inter Plans Information System; KfH QiN = registry of the KfH – Board of Trustees for Dialysis and Kidney Transplantation Quality in Nephrology programme.

[a] The start date in each data source accounts for the minimum 12-month lookback period required before the start date.

[b] IV iron was removed from the list of reimbursed medications in 2014; therefore, data on IV iron will not be available after this date.

9.2.3 Study Cohort

The study cohort comprises all adults from the source population who are first dispensed/administered IV iron during the study period, have been continuously enrolled or registered in the data source for at least 12 months prior to the first-recorded code for dispensing/administration of IV iron, and are at least 18 years of age on the date of the first dispensing of IV iron.

The same approach will be used for the anaphylaxis marker compounds that will be used as an indicator of the capture of anaphylaxis diagnoses in each data source. The selection of the compound in each data source will be based on data source–specific characteristics and data captured.

9.2.3.1 New Users

Patients will be considered new users of IV iron or of the anaphylaxis marker product (e.g., IV penicillins) if they have no documented dispensing/administration of any IV iron or anaphylaxis marker product during at least the preceding 12 months prior to cohort entry. Due to the idiosyncratic nature of hypersensitivity reactions, patients will be allowed to enter the study only once. No switches between IV iron compounds will be allowed. However, prior use of the anaphylaxis marker products will not affect the eligibility status as a new user of IV iron and vice versa, as cross-reactivity between IV iron and IV penicillins is considered to be highly unlikely.

9.2.3.2 Cohort Entry Date

The cohort entry date (day 0) is defined as the date of receiving a first dispensing/ administration of IV iron therapy or selected anaphylaxis marker compounds that qualifies the user as a “new user.”

9.2.3.3 Inclusion Criteria

All individuals meeting *all* of the following criteria during the study period are eligible for inclusion in the study:

- Aged 18 years or older as of the cohort entry date
- First dispensing/administration of one of the study IV iron compounds or IV anaphylaxis marker compounds with no code for dispensing/administration of these medications during the prior 12 months (new users)
- Continuous registration in the study data source for at least 12 months before the cohort entry date

9.2.3.4 Exclusion Criteria

Patients that qualify as new users for drug A (IV iron or the selected anaphylaxis marker product) ***will not*** be excluded because of having a prior use of drug B (anaphylaxis marker product or IV iron). However, concurrent administration of an IV iron compound and an anaphylaxis marker product within the risk window defined for the main analysis (i.e., 2-day risk window) will be an exclusion criterion.

Patients with a prior history of any hypersensitivity reaction ***will not*** be excluded, to enable assessment of the risk of anaphylactic reactions among patients with different baseline risks of these reactions.

9.2.3.5 Censoring Events and Follow-up

Patients will be followed from the cohort entry date until the first occurrence of any of the following censoring events:

- Occurrence of a study outcome (event index date)
- Death
- End of study period
- Switch between types of IV iron
- Concurrent use (i.e., within the 2-day risk window) of IV iron and IV anaphylaxis marker product
- Day 2 (main analysis) or day 8 (sensitivity analysis) after dispensing/ administration of the IV iron type that rendered the patient eligible for cohort entry, with no subsequent dispensing/administration of another IV iron product or selected IV anaphylaxis marker compound during this time window
- Disenrollment from the data source

In general-population data sources, for the main analyses, the follow-up time after a code for a dispensing/administration of the study drugs, during which outcomes will be considered, will be the same day on which this code appears and the day after. In the KfH QiN registry database in Germany, and any other data source providing the date of administration (Health Services Database of the Central Denmark Region, PHARMO In-patient Pharmacy), only the day of the administration will be considered time at risk.

For data sources with only dispensing codes available (i.e., where no data on dates of actual treatment administration are available), a sensitivity analysis will consider a follow-up time of up to 7 days after each code for dispensing of a study medication. In some data sources (e.g., GePaRD) it might be possible that patients receive a dose that is stored at the practice and get a prescription to refill (i.e., dispense) the medicine. In this situation, a sensitivity analysis using the prescription date instead of the dispensing date will be performed.

9.3 Variables

9.3.1 Exposures

Exposure to IV iron compounds in each data source will be assessed according to the Anatomical Therapeutic Chemical (ATC) classification system (code B03AC has been assigned to all parenteral iron preparations) and additional country and data source–specific coding nomenclatures or systems used for identifying substance- or product-specific information including recording of prescription, dispensing, and procedural treatment administration codes for IV drugs, as available.

The selected study IV iron products and corresponding ATC codes captured in the study data sources are presented in Table 5.

Table 5. Study IV Iron Compounds

Type of Intravenous Iron Product	ATC Drug Class / Substance Code	Country
Iron sucrose complex	B03AC/B03AC02	Denmark, Germany, Netherlands, Sweden
Ferric carboxymaltose complex	B03AC/B03AC01	Denmark, France, Germany, Netherlands, Sweden
Iron(III)-hydroxide dextran complex	B03AC/B03AC06	Denmark, Germany, Netherlands, Sweden
Iron(III) isomaltoside complex	B03AC/B03AC06	Denmark, Germany, Netherlands, Sweden
Sodium ferric gluconate complex	B03AC/B03AC07	Germany

ATC = Anatomical Therapeutic Chemical (classification system).

Note: The ATC classification version of January 2014 classified all "Iron, parenteral preparations" on the ATC 4th level only (B03AC), and the 5th-level ATC codes (e.g., B03AC01, B03AC02) were deleted. This means that the 5th-level ATC codes can be used only in combination with product names.

All IV iron compounds in each data source will be included. The type of IV iron compound will be categorised as follows for study analyses:

- Iron(III)-hydroxide dextran complex ("IV iron dextrans")
- Iron sucrose complex/iron (III)-hydroxide sucrose complex
- Ferric carboxymaltose complex
- Iron(III) isomaltoside complex
- Sodium ferric gluconate complex

For comparative analyses, IV iron dextrans will be compared with non-dextrans (all other types of IV iron). In addition, the IV iron types listed above will each be compared individually with iron sucrose complex, to the extent that numbers allow.

The data source–specific information related to study drug exposure ascertainment is summarised in Table 6.

Table 6. Outcome and Variable Assessment in Study Data Sources

Data Source	Outcome Identification and Validation	Exposure Ascertainment	Other Variables
Danish National Patient Registry (DNPR) and Health Services Database of the Central Denmark Region	ICD-10 codes Direct validation in the Central Denmark Region	Inpatient, outpatient specialist, and emergency room data for the whole country in the DNPR and electronic medical records in the Health Services Database of the Central Denmark Region (inpatient and outpatient hospital specialty clinics) Dispensed drugs for whole country; administered drugs for the Central Region. In the DNPR, iron compounds are coded as "parenteral" (code BOHC12) although the majority appear to be IV. Hospital-administered treatments may be identified in the DNPR through treatment codes if a code has been assigned for hospital reimbursement purposes Drug class or substance-specific code in the DNPR; ATC code plus product-specific information in the Health Services Database of the Central Denmark Region Active substance name, strength, brand, route of administration, amount dispensed, date of dispensing, and administration date (for drugs coded using ATC codes in the Health Services Database of the Central Denmark Region)	ICD-10 codes
PHARMO Database Network, Netherlands	ICD-9-CM and ICD-10 codes for patients requiring a hospital bed; mortality data available; partial GP Database with ICPC codes Partial direct validation might be possible (approval of hospitals is required)	Out-patient and In-patient Pharmacy and partial GP Database Prescribed or dispensed (GP data only), and/or administered ATC codes (drug class code, active substance code through free text searching on package label) Brand name, dose, date of dispensing/prescription (Out-patient Pharmacy and GP Databases), route of administration (available from dosing information for some patients in the outpatient pharmacy data and for all patients in the inpatient pharmacy data) and date of treatment administration (In-patient Pharmacy Database)	ICD-9, ICD-10-CM, and ICPC codes ATC codes for specific treatments will be added to algorithms to define some medical conditions (e.g., hypertension)

Data Source	Outcome Identification and Validation	Exposure Ascertainment	Other Variables
French National Information System Inter Plans Health Insurance Database	ICD-10 codes Partial indirect validation may be possible in the Bordeaux area	Outpatient pharmacy and inpatient pharmacy (for non-hospitalised patients only) Dispensed drugs Date of treatment administration will be available for most patients based on the date of the first outpatient nurse visit encounter after drug dispensing ATC and CIP codes Brand name, dose, dispensed. It will not be possible to differentiate IV from IM iron exposure	ICD-10 codes
German Pharmacoepi-demiological Research Database (GePaRD)	ICD-10-GM codes Indirect partial validation of case-identification algorithm through hospitals in Oldenburg area	Outpatient pharmacy data with date of prescription and dispensing, which can be linked via an identification code (PZN) to the following information: ▪ Dispensed drugs ▪ ATC codes ▪ Brand name, dose dispensed Outpatient care data (GP and specialist) procedure codes ▪ Might be used for date of administration It will not be possible to differentiate IV from IM iron exposure.	ICD-10-GM codes

Data Source	Outcome Identification and Validation	Exposure Ascertainment	Other Variables
KfH - Board of Trustees for Dialysis and Kidney Transplantation Registry (KfH QiN)	ICD-10-GM codes No validation possible	Drug administration in dialysis centre ATC codes Brand name/compound type, dosage, route, and date of administration	ICD-10-GM codes
Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information (DIMDI-DaTraV)	ICD-10 GM codes Indirect validation of case-identification algorithm through hospitals in Oldenburg area	Dispensed drugs in ambulatory pharmacy (reimbursed) PZN (Pharmazentralnummer, nationwide identification number for pharmaceuticals), number of prescriptions, date of prescription and brand name. It will not be possible to differentiate IV from IM iron exposure Drug dose can be calculated based on PZN number and DDD available through GKV-Arzneimittelindex number	ICD-10-GM codes
Swedish National Registers	ICD-10 codes in Swedish National Patient Register	Dispensed drugs in ambulatory pharmacy ATC codes Substance-specific code; dosage and date of administration. It will not be possible to differentiate IV from IM iron exposure.	ICD-10 codes

ATC = Anatomical Therapeutic Chemical (classification system); CIP = French pharmacy dispensing coding system; DDD = defined daily dose; DIMDI-DaTraV = Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information (Germany); DNPR = Danish National Patient Registry; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner or general practice; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; ICD-10-GM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification*; ICD-9 = *International Classification of Diseases, 9th Revision;* ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ICPC = International Classification of Primary Care; IM = intramuscular; IV = intravenous; KfH = Board of Trustees for Dialysis and Kidney Transplantation (Germany); PHARMO = Institute for Drug Outcomes Research (the Netherlands); QiN = Quality in Nephrology registry system for KfH (Germany).

9.3.2 Outcomes

The outcome of interest is anaphylactic reaction or severe immediate hypersensitivity reaction following exposure to a study drug. The National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) symposium defined anaphylaxis as a "serious allergic reaction that is rapid in onset and may cause death" (Sampson et al., 2006). The clinical criteria proposed by these organisations are displayed in Figure 1.

Figure 1. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Table I from Sampson et al. (2006).

Below follows a preliminary case-identification algorithm using ICD-10* codes that was adapted from the work performed by the Mini-Sentinel project on the development and validation of an algorithm based on ICD-9† codes to identify cases of anaphylaxis in US health plan administrative and claims data (Walsh et al., 2014). This algorithm will be adapted to each data source. Fatal events occurring during the defined time-at-risk windows for the outcome will also be captured. Note that cause of death will not be available in all data sources.

Algorithms will be reviewed at each data source using internal data source information and, when possible, with complete or partial medical record validation, with either potential study cases (internal or direct) or potential cases not necessarily part of the study cohort (external or indirect). Note that codes will differ somewhat among the data sources depending on the coding systems used. The specific codes used at each data source will be documented in the statistical analysis plan.

- Criterion A: T88.6 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered) or T80.5 (anaphylactic shock due to serum) or T78.2 (anaphylactic shock, unspecified) associated with an inpatient or emergency room encounter (i.e., the reason for admission, if this information is

* ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

† ICD-9 = *International Classification of Diseases, 9th Revision*.

available)

OR

- Criterion B: T88.6 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered) or T80.5 (anaphylactic shock due to serum) or T78.2 (anaphylactic shock, unspecified) associated with an outpatient encounter

  PLUS

  A code for one or more of the following symptoms, procedures, or treatments:

  – Bronchospasm (J98.01, acute bronchospasm)

  – Stridor (R06.1)

  – Hypotension (I95.0, idiopathic hypotension; I95.2, hypotension due to drugs; I95.81, other hypotension, postprocedural; I95.89, other hypotension; I95.9, hypotension unspecified)

  – Epinephrine/adrenaline (Y51.4, predominantly alpha adrenoreceptor agonists; Y51.5, predominantly beta-adrenoreceptor agonists, not elsewhere classified; or Y51.9, other and unspecified drugs primarily affecting the autonomic nervous system)

  – Injection of diphenhydramine (Y43.0, antiallergic and antiemetic drugs)

  – Cardiac arrest with successful resuscitation (I46.0)

  OR

- Criterion C: T88.7 (unspecified adverse effect of drug or medicament) or Y44.0 (adverse effects in therapeutic use: iron preparations and other antihypochromic-anaemia preparations) associated with an inpatient or emergency room encounter (i.e., the reason for admission, if this information is available)

  PLUS

  – A code for one of the following symptoms, procedures, or treatments:

    • Bronchospasm (J98.01, acute bronchospasm)

    • Stridor (R06.1)

    • Injection of diphenhydramine (Y43.0, antiallergic and antiemetic drugs)

  AND

  – A code for one of the following symptoms, procedures, or treatments:

    • Hypotension (I95.0, idiopathic hypotension; I95.2, hypotension due to drugs; I95.81, other hypotension, postprocedural; I95.89, other hypotension; I95.9, hypotension unspecified)

    • Epinephrine/adrenaline (Y51.4, predominantly alpha adrenoreceptor agonists; Y51.5, predominantly beta-adrenoreceptor agonists, not elsewhere classified; or Y51.9, other and unspecified drugs primarily affecting the autonomic nervous system)

- Cardiac arrest with successful resuscitation (I46.0)

Specific aspects by data source:

- Danish National Patient Registry (DNPR) and the Health Services Database of the Central Denmark Region: ICD-10 codes in the form of 4-digit codes (e.g., T78.2, T80.5, T88.6, I95.8) for diagnoses or symptoms are used. More detailed codes are available in some cases, but they are assigned a letter at the end and not a number. Such detailed codes need to be found on case-by-case basis. ICD-10 "Y" codes (Y40-Y59 and Y83-Y84) are not in use in Denmark (e.g., Y43, Y44 and Y51 referring to specific treatments/adverse events of treatments). Input from clinicians will be sought to learn about coding practices.
- PHARMO: ICD-9-CM up to 2010 and ICD-10 from 2014 onwards (mixed coding from 2011 through 2013) for patients requiring a hospital bed. Mortality data available. Partial general practitioner (GP) data from the GP Database with International Classification of Primary Care (ICPC) codes. Criteria A and C (those associated with an inpatient or emergency room encounter) will be captured in the Hospitalisation Database; emergency department encounters not requiring an overnight stay will not be captured. Search terms for criterion B (associated with an outpatient encounter) will be applied in the GP Database.
- SNIIRAM: ICD-10 for in-hospital discharge diagnoses. If a patient in an emergency department does not stay overnight, he/she will not be captured. Cause of death will not be available.
- GePaRD: ICD-10-GM for in- and outpatient diagnoses. Events occurring during a hospitalisation will not be captured. For outpatient diagnoses, use of EBM (Einheitlicher Bewertungsmaßstab) or OPS (Operationen- und Prozedurenschlüssel) codes referring to treatment of hypersensitivity reactions will be explored to determine the date of events. Emergency care is identified by specific EBM codes and can thus be dated. Cause of death will not be available.
- KfH QiN: ICD-10-GM codes for diagnoses/clinical events occurring in the dialysis unit are recorded in the registry. Diagnoses/events occurring outside the dialysis unit (e.g., during hospital stays) are sometimes recorded but not in a reliable manner. ICD-10-GM codes are those valid in the year of the diagnosis/event.
- DIMDI-DaTraV: ICD-10-GM codes for diagnoses in outpatient medical data/ambulatory clinics data and hospital discharge diagnoses but date available only as year and trimester. For patients who die, no patient data are available for the last year of enrolment.
- Swedish registers: ICD-10 codes for hospital discharge diagnoses in the National Patient Register. Linkage of data with other registers is feasible.

The data source–specific information related to outcome identification is summarised in Table 6.

9.3.2.1 Outcome Validation

Direct validation—i.e., confirmation of potential cases in the study cohort by examining the source record—will be possible only in selected settings. In the study, we will also conduct indirect validation—i.e. confirmation of potential cases using source records in selected hospitals that are not necessarily part of the cohort and cannot be linked to it. These potential cases will be identified using the same algorithms as in the study.

Direct Case Validation

- The Health Services Database of the Central Denmark Region will enable direct validation of all cases of anaphylactic reactions identified among users of IV iron (and, if needed, a sample of users of the chosen IV anaphylaxis marker compound) in the regional database through review of medical records. This will allow assessment of the overall positive predictive value of the case-finding algorithm in Denmark or recalculation of incidence proportions based on confirmed cases. It is noteworthy that the sensitivity of the algorithm cannot be evaluated. Nationwide estimates of anaphylactic reactions obtained in the study may be obtained by extrapolating regional estimate notes based on confirmed cases.
- The PHARMO inpatient pharmacy administration records allow targeted requests to local ethics committees for access to patient medical records in those hospitals. If access is granted, cases can be included in the validation analysis.

Indirect Validation of Case-Finding Algorithms

- Due to data protection rules, no linkage of individual patients between Oldenburg hospitals and GePaRD or DaTraV will be possible. Therefore, we will validate the case-identification algorithm. This indirect validation of the case-identification algorithm used in the GePaRD and the DaTraV database will be conducted using hospital records at hospitals in the Oldenburg area in Germany, which is part of the area covered by the GePaRD and DaTraV. Estimates obtained from the indirect validation will be used to adjust incidence estimates as appropriate.
- The case-identification algorithm used in the SNIIRAM database could be indirectly validated through hospital records at some hospitals in France. A feasibility assessment of this indirect validation approach will be required.

9.3.3 Other Variables

Variables that will be used for descriptive analyses and evaluated as risk factors or potential confounding variables for propensity score models are as follows:

- Demographic/other variables: age, sex, year of new use of IV iron
- Other variables, based on prior research including the recent Medicare (Wang et al., 2015) and Mini-Sentinel projects (Walsh et al., 2016) are listed in Table 7. Diagnosis codes for medical conditions will be evaluated from outpatient, inpatient, or emergency department encounters, depending on data available in each data source using ICD-9, ICD-10, or ICPC codes among others. Medications

will be identified using ATC codes and data source–specific codes/variables. Note that some variables may not be available in all data sources, may be underrecorded, or may be available only for a subset of the study population. Propensity score models will be calculated separately in each data source based on the available variables.

The evaluation period for each variable has been set according the chronicity of the conditions/medications and relevance as confounding variables. In general, all information available before the cohort entry date on conditions related to prior history of hypersensitivity reactions, relevant comorbidities, and specific chronic conditions that could be potential confounders will be used. For more acute conditions (e.g., GI bleeding and peptic ulcer) a shorter lookback period will be assessed. Data on prior use of medications, including use of other medications for anaemia, will be generally based on information available during the 6 months before cohort entry.

Data source–specific information related to the definition of other study variables is summarised in Table 6.

Table 7. Variables to be Considered for Propensity Score Models

Variable	Evaluation Period	Categories
Indicators of a prior history of hypersensitivity reactions (diagnosis codes)[a]		
History of anaphylaxis	Any time before but NOT including cohort entry date	Yes/no
Drug allergies	Any time before but NOT including cohort entry date	Yes/no
Food/latex/insect bite allergies	Any time before but NOT including cohort entry date	Yes/no
Atopic dermatitis	Any time before but NOT including cohort entry date	Yes/no
Allergic rhinitis	Any time before but NOT including cohort entry date	Yes/no
Other allergy	Any time before but NOT including cohort entry date	Yes/no
Indicators of the severity of anaemia		
Clinical setting where IV iron was administered[b]	On cohort entry date	Inpatient, outpatient (including hospital outpatient clinics and dialysis units), emergency department
Laboratory results[c] (e.g., haemoglobin, serum iron, serum ferritin, transferrin saturation, if available)	90 days before and including cohort entry date	Values

Variable	Evaluation Period	Categories
Prior use of other anaemia medication/treatment		
Erythropoiesis-stimulating agents and biosimilars	183 days before and including cohort entry date	Yes/no
Oral iron[d]	183 days before and including cohort entry date	Yes/no
Blood transfusion	183 days before and including cohort entry date	Yes/no
Possible indications for IV iron treatment (diagnosis and treatment/procedure codes)[e]		
Gastrointestinal or genitourinary bleeding	183 days before and including cohort entry date	Yes/no
Chronic kidney disease	Any time before and including cohort entry date	Yes/no
Peritoneal dialysis	183 days before and including cohort entry date	Yes/no
Chronic iron deficiency anaemia	Any time before and including cohort entry date	Yes/no
Intestinal malabsorption (including celiac disease)	Any time before and including cohort entry date	Yes/no
Ulcerative colitis; Crohn's disease	Any time before and including cohort entry date	Yes/no
Peptic ulcer disease	183 days before and including cohort entry date	Yes/no
Gastrointestinal cancer	365 days before and including cohort entry date	Yes/no
Haemodialysis	Any time before and including cohort entry date	Yes/no
Chemotherapy[a] or cancer-induced anaemia	365 days before and including cohort entry date	Yes/no
Anaemia complicating pregnancy, childbirth or the puerperium	183 days before and including cohort entry date	Yes/no
Anaemia (unspecified)	183 days before and including cohort entry date	Yes/no
Other possible indications (patients with none of the above indications)	183 days before and including cohort entry date	Yes/no
Indicators of other relevant comorbidities (diagnosis codes)		
Asthma	Any time before and including cohort entry date	Yes/no
Human immunodeficiency virus (HIV) infection[a]	Any time before and including cohort entry date	Yes/no
Congestive heart failure	Any time before and including cohort entry date	Yes/no

Variable	Evaluation Period	Categories
Hypertension	Any time before and including cohort entry date	Yes/no
Cancers other than gastrointestinal cancers	Any time before and including cohort entry date	Yes/no
Indicators of other relevant comorbidities (medications)[f]		
Cytostatic medications[a]	183 days before and including cohort entry date	Yes/no
Immunosuppressants (including oral and injectable steroids)	183 days before and including cohort entry date	Yes/no
Beta blockers	183 days before and including cohort entry date	Yes/no
Angiotensin-converting enzyme inhibitors	183 days before and including cohort entry date	Yes/no
Angiotensin-receptor blockers	183 days before and including cohort entry date	Yes/no
Antibiotics	183 days before and including cohort entry date	Yes/no
Antihistamines	183 days before and including cohort entry date	Yes/no
Non-steroidal anti-inflammatory drugs	183 days before and including cohort entry date	Yes/no
HIV anti-retroviral therapy	Any time before and including cohort entry date	Yes/no
Other		
Age (in years)	On cohort entry date	Continuous variable
Sex	On cohort entry date	Female/male
Calendar year of cohort entry	On cohort entry date	Continuous variable
Duration of lookback period	At cohort entry date	Continuous variable with a minimum of 365 days (12 months); may be categorised after examining frequency distribution

IV = intravenous.

Note: Variables that are indicators of prior history of hypersensitivity reactions and indicators of other relevant comorbidities (including medications) will be used for descriptive analysis of the anaphylaxis marker compound group.

Note: In the KfH QiN registry, diagnoses for medical history conditions are not systematically recorded (either as ICD-10 diagnosis or entered as free text). The date of a diagnosis code may not reflect the date of diagnosis but rather date of recording in the EMR.

Note: In GePaRD, outpatient diagnoses do not have an exact date and are available only by quarter. Thus, two quarters will be used instead of 183 days.

[a] Likely to be underrecorded (e.g., Denmark, Sweden).

[b] Most data sources do not capture IV iron treatment administered during hospitalisation.

[c] Laboratory results available in the Central Demark Region and KfH QiN, and partially in PHARMO.

[d] May be underrecorded in GePaRD and Swedish registers due to over-the-counter use; available in Denmark if reimbursed as an outpatient prescription.

[e] Patients are allowed to have more than one potential indication. Among these variables, only those that are also related to the outcome will be incorporated to the propensity score model. See Section 9.7.2.

[f] GePaRD: specific codes only for in-hospital administration of expensive medications; outpatient medication data may be very nonspecific (especially before 2008).

9.4 Data Sources

In the 2014 feasibility evaluation of potential candidate European data sources for a PASS of IV iron and severe immediate hypersensitivity reactions, 10 European data sources were assessed through a common set of questions regarding availability of exposure and outcome data. Of these, five were considered adequate to achieve the study objectives (Gutierrez et al., 2014). At the PRAC's request, in 2016, two additional data sources in Germany were assessed (Gutierrez et al., 2016).

A brief description of the study data sources, including their potential for source record validation options and information provided during the feasibility evaluation, is presented below. Research partners with access to these data sources have confirmed interest in and availability to participate in the study. Researchers from DIMDI-DaTraV confirmed interest in participating in the study in November 2016. The research group for the Swedish national registers has agreed to join the study in April 2017.

9.4.1 The Danish National Health Registries and Databases, Denmark

Denmark, a Nordic country with a population of 5.6 million (Eurostat, 2014), has a national health service that provides universal tax-funded health care to all Danish residents. Health care coverage includes visits to GPs and specialists, hospital admissions, and outpatient visits. The Danish centralised Civil Registration System assigns a unique 10-digit Central Personal Register (CPR) number to all persons at birth or immigration, which is used in all public registries and databases in Denmark and allows for individual-level record linkage of data from all Danish registers and databases (Schmidt et al., 2014). Data collected in these registries can be made available for research purposes after all necessary approvals are granted. The specific registries of interest for this project are described below.

Prescription medicine in Denmark is sold to patients through outpatient pharmacies (including outpatient pharmacies located within hospitals) or is administered directly to patients during hospital encounters. The Danish National Patient Registry (DNPR) contains information on all inpatient stays at all somatic hospitals in Denmark since 1977; data on visits to specialists at outpatient departments and emergency rooms are also reported to the registry (Schmidt et al., 2015). Primary discharge diagnosis and up to 20 discharge diagnoses are coded using ICD-10 and, all procedures and certain in-hospital treatments are likewise recorded. Results from the 2014 feasibility evaluation of

the IV iron PASS indicated that nearly all treatment with parenteral iron in Denmark takes place in hospital settings.

The Health Services Database of the Central Denmark Region, containing medications recorded in the electronic medical record (EMR) database (for research) and maintained at the Department of Clinical Epidemiology of Aarhus University, is based on EMRs from hospitals in the Central Denmark Region. This database contains individual-level data on medications prescribed and administered in the region's hospitals, including specialist outpatient clinics. Laboratory data are also available at the regional level (Grann et al., 2011). On 1 January 2013, the population of the Central Denmark Region was 1,272,510 individuals, or about one-fourth of the total Danish population (Statistics Denmark, www.statistikbanken.dk). This EMR research database has no reliable data on the indication associated with each treatment, but hospital diagnoses are available through linkage with data from the DNPR and may be used to indirectly infer indication.

Studies on the incidence of anaphylactic shock using data from the DNPR have been performed (Avillach et al., 2013; Jeppesen et al., 2016). Incidences rates per 100,000 person-years of 5.7 based on primary discharge diagnoses and 6.4 when secondary diagnoses were included have been reported (Avillach et al., 2013). Increases in the annual hospitalisation rate per 100,000 person-years for first-time diagnosis of anaphylactic shock from 4.1 in 1995 to 10.6 in 2012, corresponding to a rate ratio of 2.6 (95% CI, 2.2-3.0), were reported by Jeppesen et al. (2016). No data on validation of the outcome were provided.

A published study of patients from the Danish National Health Registries and Databases on postmenopausal women diagnosed with osteoporosis included validation of potential hypersensitivity reactions through review of medical records (Adelborg et al., 2017). Potential cases were identified by an algorithm of ICD-10 codes for primary discharge diagnoses of hypersensitivity-related events associated with an inpatient stay or an emergency department visit. The overall PPV was 100% (95% CI, 67.6%-100.0%) for the ICD-10 codes T886 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered) or T78.2 (anaphylactic shock unspecified, T78.2A exercise-induced anaphylaxis).

Direct case validation can be performed in the Central Denmark Region data through the review of medical records.

9.4.2 The PHARMO Database Network, The Netherlands

The PHARMO Institute for Drug Outcomes Research (PHARMO) in the Netherlands (http://www.pharmo.com/) has access to the PHARMO Database Network, a population-based network of health care databases that combines data from different primary and secondary health care settings in the Netherlands. These different data sources, which include data from general practices, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, the pathology registry, and the perinatal registry, are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the record linkage method can be found elsewhere (Herings and Pedersen, 2012; van Herk-Sukel et al., 2010).

More than 4 million residents of a well-defined population in the Netherlands (25% of the Dutch population) can be followed for an average of 10 years. The PHARMO Database Network includes information on patient demographics, drug dispensings from outpatient pharmacies and, for inpatient drug dispensings given during a hospitalisation, from the hospital pharmacy database, hospital morbidity, and mortality. Availability of other information is dependent on the data source. Access to medical charts and other clinical data is available within the prerequisites of the Dutch privacy regulations and subject to approval of hospital ethics committees. Results from the 2014 feasibility evaluation of the IV iron PASS indicated that with the exception of CosmoFer, most dispensings for IV iron treatments take place in hospital settings.

The linked databases in the PHARMO Database Network are updated every year. Databases are linked when the hospital admission data of the preceding calendar year become available; the updated database becomes available in the second half of the year. Dates of death returned from the Central Bureau of Genealogy have a lag time of 2 years.

One study including data from PHARMO evaluated the incidence of “anaphylactic shock” (Avillach et al., 2013). Identification of cases, in data from regional drug dispensing records, hospitalisation claims, and laboratory values, relied on ICD-9-CM codes specific for anaphylactic shock and exposure-related anaphylactic shock. The incidence rates per 100,000 person-years of anaphylactic shock were 1.9 per 100,000 using only primary discharge diagnoses and 2.4 per 100,000 when secondary diagnoses were included. No data on validation of the outcome were provided. Outcome validation studies were not identified.

Direct case validation may be performed for the inpatient data through review of hospital medical records. Approval from individual hospitals is needed to access the charts; these approvals will be requested.

9.4.3 The French National Health Insurance Inter Plans Information System /Nationwide Claims and Hospital Database

The database of the French Système National d'Information Inter-Régimes de l'Assurance Maladie [National Health Insurance Inter Plans Information System (SNIIRAM)] contains individual anonymous information from all out-of-hospital reimbursed claims that are linked to the national hospital discharge summaries database system (PMSI) and the national death registry (Tuppin et al., 2010). The database currently covers the three main health care insurance systems (the CNAM-TS for salaried workers except civil servants and students, the MSA for agricultural workers, and the RSI for self-employed workers), as well as other smaller plans, representing 98.8% of the French population. Information is available on individuals’ demographics, medical and pharmaceutical expenses related to selected long-term conditions, outpatient reimbursed health care expenditures (medical procedures, lab tests, drugs, and medical devices) and timing of encounter. Hospital data from the PMSI system includes diagnosis for main and associated diagnosis for all medical, obstetric, and surgical hospitalisations, including date and duration of hospitalisation, medical procedures, and diagnosis-related group. Drug information is available only for drugs prescribed out of the diagnosis-

related group, mainly expensive drugs, and does not include data on IV iron. Date of death is available but data on cause of death are not available.

SNIIRAM data are released yearly in the third quarter of the following year included in each period (i.e., data for 2015 will be available in the third quarter of 2016). Regular access is for a 3-year period (e.g., 2013-2015), but this period can be extended to 6 years or more upon request. Researchers at the INSERM CIC Bordeaux CIC1401, Bordeaux PharmacoEpi research unit, have conditional access to the SNIIRAM database with an authorisation process (requiring 6 to 12 months before data extraction by the CNAM-TS database operator), based on the scientific protocol and regulatory requirements/public health considerations. Approval by the Institute of Health Data and the French data protection agency (CNIL) is required before data extraction.

A 1/97 permanent representative sample of SNIIRAM (EGB) contains the same information with easier access and minimal administrative burden (1 week to 1 month). It provides access to drug utilisation data, but does not have enough power to study rare outcomes like anaphylaxis.

No studies evaluating the risk of anaphylaxis or hypersensitivity reactions have been performed using the SNIIRAM database.

The possibility of indirect partial validation using records from hospitals in the area of the University of Bordeaux will be explored.

IV iron use data captured in SNIIRAM will refer only to Ferinject, which was reimbursed by the health care system from 2011 to 2014. Other injectable iron preparations are included in routine hospital expenses, but are not recorded in the national health care system.

9.4.4 The German Pharmacoepidemiological Research Database, Germany

The German Pharmacoepidemiological Research Database (GePaRD), which has been built by the Leibniz Institute for Prevention Research and Epidemiology - BIPS, consists of claims data for reimbursement of diagnostic and therapeutic services from four German statutory health insurance providers (SHIs) covering overall 20 million insured people throughout Germany and about 15 million people cross-sectionally. The population contained in this database represents approximately 19% of the German population of 80.5 million inhabitants in 2013 (Eurostat, 2014). The database covers all SHI members who have been enrolled in one of the four SHIs since 2004 and contains core data; hospitalisation data; outpatient prescription data for all dispensed drugs prescribed in ambulatory settings, which are reimbursed by the SHIs; and outpatient care data/diagnoses starting 1 January 2004. The database covers all geographic regions of Germany. The database is updated every year, with a data availability lag time of approximately 2 years.

No studies evaluating the risk of anaphylaxis or hypersensitivity reactions or validating this outcome performed using the GePaRD were identified through the literature search or reported by the researchers at BIPS.

Indirect partial validation can be conducted through the hospitals in the Oldenburg area.

9.4.5 Carl von Ossietzky University of Oldenburg (Germany)

For the external indirect validation study in German hospitals, BIPS and RTI Health Solutions (RTI-HS) will collaborate with a team from the Carl von Ossietzky University of Oldenburg. Professor [redacted] from the university will be the principal investigator. The indirect validation study is initially planned to be conducted in a single academic hospital. However, inclusion of additional hospitals may be considered to increase statistical power.

9.4.6 KfH - Board of Trustees for Dialysis and Kidney Transplantation, Quality in Nephrology Registry (KfH QiN)

The KfH - Kuratorium für Dialyse und Nierentransplantation e.V. (KfH) [Board of Trustees for Dialysis and Kidney Transplantation], the largest provider of haemodialysis in Germany, is a non-profit organisation that comprises more than 200 dialysis clinics (kidney centres) that treat approximately 18,000 patients annually. Data from KfH kidney centres are collected electronically through the QiN (Quality in Nephrology) registry system.

The KfH QiN database started in 1999, and data are complete since 2007-2008 for adult patients undergoing haemodialysis and peritoneal dialysis at kidney centres of KfH. Patients leave the programme when they change to a non-KfH facility, receive a transplant, withdraw from dialysis, or die. Only reimbursed medications are administered. Documentation of patient treatments is kept for billing purposes. “Demographic, clinical and biochemical variables are derived from routine documentation and entered into a uniform software provided by KfH to all participating dialysis units” (Stoffel et al., 2004). The KfH QiN registry data have not been used for pharmacoepidemiology research.

Patients provide informed consent to participate in the prospective QiN registry and allow use of the collected data for research purposes. Data collection in QiN is based on an electronic health record system that is used at all KfH kidney centres. Approximately 20% to 25% of all dialysis patients in Germany are treated at KfH facilities, and more than 90% of KfH patients participate in QiN (Marquardt et al., 2015). Medical history data are not systematically recorded, and it is likely that only relevant conditions are recorded. The date of a diagnosis code does not necessarily represent the date the diagnosis was made (rather, the date the diagnosis was recorded into the electronic patient record). Only medications prescribed by KfH physicians are systematically recorded in the database; medications prescribed by other physicians may not be recorded.

Ethics committee approval would not be required because all patients have consented to the use of their data for research purposes.

Validation of outcome data is not possible in the setting of this project.

9.4.7 Information system for health care data (data transparency) of German Institute of Medical Documentation and Information (DIMDI-DaTraV), Germany

The DaTraV database was established in February 2014 by the DIMDI (German Institute for Medical Documentation and Information) as a compilation of health care data from all the statutory health insurance (SHI) providers in Germany. The main aim is to promote and allow research in health care quality or to plan for implementation of health care services.

The following information is available for approximately 70 million insurance customers in Germany (roughly 90% of the population in Germany are members of SHIs) (GKV-Spitzenverband, 2015). Currently, data are available from 2009-2012 (4-year data lag, data from 2013 will become available during Q2 2017):

- Demographics and general information: Sex, year of birth, and vital status.
- General practitioners' data: Medical diagnoses coded with ICD-10-GM codes and date (year and trimester) of disease.
- Ambulatory clinics data: Data from 85%-90% of ambulatory clinics (excluding private clinics) are available. Contains information on clinic name and medical diagnoses, coded with ICD-10-GM codes (main diagnosis and up to 20 associated diagnoses) and partial timing of diagnoses (year and trimester).
- Drugs prescribed and reimbursed from ambulatory pharmacy dispensings: Information includes PZN (Pharmazentralnummer, nationwide identification number for pharmaceuticals), number of prescriptions, and date of prescription. Brand name, drug dose, and duration of prescriptions can be calculated based on PZN number and DDD available through the GKV-Arzneimittelindex number. The date of the ambulatory pharmacy drug dispensing is not captured.
- Hospital data: discharge diagnosis codes recorded using ICD-10-GM codes and date of discharge and/or any transfer within hospital services. No date of hospital admission is captured.
- For patients who died, information is not available for their last year in the SHI.

9.4.8 Swedish National Health Databases, Sweden

Sweden, a Nordic country with a population of 9.5 million inhabitants in 2013 (Eurostat, 2014), has a tax-supported health care system that provides universal health coverage to all Swedish residents. All citizens have unrestricted access to health services, including partial or complete reimbursement of purchased medicines. Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The National Board of Health and Welfare is responsible for a number of health data registers including the Swedish Prescribed Drug Register, which contains information on all prescription medicines dispensed at pharmacies since 2005 to individuals receiving ambulatory care. Data on date of dispensing, dose, substance-specific code, and ATC code are available (Wettermark et al., 2007). The unique personal

identification number allows for the possibility of linking data collected in all Swedish registers containing civil registration numbers. Data collected in these registers can be made available for research purposes.

The Swedish National Patient Register contains data on hospital inpatient and outpatient diagnosis codes recorded as ICD-10 codes and procedure codes. A published study in patients from the Swedish National Registries on postmenopausal women diagnosed with osteoporosis included validation of potential hypersensitivity reactions through review of medical records (Adelborg et al., 2017). Potential cases were identified by an algorithm of ICD-10 codes for primary discharge diagnoses of hypersensitivity-related events associated with an inpatient stay or an emergency department visit. The overall PPV was 100% (95% CI, 67.6%-100.0%) for the ICD-10 codes T886 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered) or T78.2 (anaphylactic shock unspecified, including T78.2A, exercise-induced anaphylaxis).

Drugs administered in the hospital can be recorded in the register as a procedure code together with the ATC code for the drug. However, there is limited experience on assessing the availability of data on drug procedure treatments in the Swedish National Patient Register.

9.5 Study Size

The study will include all available patients fulfilling the inclusion criteria and with none of the exclusion criteria. Linkages to identify unique patients who are new users could not be implemented during the feasibility evaluation. Preliminary data on IV iron use from the 2014 and 2016 feasibility evaluations suggest that approximately 250,000 to 300,000 patients with IV iron prescriptions could be included, possibly more.

We provide in Table 8 the precision calculations for two scenarios defined by the risk of anaphylactic reactions for IV iron dextrans and non-dextrans reported by Wang et al. (2015). The PASS 14 software (NCSS, LLC. Kaysville, Utah; 2015. http://www.ncss.com/software/pass/) was used for the calculations.

Table 8. Study Precision Calculations

Number of Patients	Dextrans 95% CI for Risk of 6.8 per 10,000 Persons	Non-dextrans 95% CI for Risk of 2.4 per 10,000 Persons
10,000	2.69 to 14.15	0.38 to 7.85
8,000	2.34 to 15.35	0.27 to 8.87
6,000	1.88 to 17.25	0.16 to 10.52
4,000	1.25 to 20.84	0.05 to 13.75
3,000	0.85 to 24.27	0.02 to 16.91
2,000	0.39 to 30.88	0 to 23.16

CI = confidence interval.

Source of risk estimates: Wang et al. (2015).

Unless the heterogeneity of findings prevents pooling of data across data sources, based on the precision of the confidence intervals in Table 8, incidence proportions and risk ratio estimates from pooled analyses will be provided.

Preliminary data from the Health Services Database of the Central Denmark Region indicated a total of 5,804 new users of IV iron products from 2004 through 2015.

Data source–specific limits on the minimum number of counts per cell that can be reported, which are driven by data protection regulations, will need to be considered given the expected low number of outcomes (Table 9).

Table 9. Cell Counts Limits by Data Source

Data Source	Minimum Reportable Number of Individuals per Cell	Possibility of Reporting Smaller Cell Counts for Regulatory-Driven Research
Danish National Patient Registry (DNPR) and Health Services Database of the Central Denmark Region	3 individuals per cell Does not impact propensity score strata	Will explore whether limit applies to regulatory-driven studies and publications
PHARMO Database Network, Netherlands	5 individuals per cell	Does not apply to regulatory-driven reports; does apply to publications
French National Information System Inter Plans Health Insurance Database	10 individuals per cell (applies only to descriptive data). Does not impact propensity score strata	Will explore whether limit applies to regulatory-driven studies and publications
German Pharmacoepi-demiological Research Database (GePaRD)	5 individuals per cells may apply to descriptive data Does not impact propensity score strata	
KfH - Board of Trustees for Dialysis and Kidney Transplantation Registry (KfH QiN)	No established limits, will follow German rule	
Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information (DIMDI-DaTraV)	30 individuals per cell	Permission to provide cell results with five or more events could be explored within the context of this study
Swedish National Registers	5 individuals per cell may apply to descriptive data Does not impact propensity score strata	

9.6 Data Collection and Management

Routine procedures or practice will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each research partner will maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents or routine practice.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Each centre will follow its standard institutional procedures or routine practice to restore files in the event of a hardware or software failure.

9.7 Data Analysis

Each of the data sources will conduct the data analysis described below according to the common protocol and a common statistical analysis plan, with documentation of data source–specific adaptations. Data specifications that may vary between the data sources will be documented and maintained by each data source. Most analyses will be conducted using SAS.

Given the nature of KfH QiN, access to data on exposure to the study drugs before being admitted to one of its centres will be very limited, and ascertainment of the new-user status for IV iron will not be possible. Additionally, KfH QiN is likely to have less information available on the covariates planned for the study than the general-population data sources. Therefore, we plan to analyse data from KfH QiN separately, and results may not be pooled with those of the general-population data sources.

DaTraV data will be included in the sensitivity analysis.

9.7.1 Descriptive Analyses

Descriptive analyses will be performed as a first step, and results will inform final decisions on the statistical analysis plan.

Descriptive statistics will be calculated to summarise baseline characteristics (e.g., demographic information, comorbidities, and medication use) of new users of IV iron overall, by groups and specific types of IV iron product, in the IV iron cohort and in the cohorts of new users of the IV anaphylaxis marker compounds. Categorical variables will be summarised by frequencies and percentages, and continuous variables will be summarised by means and standard deviations, medians and interquartile ranges (first quartile to third quartile), and minimum and maximum values.

9.7.2 Propensity Score Analyses

The number of outcomes is likely to be small, and the number of demographic, medical, and clinical factors that may be associated with the initiation of one type of IV iron therapy versus another and also associated with the outcome is large. Therefore a propensity score approach will be used to control for confounding of measured confounders (Cepeda et al., 2003). The propensity score for each patient is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates (Braitman and Rosenbaum, 2002; D'Agostino, 1998; Perkins et al., 2000). Grouping patients into subclassifications based on their propensity score, i.e., propensity score stratification, should produce similar distributions of covariates within each subclass if the propensity scores are relatively constant within the subclass, thus controlling for the effects of the observed covariates (Perkins et al., 2000).

Simulation studies show that variables that are unrelated to the exposure but are related to the outcome should always be included in the estimation of propensity scores (Brookhart et al., 2006). Including these variables increases the precision of the estimated effect of exposure without increasing bias. In contrast, including variables that are related to the exposure but not to the outcome can decrease precision of the estimated effect of exposure without decreasing bias. In addition, simulation studies show that the use of standard model-fitting strategies may not lead to optimal propensity score functions. Therefore, propensity scores will be estimated separately in each data source.

Propensity score models will be constructed independently for the following pairs of IV iron groups and types:

- Dextrans and non-dextrans
- Ferric carboxymaltose complex and iron sucrose complex/iron(III)-hydroxide sucrose complex
- Iron(III) isomaltoside complex and iron sucrose complex/iron(III)-hydroxide sucrose complex
- Sodium ferric gluconate complex and iron sucrose complex/iron(III)-hydroxide sucrose complex
- Iron(III)-hydroxide dextran complex and iron sucrose complex/iron(III)-hydroxide sucrose complex

Variables for the propensity score models are listed in Section 9.3.

Propensity scores for each patient will be calculated by fitting a multivariable logistic regression model with the dependent variable 1 for the primary IV iron group (or type) of interest or 0 for the comparator IV iron group (or type) and including all of the prespecified covariates as independent variables. The distribution of propensity scores for each IV iron group (or type) will be compared on a graph to assess the amount of overlap between the distributions, as limited overlap can result in decreased precision of study estimates. Extreme values at each end of the propensity score distribution will be excluded by a process known as “trimming.” Common cut-off values for trimming are

below the 2.5th percentile value of the distribution of scores and above the 97.5th percentile of the distribution.

Stratification will be performed on the trimmed population, which will be divided into 10 mutually exclusive strata (depending on the available study size) defined by deciles of the propensity score distribution of the IV iron group (or type) of interest. Within each propensity score stratum, the exposure groups that are being compared should have similar values of the propensity score (Austin, 2011). If the number of patients in each propensity score stratum is insufficient, a fewer number of strata (e.g., quintiles) will be used.

To check for imbalance among key covariates in the propensity score models before and after stratification and trimming, the method described by Austin (2009) will be used to calculate an absolute standardised difference, which is the difference in the mean (continuous variables) or prevalence (categorical variables) of the variable in the primary exposure group and comparator exposure group, divided by the pooled standard deviation. According to Austin (2009), values of the standardised difference of 0.2, 0.5, and 0.8 roughly correspond to small, medium, and large differences, respectively, in the level of the covariate between the treatment and comparator groups.

Imbalance in covariates within propensity score strata will be addressed by refining the propensity score model and re-creating the trimmed cohort, which will be used for incidence analyses.

9.7.3 Incidence Proportions and Comparative Analyses

The time window at risk for outcome events for the main analyses will be the day of the dispensing/administration and the day after (2-day risk window). The incidence proportion of anaphylactic reactions will be calculated as the number of cases that occur during the 2-day risk window among new users of a study exposure of interest, and this incidence proportion will be expressed as the number of cases per 10,000 patients, with corresponding Wald-based 95% confidence intervals. In the event of a low number of new users or outcomes, the corresponding confidence intervals will be calculated using the Wilson score interval approach. Because risk of anaphylaxis is highly dependent on the history of previous administrations of the studied drug, risks will be assessed stratifying by first, second, and subsequent dispensings/administrations of the study drugs, as well as overall with all dispensings/administrations combined.

If possible, stratified incidence proportion estimates for each of the IV iron compound groups and types of interest, as listed below, will be calculated for age groups, sex, and deciles of the propensity score:

- Any IV iron
- IV iron dextrans as a group
- IV iron non-dextrans as a group
- Iron(III)-hydroxide dextran complex
- Iron sucrose complex

- Ferric carboxymaltose complex
- Iron(III) isomaltoside complex
- Sodium ferric gluconate complex

The incidence proportion of anaphylactic reactions among those exposed to the anaphylaxis marker compounds will be used to put the results for IV iron products into context, but no direct comparisons will be made with any of the IV iron groups (or types).

Risk ratios (RRs) with corresponding Wald-based 95% confidence intervals, will be used to compare the incidence proportion estimates of anaphylactic reactions between the pairs of IV iron groups and types listed in Section 9.7.2, among new users of the study drugs.

Given that the number of events is expected to be very small, adjustment of RR estimates for confounders will be conducted using stratification by propensity score deciles. We will generate stratified RRs for each propensity score decile and pool the stratified RRs using beta-binomial regression as recommended by Kuss (2015).

9.7.4 Sensitivity Analyses

9.7.4.1 Crude Analyses

The amount of confounding detected in the main analyses will be estimated. If confounding is considered to be low, the crude incidence proportion for the overall population of patients before trimming will be estimated at the first, second, and subsequent dispensings/administrations for new users for each of the IV iron groups and types of interest, and if possible, per IV iron dose. RRs with corresponding 95% confidence intervals will be also calculated to compare the crude incidence proportion estimates between the pairs of IV iron groups and types listed in Section 9.7.2. For each of these analyses (first, second, and subsequent), the patient sample will be restricted to only patients that received the appropriate treatment of interest.

9.7.4.2 Alternative Risk Windows

For data sources in which the date of administration of IV iron or anaphylaxis marker compounds is not captured by procedure codes, a sensitivity analysis will be performed using two alternative time windows at risk for anaphylactic reactions: (1) same day of the dispensing of the study drug and (2) same day of the dispensing and up to 7 days after dispensing.

9.7.4.3 Impact of Referral Letter Assessment

The risk communications following the 2013 European regulatory referral is thought to have had a large impact on IV iron prescription patterns, particularly in France and Germany, reflected by a substantial decrease in outpatient use of IV iron compounds. Therefore, incidence proportions of anaphylactic reactions overall will be estimated before and after 2013. The “before period” will be based on data through the end of 2012, and the “after period” will be based on data from 2014 through the end of

available data. To estimate these incidence proportions within the study period and across study periods, generalised estimating equations with the specification of a dichotomous outcome (anaphylactic reaction or not) will be employed. Given the expected rare nature of anaphylactic reactions, these equations may take the form of a Poisson or negative binomial regression treating each patient as a random effect and having an indicator variable specifying study period. Point estimates and 95% confidence intervals for incidence proportion will be generated for the "before period," the "after period," and the difference between these two periods.

9.7.4.4 Adjustment of Incidence Estimates by Positive Predictive Value

Results from the direct case validation (to be conducted in data from the Denmark Central Region and in PHARMO inpatient data) and the indirect validation of the case-identification algorithms will be used in probabilistic bias analysis for information bias (Lash et al., 2009). Alternatively, recalculation of incidence proportions based on validated cases will be considered. Indirect validation of the case-identification algorithm (as opposed to direct case validation) used in the GePaRD and DaTraV populations will be performed through patient records at hospitals in the Oldenburg area in Germany and, if feasible, in the SNIIRAM population at selected hospitals in France.

Estimates of the positive predictive value of the case-identification algorithms obtained from the direct and indirect validation will be used to adjust data source–specific incidence estimates and pooled incidence estimates, as appropriate.

9.7.4.5 Worst-Case Scenario Assessment

To account for data sources that identify no outcomes associated with the first dispensing/administration of a study drug, a sensitivity analysis will be performed that removes these data sources from the pooling of the aggregate data (Walsh et al., 2016). While this does introduce bias, the removal of these patients from the denominator would cause an increase in the observed incidence proportion because patients not experiencing events are being excluded. The resulting incidence proportion and risk ratio estimates could then be seen as the worst-case scenario (with resulting underestimated risk); if low, they could help strengthen the conclusions drawn from this study.

9.7.4.6 Analysis of the DaTraV Data

DaTraV is the largest database of the study, and its results would likely be major drivers of any pooled analyses. However, the exact date of the study outcome will not be known in the DaTraV database because only year and trimester are recorded in association with the corresponding ICD-10-GM codes. In an attempt to overcome this limitation, temporal information about exposure and event dates in GePaRD might be used to estimate likely date of events in DaTraV.

9.7.4.7 Assessment of Prevalent Users of IV Iron

The possibility of conducting an analysis of the main study outcome (e.g., incidence proportion and risk ratios of anaphylaxis in users of IV iron groups and types) in prevalent users of IV iron will be assessed and conducted if considered feasible.

9.7.5 Pooled Analyses

Pooled estimates will be calculated after heterogeneity has been assessed (DerSimonian and Levine, 1999). Based on the heterogeneity of the data source–specific estimates, we will be able to assess if pooling is feasible. If so, the aggregate data provided by the data sources will be used to generate pooled estimates of incidence and RRs for the IV iron groups and types of interest. Crude estimates of incidence along with the corresponding 95% confidence intervals will be generated using the combined counts for outcomes and patients.

It is expected that at least one single-zero or double-zero study will be present (i.e., studies with zero events in one or both arms, respectively). In this case, beta-binomial regression will be employed as the main pooling analysis across studies, as recommended by Kuss (2015). Beta-binomial regression is advantageous because of its ability to model dichotomous outcomes while accounting for the potential issues of correlated response and overdispersion, which could be issues of concern with rare events.

The Mantel-Haenszel estimator will be employed as a sensitivity analysis to the beta-binomial regression. To deal with sparse data, we will use data augmentation as described by Greenland et al. (2016).

To ensure that the data required for pooling are reported consistently from each data source, as part of the common statistical analysis plan, specifications related to the transfer of aggregate data will be described to limit the potential for error during the pooling process.

9.8 Quality Control

Standard operating procedures, internal process guidance, or routine practice at each research centre will be used to guide the conduct of the study. These procedures may include, among others, internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician, if possible. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

A quality-assurance audit of this study may be conducted by the sponsor, the sponsor's designees, or a regulatory agency. Note that individual patient-level data are available at the centres only. Selected data fields are not available to be viewed by pharmaceutical companies.

For work conducted at RTI-HS, an independent Office of Quality Assurance will perform internal audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer

procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures and according to country-specific laws governing audits.

9.9 Limitations of the Research Methods

The 2014 and 2016 feasibility evaluations identified a large number of important challenges for this study. For several types of IV iron treatments, the number of patients will be small. The outcome is infrequent, and full outcome validation, recommended by prior studies and required to produce robust results, will not be possible in the study. There is important heterogeneity in the type of information that will be available across data sources. This impacts the approach to outcome identification and validation, treatment, and other covariate variables. For all data sources, this will be the first study on IV iron treatment; for most data sources, this will be the first study with an outcome of anaphylactic or severe immediate hypersensitivity reactions; and for two data sources, this will be the first pharmacoepidemiology study.

New-user status may also be a challenge for data sources in countries where the first IV treatment administration occurs only in an inpatient setting and the data source captures only ambulatory administrations or dispensings. Furthermore, in Sweden, data from outpatient dispensings are available only since 2006. A similar challenge will be faced to determine the ordinal number of treatment administrations (i.e., “second” administration and “third and subsequent” administrations) if patients receive treatments in inpatient or other specialised settings. Both situations apply to most of the study data sources. A particular case is the dialysis registry in Germany (KfH QiN) because information on prior treatments will not be known, and some patients may have received IV iron treatment prior to initiation of dialysis (i.e., before registration into the dialysis registry). However, based on knowledge and experience of researchers at the dialysis registry, most patients initiate IV iron treatment at the time dialysis is started. The lack of treatment and health-related data prior to the start of dialysis could potentially introduce a depletion of susceptible patients because patients who had experienced a prior hypersensitivity reaction after treatment with IV iron will be less likely to be treated with IV iron in this dialysis network. We plan to analyse patients from the KfH QiN separately, and it is likely that results of the KfH QiN analyses will not be pooled with those of general-population data sources.

Data from the DIMDI-DaTraV data source will be affected by the lack of a specific date for diagnoses of study outcomes in data from outpatient medical/ambulatory clinics since only year and trimester will be available. Only the exact date of the prescription of IV iron will be available. This is a serious limitation since the temporality between an anaphylaxis event and a prescription of IV iron cannot be determined. To overcome this limitation, dates of exposure and events in GePaRD might be used to approximate the likely date of events in DIMDI-DaTraV. Additionally, for patients who die, no data will be available for the last year of enrolment. This will effectively exclude all fatal anaphylaxis events from the study. However, data on the proportion that fatal events represent in

relation to the overall number of anaphylaxis events observed in the GePaRD data source may be used to adjust the rates of anaphylaxis seen in DaTraV.

The rate of anaphylactic or severe immediate hypersensitivity reactions is expected to be very low. By using multiple data sources, we will include more patients, but because prescription of specific types of IV iron vary across countries, for many of the individual IV iron types, the number of new-user patients will still be small. This will impact the precision of the study, and some of the planned comparisons may not be conducted. Some of the data sources capture drug exposure only through dispensings or administrations in the ambulatory setting; therefore, not all IV iron use will be captured. In addition, contrary to studies in US databases that have used procedural codes to identify administration of IV iron treatments, records of IV iron use in some of the European data sources refer to ambulatory pharmacy dispensings or to prescribed and reimbursed products in DaTraV data, rather than actual treatment administration. This may result in some degree of exposure misclassification; however, such misclassification, which in principle should be non-differential between the different types of IV iron products, could become differential if types of IV iron are selected on the basis of risk factors for anaphylaxis. Also, in most data sources, it will be difficult to distinguish between IV and intramuscular (IM) iron administration, which is of relevance for CosmoFer, the only IV iron compound that can be administered intravenously or intramuscularly. The lack of data on route of administration is expected to apply mainly to treatment dispensing/administration capture in outpatient settings because in the inpatient settings, data will mostly refer to IV use. This may also apply to the IV anaphylaxis marker compounds in each data source.

Iron sucrose complex is planned to be used as the reference category for the comparisons between incidence proportions of IV iron types. However, the characteristics of patients using iron sucrose may differ from those of users of other IV iron types, mainly due to reasons of cost and time since market availability. If non-adjustable differences between users of iron sucrose complex and other iron types were encountered, an alternative reference category may be required.

MAHs inform that while based on marketing authorisations in the study countries, most of the IV iron dextrans should be low-molecular-weight, parallel imports could result in availability of high-molecular-weight compounds.

Information on the hourly timing of administration of the study drugs and hypersensitivity reactions will not be captured in the study data sources. This could be a limitation since the hypersensitivity reactions identified could conceivably have happened before the study drug administration and thus be unrelated. However, given the life-threatening characteristics of the anaphylactic reactions and the non–life-rescuing nature of the study drugs, it is unlikely that a reversed timing of event and exposure is of concern. The possibility of the drug not being administered on the same day of the dispensing will be assessed through sensitivity analyses that will explore alternative exposure windows.

The algorithm developed and validated by the Mini-Sentinel project for identification of anaphylaxis/hypersensitivity reactions will be adapted to ICD-10 or other clinical

diagnostic categories as required for each data source. The positive predictive value of the Mini-Sentinel algorithm, although higher than previously reported algorithms, is low (62.6%; 95% confidence interval (95% CI), 53.4% to 71.2%) (Walsh et al., 2013), and a low positive predictive value is likely to also be a concern using other clinical coding systems. The potential underascertainment of cases will be considered. Direct validation of the outcomes will be limited to a subset of the population in the Central Denmark Region and the Netherlands. Indirect validation of the case-finding algorithm will be conducted in Germany and, if feasible, in France. Therefore, misclassification of the outcome will exist.

Information on risk factors, including potential confounders, for anaphylactic reactions is limited to the information recorded in each data source and will differ between data sources. Propensity scores will be developed for adjustment purposes to account for the small number of expected events and will be based on confounders as available in each data source. Use of over-the-counter medications will not be available. We expect that the potential lack of information on covariates will be non-differential in nature.

In summary, this will be a complex study, and interpretation of results will need to take into account these challenges and their effect on study validity and precision. However, the study will be a step forward in covering the gap of knowledge about anaphylactic reactions among patients treated with intravenous iron in Europe.

10 Protection of Human Subjects and Good Research Practice

Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE, 2015) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2016b).

The ENCePP *Checklist for Study Protocols* (ENCePP, 2013) will be completed, and the study will be registered in the ENCePP EU PAS Register[*] (ENCePP, 2016a). The research team and study sponsor adhere to the general principles of transparency and independence in the ENCePP Code of Conduct (ENCePP, 2014). The research team will apply for the ENCePP Study Seal (ENCePP, 2016c).

The study is a postauthorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study provided in the 2016 Revision 2 of the *Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies* (EMA, 2016). The study will comply with the nature of non-interventional

[*] EU PAS Register = European Union electronic register of postauthorisation studies.

(observational) studies referred to in the ICH harmonised tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004).

This is a non-interventional study using secondary data collection and does not pose any risks for patients. All data used in the study will be anonymised, with no breach of confidentiality with regard to personal identifiers or health information. Patient-level analyses will be conducted at each centre; only aggregate data will be analysed centrally by the coordinating centre in Europe.

10.1 RTI Health Solutions

RTI International* (RTI) holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organisation to review and approve human subjects protocols through its IRB committees. RTI currently has three IRB committees available to review research protocols. One IRB committee is constituted to review medical research and has two members who are MDs. These IRBs have been audited by the US Food and Drug Administration and are fully compliant with applicable regulatory requirements. RTI-HS will obtain approval for the study from the RTI IRB.

10.2 National and Central Region Health Databases, Denmark

Data in the Danish national registries, collected and administered by the government, are available for research provided all required approvals are obtained. The process of accessing the Health Services Database of the Central Denmark Region requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data. To obtain data linked from different health registries, at a minimum, an approval from the Danish Data Protection Agency is required for all studies. Once obtained, a data request is submitted to the Danish Data Authority, including study description and list of variables required from each data source. Once approved, the data are securely transferred to the researcher responsible for the study. Access to medical charts (for validation purposes) requires an additional approval from the Danish National Board of Health (Danish Data Protection Agency, 2014). The estimated timeline for receipt of the National Board of Health approval is 10 to 20 weeks from the date of application. All applications have to be submitted in Danish. Submission for this latter approval in the second quarter of 2017 should allow access to data in the second quarter of 2018.

10.3 PHARMO Database Network

The PHARMO Institute conducts research according to the latest directives regarding privacy and handling of data. The PHARMO Database Network combines data from different sources (pharmacy, hospital, laboratory, etc.). Some of these databases are managed in-house, and no permissions are required for access to data. For partnership databases, permissions are required for access to data. The various databases are

* RTI Health Solutions is a unit of RTI International, a non-profit research organization.

probabilistically linked through validated algorithms that do not invade the privacy of the patients. Researchers have access only to data depleted of sensitive personal information (such as date of birth) that may be traced back to persons; study reports will contain aggregate data only. This approach is approved by the Dutch Data Protection Authority. Because of the use of de-identified data from existing databases without any direct enrolment of subjects, ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet medisch-wetenschappelijk onderzoek met mensen [WMO]), which is enforced by the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO). Access to medical charts and other clinical data is available within the prerequisites of the Dutch privacy regulations and subject to approval of hospital ethics committees.

10.4 The French National Health Insurance Inter Plans Information System/Nationwide Claims and Hospital Database

Researchers at the INSERM CIC Bordeaux CIC1401, Bordeaux PharmacoEpi research unit, have conditional access to the SNIIRAM database with an authorisation process (requiring 6 to 12 months before data extraction by the CNAM-TS database operator), based on the scientific protocol and regulatory requirements/public health considerations. Approval by the Institute of Health Data and the French data protection agency (CNIL) is required before data extraction.

CIC1401 also has access to a 1/97 permanent representative sample of SNIIRAM (EGB). Access requires only transmission of a protocol to INSERM at least 1 week before the start of a publicly funded study or 1 month before the start of a privately funded study. EGB data extraction requires complete information for only one of the following variables: date of birth, date of death, date of care, and city or county of residence. With this process, EBG data extractions are considered fully anonymised by the CNIL and may be released without further authorisation. EGB is mainly used for drug utilisation studies and to prepare for studies involving the main SNIIRAM database, for example, to test diagnostic algorithms or specify study power and the number of years to be extracted from SNIIRAM.

10.5 GePaRD

For the GePaRD, approval is needed from the four statutory health insurers providing data to the GePaRD. A summary of the protocol will be provided to the SHI agencies, outlining the public health importance of the research question. After obtaining approval from the SHI agencies, approval of the project has to be obtained from the regulatory authorities responsible for such research. Approval from an IRB is not required in Germany because this study is based on pseudonymous data.

10.6 Hospitals in the Oldenburg Area

Approval from the ethics committee of the Carl von Ossietzky University of Oldenburg (Germany) will be required for access to medical records and abstraction of data for the

study on the validation of anaphylactic reactions. Access to medical record information will be performed by a hospital staff member (under contract with the university), following ethics approval.

10.7 KfH – Board of Trustees of Dialysis and Kidney Transplantation, Quality in Nephrology Registry (KfH QiN)

Ethics committee review and approval are in principle not required because all patients have consented to the use of their data for research purposes and because the study design involves retrospective data collection. Given the nature of the project, the principal investigator will notify the ethics committee of the registry's participation in this project.

10.8 Information System for Health Care Data (Data Transparency) of the German Institute of Medical Documentation and Information (DIMDI), Germany

For data protection reasons, all insurance numbers are pseudoanonymised. The type of institutions allowed to work with DIMDI-DaTraV and the aim of the research conducted using data from DIMDI-DaTraV are regulated by law through the German Social Security Code (§§303a to 303e SGB V) (http://dejure.org/gesetze/SGB_V/303e.htmL). Among the institutions allowed to use data from DIMDI-DaTraV are certain institutions of SHI, the German Federal Joint Committee, organisations representing patients, service providers on a national/federal level, and institutions qualified for research and health care reporting (http://www.dimdi.de/static/en/versorgungsdaten/index.htm). Ethics committee review and approval are not required.

10.9 National Registers of Sweden

Data collected in the Swedish registers are protected by strict confidentiality regulations but can be made available for research purposes provided all required approvals are obtained. The process for accessing data requires collaboration with investigators affiliated with a research institute. Applications for individual-level data for research purposes generally take 6-9 months to process (Swedish National Board of Health and Welfare, 2016).

11 Management and Reporting of Adverse Events/Adverse Reactions

Current guidelines from ISPE (2015) and the EMA *Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2014) indicate that non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require reporting of adverse events/reactions.

12 Plans for Disseminating and Communicating Study Results

The common study protocol, study status, and report(s) will be included in regulatory communications, and other regulatory milestones and requirements.

Study results will be published following the International Committee of Medical Journal Editors recommendations (ICMJE, 2015), and communication in appropriate scientific venues, e.g., ISPE, will be considered. When reporting results of this study, the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (von Elm et al., 2008) will be followed.

In line with the EMA *Guideline on Good Pharmacovigilance Practices (GVP). Module VIII – Post-Authorisation Safety Studies*, the marketing authorisation holder (MAH) and the research team will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. The MAH and the research team are aware that the MAH should communicate to the EMA and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication (EMA, 2016).

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection[1]	☒	☐	☐	4, 6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.2 End of data collection[1]	☒	☐	☐	4, 6
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	4, 6
1.1.6 Final report of study results	☒	☐	☐	4, 6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7.1
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Rather than testing a statistical difference between treatments with a priori hypothesis the study aims at measuring and comparing risk estimates among groups.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.3
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	11

[1] Date from which the analytical dataset is completely available.

Comments:

3.5: Current guidelines from ISPE (2015) and the EMA *Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2014) indicate that non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require reporting of adverse events/reactions

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1, 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2.2
	4.2.2 Age and sex?	☒	☐	☐	9.2.1
	4.2.3 Country of origin?	☒	☐	☐	9.4
	4.2.4 Disease/indication?	☒	☐	☐	9.2.3
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2.3.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3.3, 9.2.3.4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	4, 9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4, 9.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2.1
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.1, 9.3.3, 9.7.2
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.1, 9.3.3, 9.7.2
7.2 Does the protocol address:	☒	☐	☐	9.7.4
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.7.4
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.4
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.1, 9.3.2.1,

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.2, 9.7.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4, 9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4, 9.3.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4, 9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.1, 9.4.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.3
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2, 9.7.3, 9.7.4
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3

Comments:

11.3 Plan to set up scientific advisory board review of study results

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1, 9.2.3.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Comments:

Name of the main author of the protocol: [redacted]

Date: 04 May 2017

Signature: [redacted]

Annex 3.
IV Iron Marketing Authorisation Holders Consortium

Table 3-1. List of Participants in the IV Iron Marketing Authorisation Holders Consortium

Name	Address	Contact Details
Accord Healthcare Limited	Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, UK	[redacted] accord-healthcare.com
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Genfarma/G.E.S Genéricos Españoles S.A.U	Calle Cólquide 6, Portal 2,1ª planta Edificio Prisma ES-28230 Las Rozas Madrid, Spain	[redacted] @genfarma.es
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