# PASS Information

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| **Title** | Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions |
| **Version identifier of the final study report** | Final Report V1.3 |
| **Date of last version of the final study report** | 20 November 2020 |
| **EU PAS Register number** | EUPAS20720 |
| **Active substance** | Intravenous iron products (ATC code: B03AC, Iron, parenteral preparations):<br>Iron(III)-hydroxide dextran complex<br>Iron sucrose complex/iron(III)-hydroxide sucrose complex<br>Ferric carboxymaltose complex<br>Iron(III) isomaltoside complex<br>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 Iron Consortium. The study will also include equivalent medicinal products of pharmaceutical companies that are not part of the IV Iron Consortium.)<br>**Denmark:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Venofer<br>▪ Ferric carboxymaltose: Ferinject<br>▪ Iron(III) isomaltoside complex: Monofer<br>**France:**<br>▪ Iron(III)-hydroxide dextran complex: Ferrisat<br>▪ Iron sucrose complex: Venofer, Fer Mylan, Fer Panpharma, Fer Arrow, Fer Sandoz<br>▪ Ferric carboxymaltose: Ferinject<br>**Germany:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Venofer, FerMed<br>▪ Ferric carboxymaltose: Ferinject<br>▪ Iron(III) isomaltoside complex: Monofer<br>▪ Sodium ferric gluconate complex: Ferrlecit<br>**The Netherlands:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Ferracin, Venofer, IJzerhydroxide saccharose complex Teva |

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| | ▪ Ferric carboxymaltose: Ferinject<br>▪ Iron(III) isomaltoside complex: Monofer |
| | **Sweden:**<br>▪ Iron(III)-hydroxide dextran complex: CosmoFer<br>▪ Iron sucrose complex: Venofer, Järnsackaros Rechon<br>▪ Ferric carboxymaltose: Ferinject<br>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.<br>FerMed: 71610.00.00 (Germany authorisation number)<br>Ferrovin: 96896/13/03-02-16, 78933/11/05-04-2013 (Greece authorisation number)<br>Ferrovin: 021660/ 09-01-2013 (Cyprus authorisation number)<br>Venofer:<br>▪ 31111 (Denmark authorisation number)<br>▪ 3400957128340 (France authorisation number)<br>▪ 6462062.00.00 (Germany authorisation number)<br>▪ RVG 20690 (The Netherlands authorisation number)<br>▪ 15754 (Sweden authorisation number)<br>Ferinject:<br>▪ 39254 (Denmark authorisation number)<br>▪ 66227.00.00 (Germany authorisation number)<br>▪ 33865 (The Netherlands authorisation number)<br>▪ France authorisation numbers:<br>– Ferinject 1 x 2 mL: 34009 386 812 4 6<br>– Ferinject 1 x 10 mL: 34009 386 924 7 1<br>– Ferinject 2 x 2 mL: 34009 219 393 1 6<br>– Ferinject 2 x 10 mL: 34009 219 394 8 4<br>– Ferinject 5 x 2 mL: 34009 386 823 6 6<br>– Ferinject 5 x 10 mL: 34009 386 933 6 2<br>– Ferinject 1 x 20 mL: 34009 585 988 5 2<br>▪ 23738 (Sweden authorisation number)<br>Monofer:<br>▪ 27791 (Sweden authorisation number)<br>CosmoFer:<br>▪ 23462 (Sweden authorisation number)<br>Fercayl:<br>▪ Fercayl 100 mg/2 mL: BE168497 (Belgian authorisation number)<br>▪ Ferrlecit:<br>▪ 638 5744.00.00, 644 1686.00.00 (Germany authorisation numbers)<br>Ferracin:<br>▪ Ferracin oplossing voor injectie/concentraat voor oplossing voor infusie: RVG 112056 (The Netherlands authorisation number) |

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| | **IJzerhydroxide saccharose complex Teva 20 mg/mL, solution for injection/concentrate for solution for infusion: RVG 33727 (The Netherlands authorisation number)** |
| **Procedure number** | 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 AG, Arrow Génériques, Baxter, Generis Farmacéutica SA, Altan Pharmaceuticals SAU, Laboratoires Sterop SA, Medice Arzneimittel Puetter GmbH & Co. KG, Mylan SAS, Orifarm Generics A/S, Panmedica (Panpharma SA), Pharmachemie BV (Teva), Pharmacosmos A/S, Rafarm SA, Sandoz SAS, Sanofi Aventis Groupe, and Vifor France |
| **Joint PASS** | Yes |
| **Research question and objectives** | To assess the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylaxis" or "anaphylactic reactions") on the day of or the day after the first IV iron use through the following parameters:<br>▪ Incidence proportion of anaphylactic reactions in patients with a first-recorded IV iron (new users) overall, by group of IV iron product—iron(III)-hydroxide dextran complex and non-dextran IV iron products—and by the individual IV iron types listed below:<br>– Iron(III)-hydroxide dextran complex<br>– Iron sucrose complex/iron(III)-hydroxide sucrose complex<br>– Ferric carboxymaltose complex<br>– Iron(III) isomaltoside complex<br>– Sodium ferric gluconate complex<br>▪ Risk ratios of anaphylactic reactions in patients with a first-recorded IV iron (new users), by group of IV iron products—iron(III)-hydroxide dextran complex versus non-dextran IV iron products, and by the individual IV iron types (as listed above) using iron sucrose complex/iron(III)-hydroxide sucrose complex as the comparator. |
| **Country(-ies) of study** | Denmark<br>France<br>Germany<br>The Netherlands<br>Sweden |
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# Marketing authorisation holder(s)

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|---|---|
| **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 2 1 in Annex 2.<br>[redacted]<br>Telephone: [redacted]<br>E mail: [redacted] |
| **MAH contact person** | As above, [redacted] on behalf of the IV Iron Consortium |

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# 1 Abstract

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

[redacted] and [redacted]; RTI Health Solutions, on behalf of the IV iron PASS research team.

**Keywords**: Intravenous iron, anaphylaxis, severe hypersensitivity reactions, cohort study, multidatabase study

**Rationale and background**: Severe hypersensitivity reactions/anaphylaxis in intravenous (IV) iron treatment are rare. However, this safety concern is poorly characterised in Europe. A multidatabase study approach was required to evaluate this rare outcome. This PASS was requested by the European Medicines Agency Committee for Medicinal Products for Human Use to assess the risk of anaphylaxis in IV iron users in Europe.

**Research question and objectives**: The primary objective of the study was to assess the risk of anaphylaxis, overall and by groups (iron non-dextrans and iron dextran) and types of IV iron (using iron sucrose as the common reference).

**Study design**: Multinational cohort study of patients initiating IV iron treatment, conducted in populations covered by sources of routinely collected health and administrative data in Europe. Given that the risk of anaphylactic reactions rapidly decreases after the first administration of a drug (i.e., due to the depletion of susceptibles), the study used a "new-user" design. Risk was estimated using beta-binomial derived combined incidence proportions (IPs) among patients receiving any IV iron medication overall, by groups and individual types. Risk ratios and 95% confidence intervals (CIs) were calculated to compare the risk of anaphylactic reactions at the first (main analysis), second, and third or subsequent IV iron exposure overall and by IV iron groups and individual types. To put the study findings into context, the risk of anaphylaxis was also assessed among users of IV penicillins.

**Setting**: The study used data from populations covered in six European databases in five countries. Researchers with access to the study databases in Denmark, France, Germany, the Netherlands, and Sweden collaborated with RTI Health Solutions (Spain) as the coordinating centre. The study period varied across data sources, spanning overall from 1999 to 2017.

**Patients and study size, including dropouts**: The study identified 304,210 patients with a first-recorded IV iron treatment of whom 6,367 (2.1%) were iron dextran users. For the second IV iron treatments, there were 148,099 patients of whom iron dextran users represented 2.1% and for the third and subsequent treatments 3,103,486 treatments in 105,634 patients were captured with iron dextran accounting for 0.3%. For the IV penicillins cohort, there were 231,294 first treatments and 984,000 total treatments.

**Variables and data sources**: Data sources were the Danish national and regional linked registers and databases, the Système National des Données de Santé (SNDS, French National Health Care Insurance System Database), the German Pharmacoepidemiological Research Database (GePaRD), the Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN) registry in Germany, the PHARMO Database Network in the Netherlands (PHARMO-NL) and the Swedish national registers. Data from the Oldenburg University Hospital in Germany were used to validate the case-identification algorithm adapted to the GePaRD data. The German Institute of Medical Documentation and Information (DIMDI-DaTraV database) could not contribute to the study because of lack of resources.

The study outcome was anaphylaxis identified through a case-identification algorithm based on a previously validated algorithm.

Exposure to IV iron was captured through drug-dispensing data from outpatient pharmacy settings and, in two data sources, from inpatient drug administration. Analyses were conducted at first, second, and third or subsequent IV iron treatments. Validation of potential anaphylaxis events was conducted in the Central Denmark Region and the PHARMO-NL by review of medical records. Validation of the case-identification algorithm was performed through Oldenburg Hospital data.

**Results**: IV iron treatment in this study reflects only partial use in each country, mostly from ambulatory drug-dispensing data. A high proportion of all third or subsequent IV iron treatments (84%) occurred in the KfH QiN dialysis registry in Germany.

At first IV iron treatment, between 13 and 16 potential cases of anaphylaxis were identified. The resulting IP ranged from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97)[1] per 10,000 first treatments (the IP is reported as a range owing to data-protection rules for counts between 1 and 4). No events among iron dextran users were identified at first IV iron treatment. Risk estimates by groups and types of IV iron were based on a very small number of events.

At first IV penicillins treatment, 30 potential cases of anaphylaxis were identified. The resulting IP was 1.16 (95% CI, 0.78-1.73)[1] per 10,000 treatments.

**Discussion**: The study found an overall IP of anaphylaxis ranging from 0.38 to 0.51 per 10,000 first treatments, from 0.44 to 0.55 for iron non-dextrans and not assessable for iron dextran. These IPs were lower than the estimates of 2 and 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in studies in the United States (US) (Walsh et al., 2016; Wang et al., 2015). The IP of anaphylaxis in users of penicillins in our study was consistent with the incidences reported in the literature.

[1] IPs and 95% CIs estimates in the abstract have been corrected because they were inadvertently not updated in the previous March 24, 2020 and May 06, 2020 final study reports. Please note that all estimates in the text and tables of the report have been reported correctly in all versions of the report.

Owing to the small number of events, the originally planned adjusted analyses, including comparison of IV iron types, could not be performed. Results presented are potentially subject to confounding.

A potential for misclassification of repeated users of IV iron as first users, because of the impossibility of capturing use in-hospital and in specialty clinics in most data sources, may have resulted in lower IPs of anaphylaxis.

Due to methodological limitations, the study cannot exclude the possibility of a high risk of anaphylaxis associated with the administration of injectable iron and whether there are differences in the risk between the different types of IV iron. Some sensitivity analyses yielded risk ratios above the unity when comparing the risk of anaphylaxis for iron dextran versus iron non-dextrans; however, these analyses were based on very few cases, all of which had important validity concerns, and therefore conclusions cannot be drawn.

**Marketing authorisation holder(s)**: IV Iron Marketing Authorisation Holders Consortium, comprising the following marketing authorisation holders (MAHs): Accord Healthcare Limited, Acino AG, Arrow Génériques, Baxter, Generis Farmacéutica SA, Altan Pharmaceuticals SAU., Laboratoires Sterop SA, Medice Arzneimittel Puetter GmbH & Co. KG, Mylan SAS, Orifarm Generics A/S, Panmedica (Panpharma SA), Pharmachemie BV (Teva), Pharmacosmos A/S, Rafarm SA, Sandoz SAS, Sanofi Aventis Groupe, and Vifor France.

**Names and affiliations of principal investigators**:

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- PHARMO Institute for Drug Outcomes Research, [redacted]
- University of Bordeaux, INSERM CIC1401, Bordeaux PharmacoEpi Research Unit, [redacted]
- Leibniz Institute for Prevention Research and Epidemiology – BIPS, [redacted]
- Carl von Ossietzky University Oldenburg, [redacted]
- University Hospital of Cologne, [redacted] QiN-group
- German Institute of Medical Documentation and Information, [redacted]
- Karolinska Institutet, [redacted] Centre for Pharmacoepidemiology

# Approval Page: Research Partners

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

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|---|---|
| Authors and reviewers | [redacted]<br>(RTI Health Solutions)<br>[redacted]<br>(Aarhus University Hospital, Department of Clinical Epidemiology, Denmark)<br>[redacted]<br>(University of Bordeaux, INSERM CIC1401, Bordeaux PharmacoEpi Research Unit, France)<br>[redacted]<br>(Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS, Germany)<br>[redacted]<br>(Carl von Ossietzky University of Oldenburg, Germany)<br>[redacted]<br>(University Hospital of Cologne, Department II of Internal Medicine – QiN-group in collaboration with Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme [KfH QiN], Germany)<br>[redacted]<br>(PHARMO Institute for Drug Outcomes Research, the Netherlands)<br>[redacted]<br>(Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information) (DIMDI-DaTraV), Germany<br>[redacted]<br>(Centre for Pharmacoepidemiology, Karolinska Institutet)<br><br>**The members of the IV Iron Consortium and Michael Forstner as Coordinator of the Consortium have reviewed this report** |
| Version and date: | Final Report Version 1.3, 20 November 2020 |

On behalf of the IV iron PASS Research team:

[redacted]

20 NOV 2020

*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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**The members of the IV Iron Consortium and Michael Forstner as Coordinator of the Consortium have reviewed this report**

Version and date: Final Report Version 1.3, 20 November 2020

On behalf of the IV Iron MAH Consortium

[redacted]

20-Nov-2020

*Date*

# 2 List of Abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical (classification system) |
| BIPS | Leibniz Institute for Prevention Research and Epidemiology - BIPS |
| BP | blood pressure |
| CI | confidence interval |
| CIP | French pharmacy dispensing coding system |
| CNAM-TS | French health care insurance system for salaried workers |
| DDD | defined daily dose |
| DIMDI-DaTraV | Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information |
| DNPR | Danish National Patient Registry |
| EMA | European Medicines Agency |
| EMA-PRAC | European Medicines Agency, Pharmacovigilance Risk Assessment Committee |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| ER | emergency room |
| EU PAS Register | European Union electronic register of postauthorisation studies |
| FMM | finite mixture model |
| GePaRD | German Pharmacoepidemiological Research Database |
| GP | general practitioner |
| GVP | Good Pharmacovigilance Practices |
| HSR | hypersensitivity reaction |
| IBD | irritable bowel disease |
| ICD | International Classification of Diseases |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, 10th Revision |
| ICD10-GM | International Classification of Diseases, 10$^{th}$ revision German modification |
| ICPC | International Classification of Primary Care |
| IM | intramuscular |
| IP | incidence proportion |
| 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 |
| MAH | marketing authorisation holder |
| Max | maximum |
| Min | minimum |
| NA | not applicable |
| NE | not estimable |

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| PASS | postauthorisation safety study |
| PEF | peak expiratory flow |
| PHARMO | PHARMO Database Network or PHARMO Institute for Drug Outcomes Research |
| PHARMO-NL | PHARMO Database Network in the Netherlands |
| PPV | positive predictive value |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PZN | Pharmazentralnummer, nationwide german identification number for pharmaceuticals |
| RD | risk difference |
| REF CAT | reference category |
| RMP | risk management plan |
| RR | risk ratio |
| RTI-HS | RTI Health Solutions |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SHI | German statutory health insurance provider |
| SNDS | Système National des Données de Santé (French National health care insurance system database, previously named French National Health Insurance Inter Plans Information System Database [SNIIRAM]) |
| US | United States |

# 3 Investigators

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At RTI Health Solutions (RTI-HS): [redacted] for project management and administration; [redacted] for epidemiology support, [redacted] for editorial review, and [redacted] for graphics design.

At Aarhus University Hospital: [redacted] research nurse, for medical record review, [redacted] for clinical advice, and [redacted] for statistical support.

At PHARMO-NL: [redacted] (Senior Research Manager for this project until [redacted]) and health care providers contributing information to the PHARMO Database Network.

At BIPS: [redacted] and [redacted] (Senior Epidemiologist for this project until [redacted]).

At the Carl von Ossietzky University Oldenburg: [redacted] (liaison coordinator at Oldenburg Hospital), [redacted] (project student), [redacted] (data manager until [redacted]) and, all clinical directors participating at Oldenburg Hospital.

At the Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN), Germany: The patients and staff of all KfH dialysis centres for their contribution to the QiN registry.

At the Centre for Pharmacoepidemiology, Karolinska Institutet: [redacted] for project administration and editorial review.

# 4 Other Responsible Parties

## External Scientific Advisory Board

The study oversight was conducted by a scientific steering committee, and an external scientific advisory board set up between the research partners, both data sources, the coordinating centre (RTI-HS), and the sponsor. The members of the external scientific advisory board were as follows:

- Prof. [redacted], MD, pharmacoepidemiologist, [redacted]
- Prof. [redacted], MD, gastroenterologist, [redacted] United Kingdom
- Prof. [redacted], MD, allergologist, Dermatology Department, University Hospital, [redacted]
- Prof. [redacted], MD, biostatistician, Medical Department, [redacted] University, France

- Ad hoc external consultant:

  Dr. [redacted], also advised on methodological aspects with a focus on the case-identification algorithm

## Study Sponsor

**IV Iron Consortium**

**Mesama Consulting, Bangertenweg 460, CH-4252 Bärschwil, Switzerland**

- [redacted] on behalf of IV Iron MAH Consortium
- For a list of Marketing Authorisation Holders, Consortium member names and contact details, see Table 2 1 Annex 2

# 5 Milestones

| Milestone | Estimated / Actual Date Protocol V1.1, May 4, 2017 | Revised Timeline Protocol V2.1, 26 September 2019 | Actual |
|---|---|---|---|
| Protocol submission to EMA-PRAC: 3 months after receipt of the final assessment of the extended feasibility study report | 21 December 2016 | 21 December 2016 | 21 December 2016 |
| EMA-PRAC protocol endorsement | Anticipated by 3Q 2017 | 01 September 2017 | 01 September 2017 |
| Registration in the EU PAS Register including the protocol (following regulatory endorsement) | 3Q 2017 | 30 November 2017 | 30 November 2017 |
| Ethics or other relevant approvals and data source-specific adaptation of study materials | 3Q-4Q 2017 | 20 September 2017- 23 May 2019 | 20 September-23 May 2019 |
| Start of data collection[a] i.e., retrieval (first data source) | 1Q 2018 | 09 March 2018 | 09 March 2018 |
| Start of outcome validation studies | To be determined | 01 December 2018- 30 April 2019 | 01 December 2018-30 April 2019 |

| Milestone | Estimated / Actual Date Protocol V1.1, May 4, 2017 | Revised Timeline Protocol V2.1, 26 September 2019 | Actual |
|---|---|---|---|
| End of data collection[b] i.e., complete analytical data set (last data source for main analyses) | 4Q 2018-1Q 2019 | 4Q 2019 (including validation but not including DaTraV data) | 12 March 2020 |
| Data source analysis | 1Q-2Q 2019 | November 2018-4Q 2019 (including validation results but not DaTraV) | November 2018-February 2020 (including validation results but not DaTraV) |
| Pooled analysis | 2Q-3Q 2019 | 4Q 2019 | 22 February 2020 |
| 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) | 1Q 2020 (including validation results) | 24 March 2020 (including PHARMO validation results) |
| Final report of study results V.1.1 | NA | NA | 6 May 2020 (updated including Danish validation results). |
| Final report of study results V.1.2 | NA | NA | 10 September 2020 (revised conclusion following PRAC review) |
| Final report of study results V.1.3 | NA | NA | 20 November 2020 (revised conclusion following PRAC review) |
| Final report of study results including DaTraV data | TBD | TBD | Will not be available |

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
NA = not applicable.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are completed. Timelines may be affected 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, 2017a).

[b] End of data collection is "the date from which the analytical data set is completely available" (EMA, 2017a).

# 6 Rationale and Background

## 6.1 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 (HSRs) 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 relationship 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, 2013).

As a result of this evaluation, the EMA imposed a labelling update reinforcing risk information on HSRs 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, 2017a).

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 countries.

## 6.2 Background

The occurrence of anaphylactic shock from any cause (food, medications, insect bites, and other) in the general population was reported to be 0.2 to 1.2 per 10,000 person-years in a study conducted across several European health databases within the context of the European initiative "Exploring and understanding adverse drug reactions by integrative mining of clinical records and biomedical knowledge" (EU-ADR) (Avillach et al., 2013). Rates of hospitalisation with anaphylaxis from any cause in the general population from the Danish National Health Databases averaged 0.65 per 10,000 person-years between 1995 through 2012 (Jeppesen et al., 2016).

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; Durup et al., 2020; Ehlken et al., 2019; Nathell et al., 2020; Walsh et al., 2016; Wang et al., 2015).

Studies based on spontaneous reports have reported rates of serious allergic reactions, per gram of IV iron per million inhabitants between 0.1 per $10^{-3}$ and 10.5 per $10^{-3}$ for sodium ferric gluconate, between 0.9 per $10^{-3}$ and 47 per $10^{-3}$ for iron dextran, between 0.2 per $10^{-3}$ and 2.7 per $10^{-3}$ for iron sucrose (Bailie and Verhoef, 2012). Ehlken et al. (2019) reported rates of severe HSRs in Europe between 0.3 and 0.5 per 100 mg dose-equivalents of iron for ferric carboxymaltose, and between 2.4 and 5.0 per 100 mg dose equivalents of iron for iron (III) isomaltoside 1000. Nathell et al. (2020) reported rates of severe HSRs in European countries per 100 mg dose-equivalents of iron for iron sucrose from 0.03 to 0.20, for ferric gluconate from 0.02 to 0.14, for ferric carboxymaltose from 0.18 to 1.47 , for iron dextran from 0.22 to 2.80 and for iron (III) isomaltoside 1000 from 0 to 7.94. Durup et al. (2020) reported global annual rates for eight categories of HSRs ranging from 0.59 to 1.00 per 100,000 defined daily dose for iron dextran and from 2.77 to 12.2 for iron carboxymaltose.

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% 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 low use of high-molecular-weight iron dextran ascertained during a study interval period suggests that the results likely represent the risk of the low-molecular-weight dextran.

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., 2016). 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 new users of iron dextran (95% CI, 2-8) and 2 per 10,000 new users of other iron products (95% CI, 1-3), with a 2.6-fold greater risk of anaphylaxis among IV iron dextran new users than among new users of non-dextran IV irons (Walsh et al., 2016). Walsh and colleagues had previously reported on the validation of an algorithm developed to identify anaphylaxis using health plan administrative and claims data within the Mini-Sentinel programme (Walsh et al., 2013). Using the clinical criteria by Sampson et al. (2006) as the gold standard, the positive predictive value (PPV) for the algorithm based on International

Statistical Classification of Diseases, 9th Revision, Clinical Modification codes was 63.1% (95% CI, 53.9%-71.7%).

Akhuemonkhan et al. (2018) conducted a cohort study to examine adverse reactions after IV iron infusion among patients diagnosed with irritable bowel disease (IBD) and ulcerative colitis using the US Truven Health MarketScan Commercial Claims and Encounters database from 2010 to 2014. This database collects data from service-level claims for inpatient and outpatient services and outpatient prescription drugs. The risk of anaphylactic reactions within 7 days of any IV iron administration was calculated using Poisson regression after adjusting for type of IBD, type of IV iron, sex, age at first IBD encounter, and receiving a biologic infusion on the same day as IV iron. Risk and 95% CI per 10,000 infusions was 4.4 (1.4-13.8) for ferric gluconate users, 1.7 (0.2-12.3) for iron dextran users and 1.4 (0.4-4.3) for iron sucrose users. Ferric carboxymaltose users experienced no anaphylactic events (Akhuemonkhan et al., 2018). Adjusted incidence rate per 10,000 infusions in Crohn's disease patients ranged from 2.4 (0.6-9.7) for iron sucrose users to 16.3 (4.1-65.9) in ferumoxytol users. Ulcerative colitis incidence rate per 10,000 infusions were 1.2 (0.2-8.7) for iron sucrose and 91.3 (9.5-879) for ferric gluconate. There were six infusions of ferric carboxymaltose and none of them led to an anaphylaxis event.

Pollock and Biggar (2020) compared the occurrence of serious or severe HSRs for three IV iron formulations by pooling data from 21 published, prospective clinical studies including over 8,500 patients treated with IV iron. By using various meta-analytic techniques, the odds ratio of any serious or severe HSRs of isomaltose relative to iron carboxymaltose or iron sucrose ranged from 0.39 to 0.56.

# 7 Research Question and Objectives

The primary objective of the study was to assess the risk of anaphylactic or severe immediate hypersensitivity reactions (hereafter, "anaphylactic reactions" or "anaphylaxis"), overall and by groups and types of IV iron, among patients with any indication for IV iron, including patients undergoing dialysis, in routine clinical practice in European populations.

The following parameters were estimated:

- Incidence proportion (IP; risk) of anaphylactic reactions occurring on the day of or the day after exposure to the first (new users), second, and third or 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 (RRs) were estimated to compare the risk of anaphylactic reactions between IV iron groups (i.e., iron dextran vs. iron 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, was used as the comparison reference group) at the first, second and third or subsequent and overall exposure.
- The IP of anaphylactic reactions in patients dispensed or administered IV penicillins, the selected anaphylaxis marker compound, were calculated to provide context for the incidence of anaphylactic reactions from a medication group with a well-recognised risk of anaphylaxis.

As part of good research practices, the protocol and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist were registered in the EU PAS Register (ENCePP, 2016) before the start of data collection (30 November 2017). The study was designed and implemented in line with the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices* (ISPE, 2015); EMA *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII – Postauthorization Safety Studies* (EMA, 2017a); ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2018); and Food and Drug Administration *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Guidance* (FDA, 2013). The contract for the implementation of the study between RTI-HS and Vifor (Vifor acting on behalf of the Iron Consortium) included independent publication rights.

On 20 September 2017, the RTI-HS study team received the determination made by the RTI International institutional review board of the study as research not involving human subjects (RTI-HS will have no interaction with human subjects). Registration into EU PAS Register and ENCePP Study Seal application was completed on 30 November 2017 - EU PAS 20720.

Researchers at the University of Aarhus Epidemiology Department notified the Danish Data Protection Agency about the study on 13 December 2017. The study was listed on the University's overview of research projects covered by the notification, the Data Inspectorate's record number 2015-57-0002, and Aarhus University's journal number 2016-051-000001, serial number 810. On 10 October 2019, the Patient Safety Board granted approval for the study validation component.

Approvals for accessing the Système National des Données de Santé (SNDS, French National Health Care Insurance System Database) were obtained from the Comité d'Expertise pour les Recherches les Études et les Évaluations dans le domaine de la Santé on 18 January 2018, the Commission Nationale de l'Informatique et des Libertés on 11 June 2018, and on 23 May 2019 from the French health care insurance system for salaried workers.

Approvals for accessing the German Pharmacoepidemiological Research Database (GePaRD) health data from the Statutory Health Insurances (SHIs) in Germany were obtained for the first SHI on 14 November 2017 and for the two additional SHIs on 16 April 2018.

No ethics committee approval was required for access to the KfH QiN dialysis registry data in Germany. Researchers from the University of Cologne in Germany received a letter from the Ethics Board agreeing to the use of the data for this study.

Ethics approval from the Oldenburg University Hospital for the indirect validation activities was obtained on 15 March 2018.

Ethics approval is not required for anonymised database research in the Netherlands. However, this study fulfilled the requirements, as checked by the PHARMO Compliance Commission on 7 October 2011, to use data from PHARMO-NL for this specific study. Approvals from four hospitals were obtained for accessing patient records where case validation of PHARMO-NL data was performed.

The Centre for Pharmacoepidemiology at Karolinska Institutet received ethics approval for the study on 28 February 2018, and approval to use data from the Swedish registers from the National Board of Health and Welfare on 7 November 2018.

# 8 Amendments and Updates

The protocol version 1.1, dated 4 May 2017, was the protocol endorsed by the EMA and first posted in the EU PAS Register, EUPAS20720. The protocol version 2.1, dated 26 September 2019, was the protocol amended to reflect substantial changes proposed after the start of data collection and before the final implementation of the IV iron PASS. This amended protocol version 2.1, was endorsed by the EMA on 4 October 2019. Listed below are the specific amendments reflected in the protocol version 2.1.

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| 2.1 | 26 Sep 2019 | PASS Information, Approval pages and Section 4, Abstract | Updated protocol version and date | Reflect updates in amended protocol version 2.1 |
| 2.1 | 26 Sep 2019 | Section 4, Abstract; Section 6, Milestones and Timeline | Updated timelines with actual and revised timelines for some milestones | Reflect actual dates for achieved milestones; delays in completion of outcome validation |
| 2.1 | 26 Sep 2019 | Section 5, Amendments and Updates | Added specifications on the revisions incorporated in the amended protocol | Reflect updates in amended protocol 2.1 |
| 2.1 | 26 Sep 2019 | Section 7.2, Background | Added published estimates on the occurrence of | Address requests from the EMA-PRAC preliminary |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| | | | anaphylaxis in the general population<br>Clarified meaning of estimates from Bailie and Verhoef (2012) and corrected figure | assessment report (PAR) |
| 2.1 | 26 Sep 2019 | Section 9.3.3, Other Variables, Table 8 | Added column to indicate availability of study covariates across data sources | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.4, Data Sources | Clarified generalisability of PHARMO-NL data to the Dutch population and added population size for the French SNDS database | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7, Data Analysis | Added text to clarify that the study aims to evaluate risk of anaphylactic reactions at first, second, third or subsequent and any IV iron exposure and at first and any IV penicillins exposure | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7.2, Crude Incidence Proportions and Crude Comparative Analyses | Added text to clarify propensity score methodology and highlight the impact of potential zero events in some IV iron subtypes | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7.4.7, Sensitivity Analyses: Worst-Case Scenario Assessment | Corrected error | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 9.7.5, Pooled Analyses | Added text to clarify pooling methods in relation to heterogeneity | Address EMA-PRAC PAR request |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| 2.1 | 26 Sep 2019 | Section 9.9, Limitations of Research Methods | Added text to acknowledge capture of a single type of IV iron in France | Address EMA-PRAC PAR request |
| 2.1 | 26 Sep 2019 | Section 10, Protection of Human Subjects and Good Research Practice, and Section 11, Management and Reporting of Adverse Events/Adverse Reactions | Added mention to updated versions of EMA GPV guidelines | Address EMA-PRAC PAR request |
| 2.0 | 04 Jul 2019 | PASS Information | Added EU PAS Register number, updated MAH list and MAH contact person | Protocol has been registered in the EU PAS Register; change in MAH members of the IV Iron Consortium; changes in contact information for MAH contact person |
| 2.0 | 04 Jul 2019 | Approval pages | Updated authors and reviewers and affiliation of MAH contact person | Change in research team members; change in contact information of MAH contact person |
| 2.0 | 04 Jul 2019 | Section 3, Responsible Parties | Updated members for responsible parties | Changes in responsible parties |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.2.3, Study Cohort; 9.2.3.2, Cohort entry date; 9.2.3.3, Inclusion criteria | Clarified wording for inclusion of second and subsequent dispensing or administration of study drugs | Align text with original planned analysis |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.2.2, Study Period | Updated year for end of study period; change in name of French database | Change to reflect additional year of data available in one centre |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 6, Milestones and Timeline | Updated timelines with actual and revised timelines | Reflect actual dates for achieved milestones; |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| | | | for some milestones | delays in completion of some intermediate milestones |
| 2.0 | 04 Jul 2019 | Section 9.3.2, Outcomes | Updated Criterion B and Criterion C of the main outcome algorithm | Reflect input from external scientific advisory board June 2017 |
| 2.0 | 04 Jul 2019 | Section 9.3.3, Other Variables; Table 7 | Added new variables to the list of covariates of interest | Updates based on research team discussions and input from external advisers in June 2017 |
| 2.0 | 04 Jul 2019 | Section 9.5, Study Size; Table 9 | Modified cell-count reporting limits for Danish and Swedish data | Updated input from researchers |
| 2.0 | 04 Jul 2019 | Section 9.6, Data Collection and Management | Added text for use of secure file transfer protocol site as a method to transfer study data between the research data centres and the coordinating centre | To comply with data-protection requirements of some centres |
| 2.0 | 04 Jul 2019 | Section 9.7.2, Crude Incidence Proportions and Comparative Analyses | Re-ordered section to indicate higher priority of crude incidence and crude comparative analyses.<br>Added text to clarify definition of “risk windows” | Crude incidence analyses will be performed as part of the main analyses due to low number of events in preliminary descriptive results.<br>Time-at-risk definitions vary according to type of exposure data |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.7.3, Propensity Score Analyses | Revised text to highlight that the conduct of all propensity score-adjusted analyses will be dependent | Based on low number of events in preliminary descriptive results, the |

| Version Number | Date | Section(s) of Study Protocol | Amendment | Reason |
|---|---|---|---|---|
| | | | on the number of events. | propensity score-adjusted analyses do not seem feasible |
| 2.0 | 04 Jul 2019 | Section 4, Abstract; Section 9.7.4, Sensitivity Analyses | Added text on new planned sensitivity analyses for the expanded outcome algorithm, IV iron switchers, and dialysis patients. In addition, new text was added to describe timing of events up to 21 days after the risk window and listing of causes of death. | Additional analyses were triggered by the low number of events in the preliminary descriptive analyses and the research team agreements to perform further explorations of the available data |
| 2.0 | 04 Jul 2019 | Section 9.7.4.3, Sensitivity Analyses: Alternative Risk Window | Removed text for alternative risk window analysis based on “same day” of dispensing of the study drug. | Analysis dropped due to low number of events |

EMA = European Medicines Agency; EMA-PRAC = Pharmacovigilance Risk Assessment Committee; EU PAS Register = European Union electronic register of postauthorisation studies; GPV = Good pharmacovigilance; IV = intravenous; MAH = marketing authorisation holder; PAR = Preliminary assessment report; PASS = postauthorisation safety study; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database).

# 9 Research Methods

## 9.1 Study Design

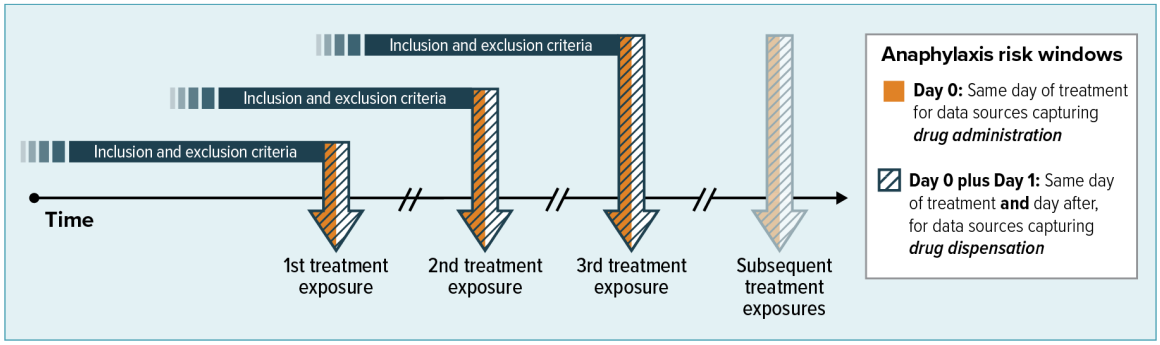
This was a multinational cohort study of patients initiating IV iron treatment, conducted in populations covered by sources of routinely collected health and administrative data in Europe. To obtain a sufficient number of IV iron new users to address the study objectives given the low risk of anaphylactic reactions, the study included national- or regional-level data from five countries: Denmark, the Netherlands, France, Germany, and Sweden.

Given that the risk of anaphylactic reactions rapidly decreases after the first administration of the drug, the study used a “new-user” design (main analysis) which allowed for more comparable study groups. However, prevalent users (i.e., users with a second and third or subsequent IV iron exposure), were also included to assess the evolution of risk beyond the first exposure as part of the sensitivity analyses.

The study aimed 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 was estimated using the IP among patients receiving any IV iron medication overall, by defined groups and individual types. Risk ratios and 95% CIs were calculated to compare the risk of anaphylactic reactions at the first (main analysis), second, and third or subsequent IV iron exposure overall and by the defined IV iron groups and individual types of IV iron.

To provide context to the estimated risk of anaphylactic reactions associated with exposure to IV iron, we estimated the risk of anaphylactic reactions in patients initiating treatment with IV penicillins, in the data sources where it was feasible. Penicillins have a well-characterised anaphylaxis risk that can help to validate the methodology.

**Figure 1. Study Design**

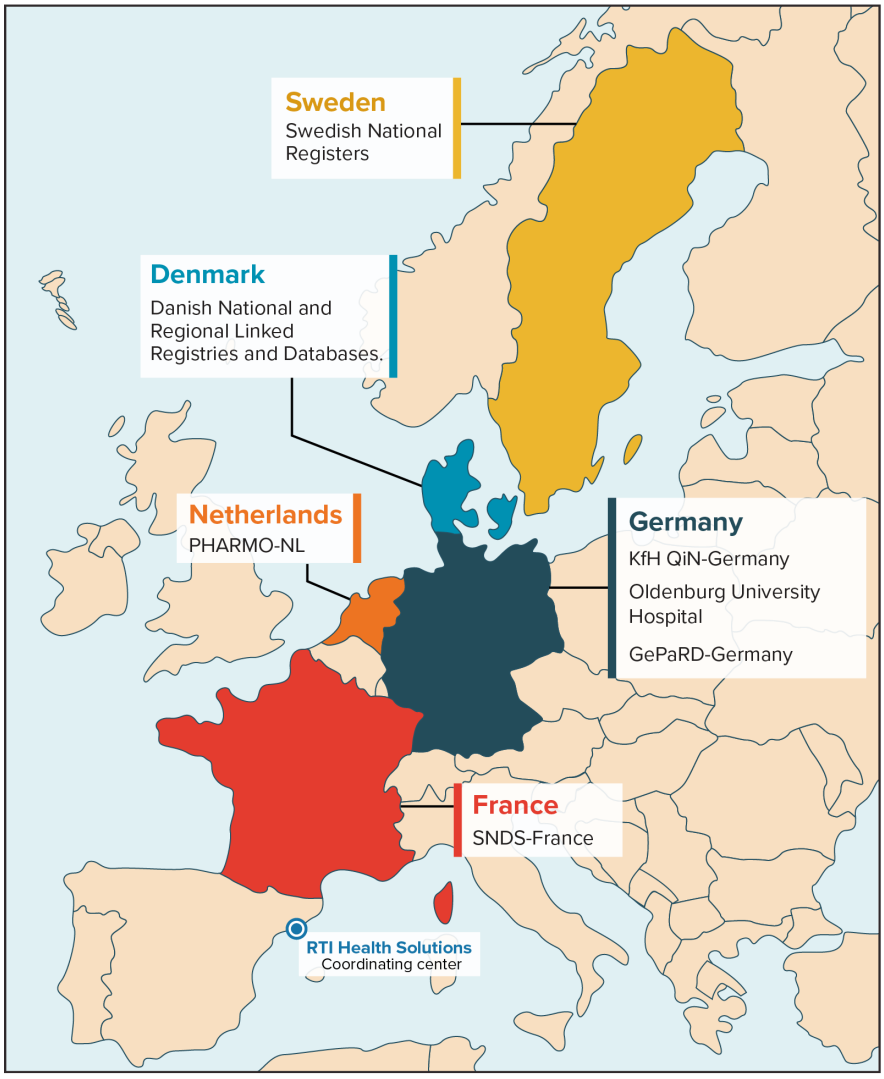



## 9.2 Setting

The study was conducted following a common core protocol in population-based health databases and registries in five countries in Europe that are available for research and that provide access to health-related data, including drug dispensing or administration data. RTI-HS was the coordinating centre also responsible for the conduct of the meta-analyses of aggregate data from all data sources. Figure 2 displays the data sources and countries participating in this study.

- Data from the German Institute of Medical Documentation and Information (DIMDI-DaTraV), Germany were originally planned to be included in the study. However, multiple issues were encountered that precluded contribution of data from DIMDI-DaTraV to this study. Details are provided in Section 9.9.5.

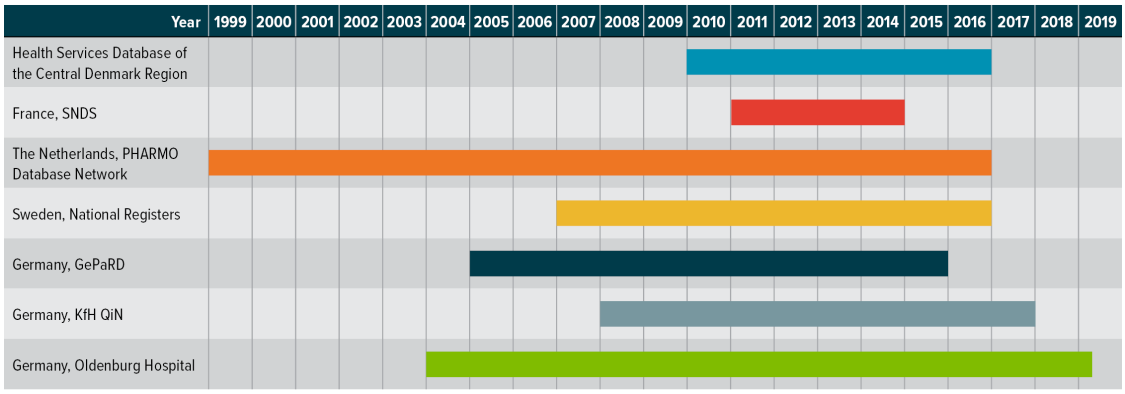
**Figure 2. Study Countries and Data Sources**




GePaRD = German Pharmacoepidemiological Research Database; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database); KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands.

The study period was defined in each data source as the time between the date of the first-eligible recorded code for dispensing or administration of IV iron (i.e., first-recorded code for dispensing or administration of IV iron after 1 year of continuous enrolment in the database) and the latest date of data availability (see Figure 3). The start date in each data source in Figure 3 reflects the time of "first IV iron/IV penicillin use" after the minimum 12-month lookback period required before cohort entry. In the French SNDS database, IV iron was removed from the list of reimbursed medications in 2014; therefore, data on IV iron were not available after this date.

**Figure 3. IV Iron PASS: Study Period for Each Data Source**




GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PASS = postauthorisation safety study; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

## 9.3 Subjects

The study cohort comprised all adults from the source population who had a first-recorded dispensing/administration of IV iron during the study period, were continuously enrolled or registered in the data source for at least 12 months before the first recorded iron treatment and were at least 18 years of age on the date of the first dispensing/administration of IV iron (see Figure 4). Second or subsequent dispensing/administration of the same type of IV iron meeting the inclusion criteria were also considered for the corresponding analyses (see Figure 4). For the KfH QiN dialysis registry in Germany, the eligibility requirement for a minimum continuous enrolment of 12 months before the first IV iron administration was not applied because medical information is captured only from the date patients' initiate dialysis.

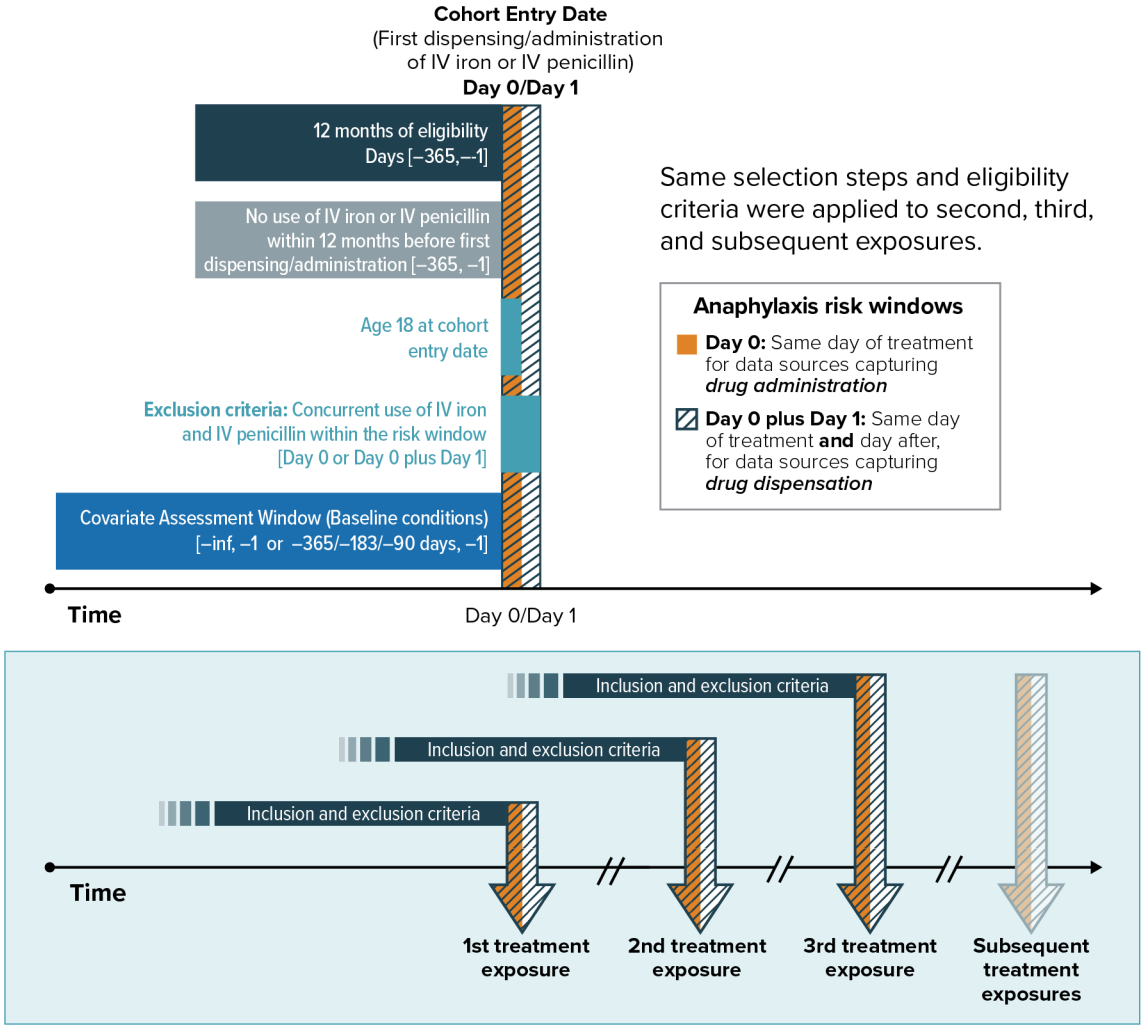
The same selection criteria were applied to the IV penicillins cohort in the data sources where IV penicillins use was captured (i.e., Danish national and regional linked registries and databases, PHARMO-NL, SNDS in France, and GePaRD in Germany).

### *9.3.1 New Users*

New users were defined as individuals initiating treatment with IV iron or IV penicillins without a recorded code for dispensing/administration of these drugs within at least 12 months before entry date (defined in Section 9.3.2).

Due to the idiosyncratic nature of hypersensitivity reactions, patients were allowed to enter the study only once. No switches between IV iron groups or individual types were allowed for the main analysis. However, prior use of IV penicillins compounds did 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.

**Figure 4. Study Inclusion and Exclusion Criteria**




IV = intravenous.

### *9.3.2 Follow-up*

The follow-up of eligible patients for identification of anaphylaxis in the main analysis is described below (see also Figure 5):

The cohort entry date (Day 0) was defined as the date of a record for a first qualifying dispensing/administration of IV iron or IV penicillins in the study data sources.

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

- Occurrence of the study outcome (event date)
- Death
- End of study period
- Switch between types of IV iron

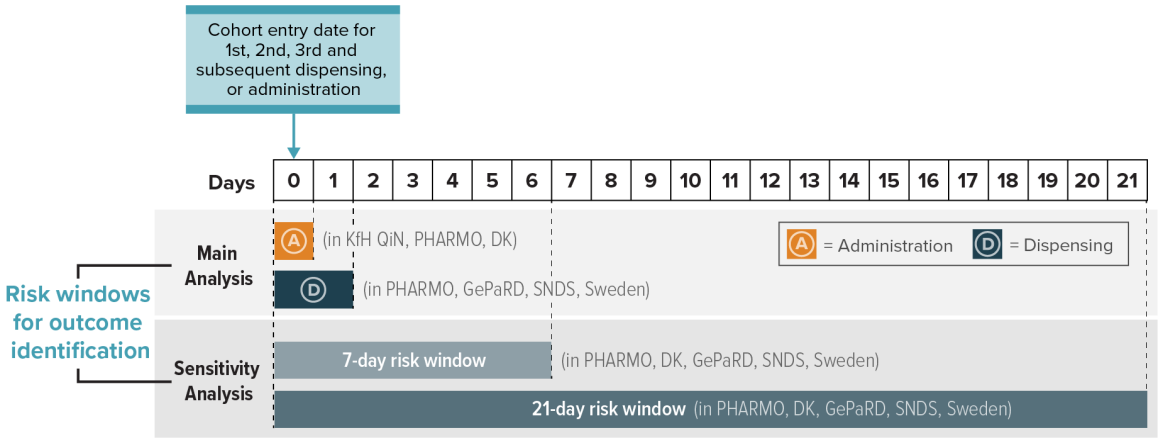
- Concurrent use (i.e., within Day 0 [“same day”] or Day 0 and Day 1 [“same day and day after”] of a recorded exposure) of IV iron and IV penicillins
- Day 0 (same day) for data sources capturing drug administration data or Day 0 and Day 1 (main analysis) after dispensing/administration of IV iron for data sources capturing drug-dispensing data
- Disenrollment from the data source

Drug administration data were captured in the KfH QiN dialysis registry in Germany, the Health Services Database of the Central Denmark Region, and the PHARMO-NL inpatient Pharmacy Database.

Drug-dispensing data were available (i.e., no data on dates of actual treatment administration were available) in the SNDS in France, PHARMO-NL Outpatient Pharmacy and General Practitioner (GP) Database, GePaRD in Germany, and the Swedish national registers (see Figure 5).

Alternative risk windows (i.e., 7-day and 21-day risk window) were also considered for sensitivity analyses as shown in Figure 5 (see Section 9.9.4).

**Figure 5. Study Follow-up**




DK = Denmark; GePaRD = German Pharmacoepidemiological Research Database; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database); KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO = PHARMO Database Network.

## 9.4 Variables

### *9.4.1 Outcome Variable*

The outcome of interest was anaphylactic reaction or severe immediate hypersensitivity reaction following exposure to a study drug. The definition of anaphylactic reactions followed the definition by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network symposium 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 6.

## Figure 6. 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.

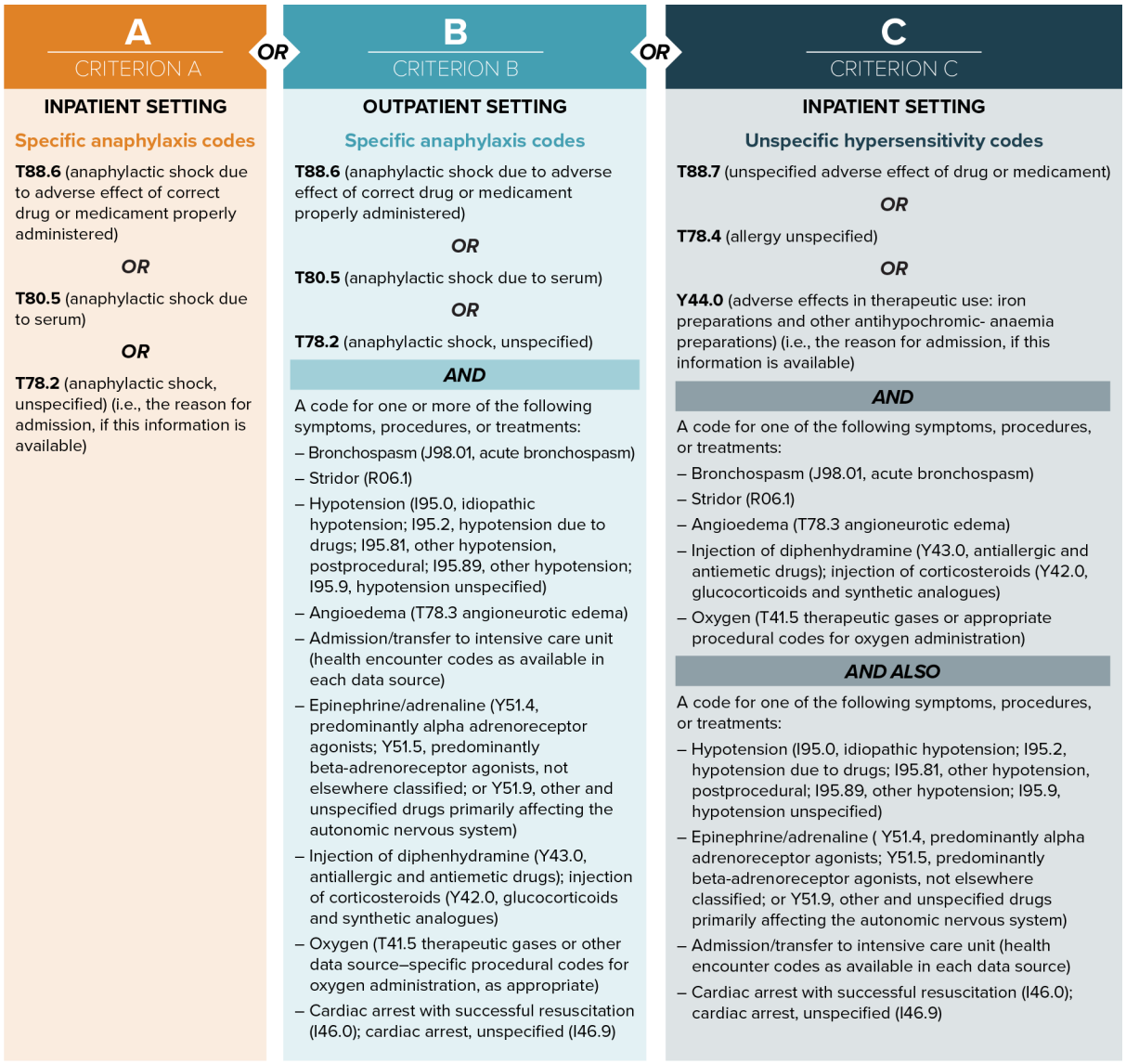
Source: Table I from Sampson et al. (2006).

#### 9.4.1.1 Outcome Identification

### Main Anaphylaxis Algorithm

Anaphylactic reactions were identified using an algorithm created using International Classification of Diseases, 10th Revision (ICD-10) codes based on the algorithm developed and validated by investigators from the US Mini-Sentinel project based on International Classification of Diseases, 9th Revision codes (Walsh et al., 2014). The algorithm was adapted to each data source. Fatal events occurring during the defined time-at-risk windows for the outcome were also captured. Note that cause of death was not available in all data sources. The event-finding algorithm used for further data-source adaptations for the main analysis is presented in Figure 7.

**Figure 7. Main Anaphylaxis Algorithm**




### Expanded Anaphylactic Reactions Algorithm

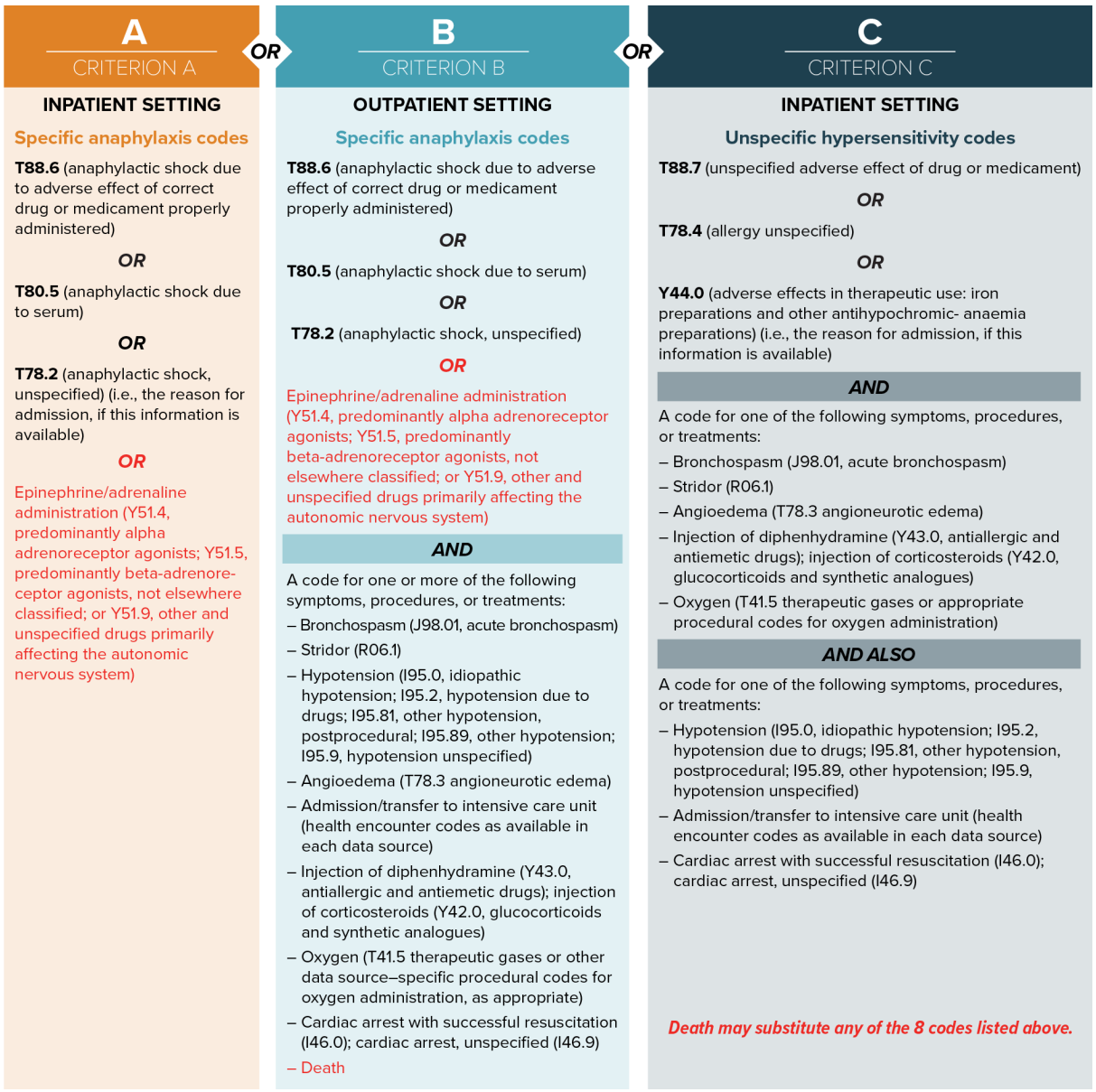
An expanded algorithm was developed for a sensitivity analysis including the following modifications to the main algorithm (Figure 8):

- Adrenaline administration within the defined risk window, in data sources capturing "actual" administration of adrenaline, was considered indicative of anaphylaxis in an inpatient setting. Consequently, adrenaline administration was removed from the list of additional clinical information for Criterion C. For Criterion B (outpatient setting), adrenaline was removed from the list of additional clinical information, and at least one of the remaining clinical items was required for ascertainment of an anaphylaxis.

- Death occurring within 72 hours after IV iron or IV penicillins treatment and allergic urticaria were added as equivalent to the additional clinical information required for Criterion B and Criterion C.

These modifications to the algorithm were agreed by the research team and endorsed by the external scientific advisory board in March 2019. The addition of the expanded algorithm was also documented in the amended protocol of 26 September 2019 (Section 9.7.4.1).

## Figure 8. Expanded Anaphylaxis Algorithm



#### 9.4.1.2 Outcome Validation

Direct validation—i.e., confirmation of potential cases in the study cohort by examining the source record—was feasible only in the Danish national and regional linked registries and databases and in PHARMO-NL. We also conducted indirect validation—i.e., confirmation of potential anaphylaxis reaction events of any origin using source records in the Oldenburg Hospital in Germany with no possibility to establish a link to the potential study cases identified in the GePaRD database. These potential anaphylaxis events were identified using algorithms approximating the case-identification algorithms applied to the GePaRD data in Germany.

**Direct Case Validation in Denmark and The Netherlands**

In Denmark, it was possible to conduct direct validation of all potential cases of anaphylactic reactions identified through linked data sources through review of medical records. The Danish Patient Safety Board granted permission to perform validation of all potential cases identified through the main and expanded algorithms among users of IV iron and potential cases identified through the main algorithm only among users of IV penicillins.

The PHARMO Institute performed direct case validation of all potential cases identified through the main and expanded algorithms among users of IV iron and IV penicillins in the PHARMO-NL. PHARMO-NL worked with a third-party organisation, Stichting Informatievoorziening voor Zorg en Onderzoek, to de-anonymise the potential cases and request local ethics committees' approvals at the individual hospitals for access to patient medical records. Only cases from the hospitals that granted approval were included in the validation analysis.

**Indirect Validation of Case-Identification Algorithm in Germany**

Owing to data-protection rules, no linkage of individual patients between the Oldenburg Hospital and GePaRD was possible. Therefore, we validated the case-identification algorithm. This indirect validation of the case-identification algorithm used in the GePaRD was conducted using the Hospital Information System (digitalised inpatient/emergency room discharge diagnoses coded using the German modification International Classification of Diseases, 10$^{th}$ revision (ICD10-GM) codes and outpatient clinic visit diagnoses) and electronic medical record data (clinical data) at the Oldenburg University Hospital in Germany, which is part of the area covered by the GePaRD. All potential cases identified through the anaphylaxis-identification algorithm, regardless of exposure/trigger, among patients aged 18 years or older discharged between 01 January 2004 up until 30 April 2019 from the departments that agreed to contribute data (i.e., cardiology, nephrology, dermatology, and emergency medicine) were eligible for validation. The estimated PPV and 95% CIs of the algorithms used to identify anaphylaxis events were calculated.

### *9.4.2 Study Exposures*

The Anatomical Therapeutic Chemical (ATC) classification system code B03AC (parenteral iron preparations) was used to identify IV iron exposure in each data source. Additional country and data source-specific coding nomenclatures were also 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 1.

## Table 1. Study IV Iron Compounds

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

ATC = Anatomical Therapeutic Chemical (classification system); IV = intravenous.

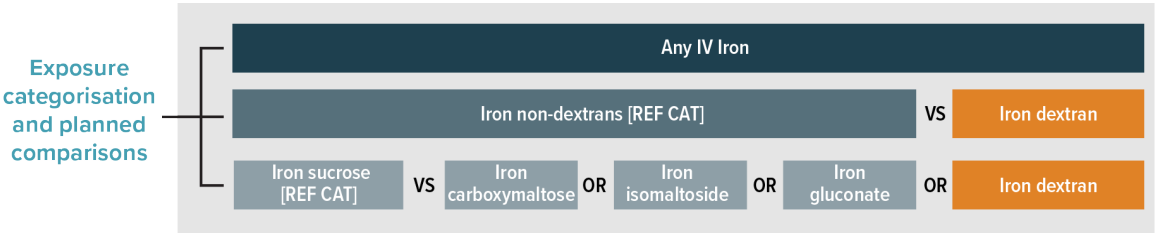
*The IV iron naming convention terminology is used throughout this document to refer to individual types of IV iron products using a simplified name.

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 4th-level ATC codes can be used only in combination with product names.

To address the study objectives, IV iron exposure data were categorised by group of IV iron and where feasible, by individual IV iron types as shown in Figure 9.

For comparative analyses, iron dextran was compared with iron non-dextrans. In addition, the individual IV iron types listed in Figure 9 below were each compared with iron sucrose, the IV iron type with longest time since marketing authorisation and the largest expected number of users.

## Figure 9. IV Iron Exposure Categorisation




IV = intravenous; REF CAT = reference category for the comparison by iron group (iron dextran vs. iron non-dextran) and by individual iron types.

### *9.4.3 Covariates*

The following variables were assessed through descriptive analyses as risk factors or potential confounding variables for potential adjustment of incidence estimates:

- Demographic/other variables: age, sex, year of new use of IV iron.
- History of medical conditions considered to be proxies of prior history of hypersensitivity reactions, severity of anaemia, possible indications of IV iron treatment and other relevant comorbidities. Prior use of selected medications was also considered. Diagnosis codes for medical conditions were evaluated from outpatient, inpatient, or emergency department encounters, depending on data available in each data source using International Classification of Diseases (ICD), 9th or ICD-10 Revision, or International Classification of Primary Care codes among others. Medications were identified using ATC codes and data source-specific codes/variables. Note that some variables were not available in all data sources, were underrecorded, or available only for a subset of the study population.

The evaluation period for each variable was set according to the chronicity of the conditions/medications and relevance as confounding variables. In general, the research team used 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. For more acute conditions (e.g., GI bleeding and peptic ulcer) a shorter lookback period was assessed. Data on prior use of medications, including use of other medications for anaemia, were generally based on information available during the 6 months before cohort entry.

## 9.5 Data Sources and Measurement

The study was conducted following a common core protocol and a core statistical analysis plan in populations covered in the six population-based health databases and registries in Europe listed in Section 9.2. The DIMDI-DaTraV database was unable to contribute data to the study (see Section 9.9.5). Summary information on main characteristics of the data sources and availability of health information relevant to this PASS is presented in Table 2.

## Table 2. Selected Characteristics and Outcome and Variable Assessment in Study Data Sources

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| Database population | 1,295,584 (adult population 1,021 908 as of 2016) of the Central Denmark region | 66,600,000 | 3,200,000 | ~25,000,000 | 18,000 dialysis patients annually | 70,000,000 | 9,995,153** (as of 2016) |
| Database type | Administrative routinely collected data linked from several databases and restricted to the catchment population of the area served by the hospitals in the Central Denmark Region, as data on hospital-based IV iron administration were complete | Contains information from all out-of-hospital claims linked to the national hospital discharge summaries database system and the national death registry. Covers the three main health care insurance | PHARMO-NL holds several databases, linked on patient level. For this study, GP data, outpatient pharmacy data and inpatient pharmacy, and hospitalisation data, were used. | Contains claims data for reimbursement of diagnostic and therapeutic services from four Statutory Health Insurance providers (SHIs). Population represents approximately 17% of the German population. | KfH is the largest provider of haemodialysis in Germany. Comprises more than 200 dialysis clinics. Data for adult patients undergoing dialysis are collected electronically through the QiN registry system. | Contains claims data from Statutory Health Insurance providers (SHIs) approximately representing 90% of German population. | Prescribed Drug Register since 1-Jul-2005<br>Patient registers: hospital admissions and hospital outpatient visits<br>Register of the total population<br>Cancer register |

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| | | systems plus a majority of smaller ones, representing approximately 99% of the French population. | | | | | |
| **Drugs** | | | | | | | |
| Administered/Dispensed drugs | Prescribed and administered treatments (from inpatient hospitals' data and hospital outpatient specialists clinics as recorded in the Health Services Database of the Central Denmark Region). ATC code plus active substance name, strength, brand, route of administration, | Dispensed reimbursed drugs from outpatient pharmacy and inpatient pharmacy (only for a list of expensive drugs).<br>Date of treatment administration based on the date of the first outpatient nurse visit encounter | Out-patient Pharmacy Database (dispensed drugs), Inpatient Pharmacy Database (administered treatments, date and route of administration), and partial GP Database (prescribed or dispensed).<br>ATC codes (drug class code, active substance code through free text searching on package label)<br>Brand name, dose, date of prescription/dispensing | Prescribed and dispensed treatments from outpatient pharmacies with date of prescription and dispensing, linkable via an identification code (PZN) to ATC codes, brand name, active substance name, strength, dosage form and dose dispensed | Administered reimbursed treatments in dialysis centres.<br>ATC codes<br>Brand name/compound type, dosage, route, and date of administration | Outpatient pharmacy data with date of prescription (date of dispensing not captured).<br>Brand name, dose and duration based on PZN number and DDD | Drugs dispensed by prescription in community pharmacies since July 1, 2005, (reimbursed and not reimbursed medications). For this study drug exposure data captured since Jan 1, 2007, (2006 as wash-out)<br>ATC codes<br>Brand name/compound type; dosage and date of dispensing |

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| | amount dispensed, date of dispensing, and administration | after drug dispensing (when available)<br>ATC and CIP codes, brand name, dosage, quantity of packs dispensed | (Out-patient Pharmacy and GP Databases), route of administration (partially from dosing details in the outpatient pharmacy data) | | | | |
| **Study outcome & other variables and outcome validation** | | | | | | | |
| Hospital diagnoses | Yes, ICD 10 codes for discharge diagnoses, through linkage with data from the Danish National Patient Registry (DNPR). ER, only if overnight stay | Yes, ICD 10 codes. Discharge diagnoses. ER diagnoses only if overnight stay | Yes, ICD 9 & ICD 10 codes. Discharge diagnoses. ER diagnoses, only if resulting in overnight stay | Yes, ICD 10-GM codes. Admission and discharge diagnoses including secondary and ancillary diagnoses and corresponding dates | Yes, ICD 10-GM codes | Yes, ICD 10-GM codes. Discharge diagnoses (month of discharge) | Yes, ICD 10 codes, admission and discharge. ER diagnoses captured*** |
| Outpatient diagnoses | Yes, ICD 10 codes from hospital outpatient | Not available | GP data (ICPC codes) for a subset population | Yes, ICD 10-GM codes. Outpatient care diagnoses (quarter of visit) | Not available | Yes, ICD 10-GM, date of visit as | Yes, hospital outpatient clinics diagnoses |

| Characteristic | Danish National and Regional Linked Registries and Databases | SNDS, France | PHARMO-NL | GePaRD, Germany | KfH QiN, Germany | DIMDI-DaTraV, Germany* | Swedish National Registers |
|---|---|---|---|---|---|---|---|
| | clinics diagnoses at DNPR | | | including primary care (GP) and specialists diagnoses. Procedures and prescriptions were used to derive the exact date for outpatient diagnoses | | quarter and year | |
| **Study outcome** | | | | | | | |
| Outcome validation | Yes, through review of medical records | No access to medical record data possible. | Yes, through clinical review of hospital medical records | No access to medical record allowed.<br>Clinical review of patient profiles (i.e., reconstructed patient medical record based on claims).<br>Indirect validation of anaphylaxis algorithm through Oldenburg University Hospital | No access to medical record allowed. | No access to medical record allowed. Indirect validation of anaphylaxis algorithm through Oldenburg University Hospital | No access to medical record allowed. |

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; DNPR = Danish National Patient Registry; ER = emergency room; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; ICD = International Classification of Diseases; ICPC = International Classification of Primary Care; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; PZN = Pharmazentralnummer, nationwide german identification number for pharmaceuticals; SHI = statutory health insurer; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

* In the end, DIMDI-DaTraV did not provide data for the study.

** In 2016, 6,530,258 individuals had had at least one drug dispensed out of a total of 9,995,153 people covered by the national registry.

*** In the Swedish National Patient Register, ER visits are captured by the use of information on “unplanned visits”.

## 9.6 Bias

### *9.6.1 Confounding*

In this study, the initial plan was to control for confounding through propensity score stratification using relevant baseline covariates. However, the small number of events identified precluded this approach (see Section 9.9.5).

### *9.6.2 Outcome Misclassification*

In all data sources, the anaphylactic reactions outcome was identified through electronic algorithms (see Section 9.4.1.2). In data sources where medical record review was feasible (the Central Denmark Region and PHARMO-NL), validation via medical record review was performed for all identified potential cases for hospitals/departments where access to records was permitted. Indirect validation of the anaphylaxis algorithm applied to the GePaRD data in Germany was conducted through review of medical records of potential cases of anaphylaxis reactions in the Oldenburg University Hospital, in Germany.

## 9.7 Study Size

The study included all available patients fulfilling the inclusion criteria and none of the exclusion criteria. Preliminary data on IV iron use obtained from the 2014 and 2016 feasibility evaluations suggested that approximately 250,000 to 300,000 patients with IV iron dispensings or administrations would be available across all data sources. As detailed in the final endorsed study protocol, the focus was on the study precision calculations derived from the estimates of risk of anaphylactic reactions for IV iron dextran and non-dextrans reported by Wang et al. (2015). Table 3 shows the study precision calculations for two risk scenarios for IV iron dextran and non-dextrans. The PASS 14 software (NCSS, LLC. Kaysville, Utah; 2015. http://www.ncss.com/software/pass/) was used for the calculations.

**Table 3. Protocol 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).

## 9.8 Data Transformation

At each research centre, raw data were obtained and transformed and harmonised into a study specific common data model (minimal informative data sets for demographics, drugs, diagnoses and person characteristics). At each centre, analysis data sets were derived from these data.

The following transformations were made to the analytical data sets:

- Age was categorised according to 10-year age groups except for the groups aged 18 to 24 years and 85 years or older.
- IV iron exposure was categorised into iron dextran and iron non-dextrans (all other iron types). IV iron exposure was also categorised into individual IV iron types as described in the Section 7 (Research question and objectives).
- IV penicillins were categorised into subtypes i.e., natural penicillins, betalactamase-resistant penicillins, aminopenicillins, carboxypenicillins, ureidopenicillins and other penicillins.

## 9.9 Statistical Methods

Data analyses occurred in two stages: (1) an analysis conducted at each data source and (2) a combined analysis of aggregated data conducted by the coordinating centre, where summary data from each data source were integrated.

The objective of the study was to assess the risk of anaphylaxis among users of IV iron across all study data sources. Comparisons between data sources were not part of the objectives.

All analyses were conducted according to the originally endorsed study protocol dated 04 May 2017, the endorsed amended protocol of 26 September 2019, and the plan of analyses detailed in the statistical analysis plan (SAP) dated 19 December 2017, with documentation of data source-specific adaptations. Data specifications that varied between the data sources were documented and maintained by each data source. Amendments to and deviations from the SAP are described in Section 9.9.5.

Not all data sources captured data for all IV iron compounds targeted for analyses or for the IV penicillins cohort; therefore, each research centre performed the analyses that were applicable to their data.

Most research partners conducted analysis using SAS software (SAS Institute, Inc, Cary North Carolina), researchers from the KfH QiN dialysis registry in Germany conducted analysis using R software.

Analyses of data across data sources included estimates for IPs and RRs and risk differences (RDs) using iron sucrose as the common reference. Crude pooled analysis and beta-binomial meta-regression techniques were employed to integrate the data across sources.

### *9.9.1 Main Summary Measures*

Categorical variables were summarised by frequencies and proportions, and continuous variables were summarised by means and standard deviations, medians and interquartile ranges (first quartile to third quartile), and minimum and maximum values.

Crude IPs of anaphylactic reactions were calculated for each IV iron exposure group and the IV penicillins cohort expressed per 10,000 person-years with Wilson score 95% CIs.

Crude RRs and RDs with corresponding 95% confidence intervals (CIs) derived from the Miettinen-Nurminen method were estimated to compare the IP estimates of anaphylactic reactions between the pairs of IV iron groups.

For all analyses and for reporting purposes, country-specific data-protection rules were taken into consideration (see Table 4 for cell-count limit specifications).

### *9.9.2 Main Statistical Methods*

#### 9.9.2.1 Descriptive Statistics

Descriptive analyses were performed as a first step, to inform final decisions on the analytical approach.

At each data source, patients were identified after the application of each inclusion and exclusion criterion, beginning with the total number of registered patients in the data source and ending with the number of patients ultimately included in the IV iron cohort based on the first exposure. The process of cohort identification was repeated for users of IV iron compounds based on second exposure, third or subsequent exposure, and any exposure. For the IV penicillins cohort, the number of patients for each IV penicillins compound were identified where applicable. This process was repeated based on any treatment of an IV penicillins compound (regardless of the type) in which the number of patients and number of treatments were tabulated for each criterion.

Descriptive statistics were calculated to summarise baseline characteristics (e.g., demographic information, comorbidities, and medication use) of users of IV iron and new users of IV penicillins compounds. These baseline characteristics were presented only for the “any” dispensing/treatment of interest. Separate tables were generated for users of each exposure of interest, grouped as follows:

- Any IV iron product; iron dextran and iron non-dextrans
- Iron carboxymaltose, iron isomaltoside, iron gluconate, iron dextran, and iron sucrose
- Intravenous penicillins

Data source-specific limits on the minimum number of counts per cell that can be reported, which are driven by data-protection regulations, were considered given the expected low number of outcomes (Table 4).

**Table 4. 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 and regional linked registries and databases | 5 individuals per cell | Limit applies to regulatory-driven studies and publications |
| PHARMO Database Network, the Netherlands (PHARMO-NL) | 5 individuals per cell | Does not apply to regulatory-driven reports; does apply to publications |
| French National Health Care Insurance System Database (SNDS, France) | 10 individuals per cell (applies only to descriptive data) | Does not apply to regulatory-driven reports and publications |
| German Pharmacoepi-demiological Research Database (GePaRD, Germany) | No established limits, data must be fully de-identified | |
| Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme (KfH QiN, Germany) | No established limits, data must be fully de-identified | |
| Swedish National Registers | No established limits, data must be fully de-identified | |

GePaRD = German Pharmacoepidemiological Research Database; PHARMO-NL = PHARMO Database Network in the Netherlands; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; SNDS = Système National des Données de Santé (French National Health Care Insurance System Database).

#### 9.9.2.2 Crude Incidence Proportions and Crude Comparative Analyses

**Analysis Performed at Each Data Source**

The time window at risk for outcome events for the main analyses was the day of the administration (1-day risk window) for data sources capturing actual drug administration and the day of dispensing and the day after (2-day risk window) for data sources capturing drug dispensing.

Incidence proportions were calculated as the number of patients with an incident anaphylaxis event (E) that occur during the 1-day or 2-day risk window among IV iron users divided by the total number of patients or patient treatments at risk (N). In the results tables, the IP are expressed per 10,000 patients:

$$IP = \frac{E}{N} \qquad \text{[Equation 1]}$$

Given that the incidence of anaphylaxis was expected to be very small, the 95% CIs for IP estimates were calculated as follows using the Wilson score interval, which is recommended as the most robust for rare events (Brown et al., 2001):

$$IP_{95\%} = \frac{IP + \frac{z^2_{0.025}}{2N} \pm z_{0.025}\sqrt{\frac{IP(1-IP)}{N} + \frac{z^2_{0.025}}{4N^2}}}{1 + \frac{z^2_{0.025}}{N}} \qquad \text{[Equation 2]}$$

In the above equation, the term *z* represents the value of the standard normal distribution associated with the indicated level of confidence.

These unadjusted estimates served as an initial step in characterising risk and providing insight into the feasibility of conducting subsequent analyses. Among the crude IV penicillins compound populations, the total number of patients or patient treatments at risk and the number of anaphylaxis events were also calculated. Using equations 1 and 2, respectively, crude IP estimates and 95% CIs were calculated separately for initiators of IV penicillins compounds and for any dispensing/treatment of IV penicillins. The IP of anaphylactic reactions among those exposed to the IV penicillins compounds was used to gauge the performance of the case-identification algorithm which helped provide context to the results for IV iron products. The study was not designed for direct comparisons between the IV penicillins cohort and any of the IV iron groups (or types).

Incidence proportion estimates of anaphylaxis between the pairs of IV iron groups and types listed below were compared with RRs and RDs.

The RR is the IP of one type of IV iron compound (referred to using the subscript "*i*") divided by the IP of another type of IV iron compound that serves as a referent compound (subscript "*Ref*"). Thus, RR estimates of predicted compound initiators relative to referent compound initiators were computed as follows:

$$R = \frac{IP_i}{IP_{Ref}} = \frac{E_i/N_i}{E_{Ref}/N_{Ref}} \qquad \text{[Equation 3]}$$

The RD was also calculated to compare the occurrence of anaphylaxis between initiators of various types of IV iron compounds. The RD estimates were computed as follows:

$$RD = IP_i - IP_{Ref} \qquad \text{[Equation 4]}$$

The 95% CIs for RR and RD estimates were then calculated using the Miettinen-Nurminen method (Miettinen and Nurminen, 1985), which performs well in cases of rare events (Klingenberg, 2014). Miettinen-Nurminen CIs for RR and RD estimates are standard options implementable in the FREQ procedure in SAS version 9.4.

For users of each type of IV iron compound, unadjusted IP estimates and 95% CIs were calculated (using equations 1 and 2). Additionally, between IV iron compounds of interest, unadjusted RR and RD estimates and their 95% CIs were calculated and summarised. Because risk of anaphylaxis is highly dependent on the history of previous administrations of the studied drug, risks were assessed stratifying by first, second, and subsequent dispensings/administrations of the study drugs, as well as overall with all dispensings/administrations combined.

These estimates are presented for the following IV iron groups and IV iron subtypes:

- Any IV iron compound, iron dextran, and iron non-dextrans; RR and RD estimates comparing iron dextran to iron non-dextrans (referent compound)

  - New users or first dispensing or administration
  - Second dispensing or administration
  - Third or subsequent dispensing or administration
  - All dispensing or administration where the exposure and number of events for each patient are accumulated over the entire observation period

- Iron carboxymaltose, iron isomaltoside, iron gluconate, iron dextran, and iron sucrose; RR and RD estimates comparing each individual compound to iron sucrose (referent compound)
  - New users or first dispensing or administration
  - Second dispensing or administration
  - Third or subsequent dispensing or administration
  - All dispensing or administration where the exposure and number of events for each patient are accumulated over the entire observation period

**Meta-analyses Performed at the Coordinating Centre**

Meta-analyses of data across research centres focused on summarising IP, RR, and RD estimates. The coordinating centre compiled aggregated data from each research centre into integrated data sets for analysis. Summary data of IP, RR, and RD estimates specific to each research centre were combined into a single source for a comprehensive presentation alongside the meta-analysed estimates across data sources.

As an initial step, crude methods were applied to summarise data across research centres. For each IV iron compound and for IV penicillins, IP estimates were generated by summing the number of potential anaphylaxis events across research centres (numerator), summing the total number of treatments or patients across research centres (denominator), and dividing these two values (numerator divided by denominator). Crude RR and RD estimates were computed using equations 3 and 4, respectively, to compare IV iron dextran to IV iron non-dextrans and to compare each individual type of IV iron to IV iron sucrose. As in the analyses conducted by each individual research centre, 95% CIs were derived from the Wilson score method for the IP and from the Miettinen-Nurminen method for the RR and RD.

Crude methods, while insightful as an initial step, are susceptible to bias due to the assumption of the same underlying risk of anaphylaxis across research centres (Altman and Deeks, 2002; Lievre et al., 2002). Meta-analytic methods are typically applied to stem this potential bias. However, in situations where research centres have zero events, these traditional methods either ignore information from these research centres or apply continuity corrections, both of which have the potential to introduce error (Kuss, 2015).

In situations of rare events, particularly when some studies have zero events, simulation studies have recommended the use of beta-binomial regression (Kuss, 2015; Ma et al., 2016), which is a type of binary regression that accounts for overdispersion, to provide summary estimates across research centres. Beta-binomial regression was implemented

using the finite mixture model (FMM) procedure in SAS with default iteration and convergence parameters and the dual quasi-Newton optimisation technique to obtain maximum likelihood estimates. The logit link was used to estimate regression coefficients, and the inverse logit function was applied to these regression coefficients to derive IP point estimates for each compound of interest. For comparative analyses, RR point estimates were derived by dividing corresponding model-derived IP estimates (Equation 3), and RD point estimates were derived by subtracting corresponding model-derived IP estimates (Equation 4).

To avoid relying on assumptions of IP, RR, and RD distributions in this situation of very rare events, confidence intervals around these parameter point estimates were derived from Monte Carlo methods. From the results of each beta-binomial model, 10,000 random samples of the regression coefficients were drawn from the multivariate normal distribution while incorporating model-derived regression coefficient point estimates and their corresponding variance-covariance matrix. For each random sample of regression coefficients, the inverse logit function was applied to derive IP values for each compound, and RR and RD values were computed using equations 3 and 4, respectively, for comparative analyses. For each of these derived parameters, the 2.5th and 97.5th percentiles across all 10,000 random samples were computed to serve as the lower and upper bounds of the 95% CI.

**Validation Analysis**

As described in section 9.4.1.2, direct validation of potential anaphylaxis events through medical record review was only possible in the Central Denmark Region and PHARMO-NL database. The validity of the main and modified algorithms used to identify potential anaphylaxis events in these two study populations were assessed by calculating their positive predictive values. The PPVs for the algorithms are presented with 95% CIs for binomial proportions by the exact method.

The PPV was defined as the probability that a patient classified as a potential anaphylaxis event by the algorithm was a confirmed case of anaphylaxis. Positive predictive values were calculated among the total number of potential cases originally identified by the algorithm that were accessible for abstraction of medical records. In addition, PPVs were also calculated including in the denominator all potential events identified by the case-identification algorithm, irrespective of medical record accessibility.

Adjustments of the IPs based on the PPVs could be performed in PHARMO-NL data for IV penicillins. In the Central Denmark Region the adjustment of the IPs could ultimately not be performed due to data privacy rules aimed at preventing the identification of individual patients.

### *9.9.3 Missing Values*

Information on some covariates (e.g., laboratory test results) was not available in all the study data sources. When information on a variable was not available in a study data source, this variable was not evaluated in descriptive tables. For all other variables (both continuous and categorical), the number of non-missing observations were reported as part of the descriptive summary. No regression analyses were performed at the research partner level due to the rareness of the event. All meta-analyses were performed using only observed data of numerators (number of anaphylaxis events) and denominators

(number of patients exposed to, or dispensings of, the compound of interest) in applicable data sources. Thus, no imputation methods for missing data were performed as the potential for missing covariate data did not factor into any regression analyses.

### *9.9.4 Sensitivity Analyses*

Sensitivity analyses were focused on the calculation of IPs, RRs and RDs of anaphylactic reactions among the different types of IV iron compounds assuming different scenarios of risk. Estimates were derived using the same methods described in Section 9.9.2.2. The following risk scenarios were considered:

- *Expansion of the case-identification algorithm* (See Section 9.4.1.1): In this analysis, the criteria of the "Main Outcome Algorithm" were modified to assess the potential for missed study outcomes among IV iron first, second, third and subsequent and any users by group and individual types and for IV penicillins among first and any users and by IV penicillins (any) subtype.

- *Expansion of the risk window from day 0 to day 7*: The expansion of the risk window was conducted in all data sources except in the KfH QiN dialysis registry in Germany, where date of IV iron administration and date of anaphylaxis diagnoses were captured. In all sites except KfH QiN, all potential events were identified using the main case identification algorithm during a 7-day period after the date of exposure to a first, second, third or subsequent IV iron use by group and by type. The calculations of IPs and incidence RRs were based on all sites including KfH QiN that contributed data for day 0 only.

- *Risk among IV iron switchers:* This analysis assessed the occurrence of potential events among patients switching between different types of IV iron at the first and any switch by IV iron group and type.

- R*isk among IV iron users (any) before 01 January 2013 and after 31 December 2013:* This analysis assessed the potential effect of the EMA Referral Assessment Letter. Cases identified during 2013 were not accounted for.

- *Analysis removing data sources with no study cases from the pooling of the aggregate data (IV iron and IV penicillins)*: This analysis represented a "worst-case scenario" because the removal of these patients from the denominator would cause an increase in the observed IP which would result in an overestimation of the risk.

- *Analysis of any use of IV iron:* This analysis assessed the risk of anaphylaxis among new and prevalent users of IV iron.

- *Number of potential anaphylaxis reactions identified after the risk window (up to 21 days):* This analysis was intended to address the potential delayed administration of a dispensed IV iron among users (any) of IV iron by group and type and among IV penicillins users.

- *Listing of causes of death of fatal cases*: in data sources where these data were available.

- *Risk among IV iron users excluding dialysis patients:* Given the differences between the population of patients undergoing dialysis receiving IV iron treatment compared with patients treated for other indications, this analysis was of relevance. Applied to IV iron users at first, second, third or subsequent and any dispensing/treatment by group and by type.
- *Risk among IV iron dialysis patients only*: Applied to IV iron users (any) by group.

### *9.9.5 Amendments to the Statistical Analysis Plan*

The PRAC-endorsed amended protocol dated 26 September 2019 incorporated most deviations to the original analyses detailed in the SAP dated 19 December 2017. Listed below are the complete list of deviations to the SAP.

**SAP Section 2 (Study Design), Section 2.1 (Data Sources), Section 2.2 (Population)**

DIMDI-DaTraV Database: In spite of the highly engaged and motivated DIMDI principal investigator, the limited resources available at DIMDI to perform study-related activities precluded inclusion of this database in the study. Furthermore, the rules at DIMDI did not allow to fund additional resources for the study. This situation was further complicated by the ongoing merger between the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizineprodukte [BfArM]) and DIMDI. As of February 4, 2020, no data from DaTraV are available for the final report. It is worth noting that the critical limitation identified during the study feasibility assessment concerning the lack of date on hospital admission combined with the lack of the last year of data for patients who died remains unchanged.

**SAP Section 2.5.1 Descriptive Analyses (Crude Risk Ratios and Risk Differences)**

Due to the low number of events identified in the study, the planned Wald-based approach for calculation of the 95% CIs for the RRs could not be performed. Similarly, the planned calculations provided for the 95% CIs for the RD were modified accordingly. For both the RR and RD, the Miettinen-Nurminen method was used to calculate the 95% CIs of RRs.

**SAP Sections 2.5.2 and 2.5.3 Propensity Score Analyses and Adjusted Incidence Proportions and Comparative Analyses**

The PRAC-endorsed protocol of 04 May 2017 proposed the use of propensity scores to adjust the RR estimates, a method that was chosen because of its usefulness in situations where a small number of events is expected. Preliminary descriptive results reviewed by the study investigators in March 2019 indicated that the number of events identified through the main analyses were very low. Additional sensitivity analyses performed to address the potential for missing study outcomes provided similar results. Propensity score methods and other methods to address confounding are not able to deal with situations of extremely small numbers of study events, as encountered in this study. Therefore, the research team agreed that the low number of events did not allow

for the planned implementation of propensity scores and estimation of adjusted comparative analyses.

**SAP Section 2.5.5 Analysis of Validated Cases (Only Research Partners Performing Case Validation)**

The originally planned analyses considering only confirmed cases of anaphylactic reactions after validation among research partners, were not performed due to impossibility to validate all potential cases and also due to Danish data-protection rules in low count situations.

**SAP Section 2.5.4 Sensitivity Analyses**

The following additional sensitivity analyses were performed (see Section 9.9.4 for additional information):

- Expanded anaphylaxis-identification algorithm
- Incidence proportions by subtype of penicillins
- Description of events occurring up to 21 days after the risk window
- Exclusion of dialysis patients

The planned listing of causes of death among fatal cases was not possible due to lack of cause of death data most from data sources or absence of fatal cases when cause of death was available (i.e., no fatal cases identified in Sweden).

## 9.10 Quality Control

The standard operating procedures, internal process guidance, or routine practice at each research centre were used to guide the conduct of the study. These procedures included, 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 was reviewed independently by a different analyst, with oversight by a senior statistician, if possible. All key study documents, such as the study protocol, SAP, validation plan, abstraction forms, and study reports, underwent quality-control review, senior scientific review, and editorial review. The quality and audit trails are centre specific, and each research partner followed its own quality and audit trail procedures. 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 performed internal audits and assessments that involved various aspects of the project, including but not limited to education and training documentation, data transfer procedures and documentation, and institutional review board documentation.

# 10 Results

**Owing to the reporting restrictions for cell counts below five for Denmark, the number of events and incidence estimates for the Central Denmark Region and for some estimates from the meta-analyses are reported as minimum and maximum ranges. Also, when data source-specific estimates are presented, numerators and denominators for the Central Denmark Region data are rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.**

Complete results for all the analyses conducted at each data source and for the meta-analyses are provided in Annex 3 and Annex 4.

## 10.1 Participants

The study population consisted of all eligible patients with a recorded first, second, and third or subsequent exposure to IV iron compounds meeting all inclusion criteria and none of the exclusion criteria during the study period in each participating data source. The participating data sources provided data on the use of IV iron products in the general population in each country and also from a network of dialysis centers in Germany. The main results of the final cohort selection across data sources are summarised in this section.

Complete results of the IV iron cohort attrition process for each data source are provided in Annex 3, Cohort Attrition excel file, Tabs IV Iron-1st (first users), IV iron-2nd (second users), and IV Iron-3rd_Sub (third or subsequent users).

The same cohort selection criteria were applied to identify eligible patients for inclusion in the IV penicillins cohort. Complete results of the IV penicillins cohort attrition process for each data source are provided in Annex 3, Cohort Attrition excel file, Tabs Penicillin-1st (first users) and Penicillin-Any (any users).

### *10.1.1 IV Iron Cohort*

#### 10.1.1.1 Overall and by IV Iron Groups: Iron Dextran and Iron Non-Dextrans

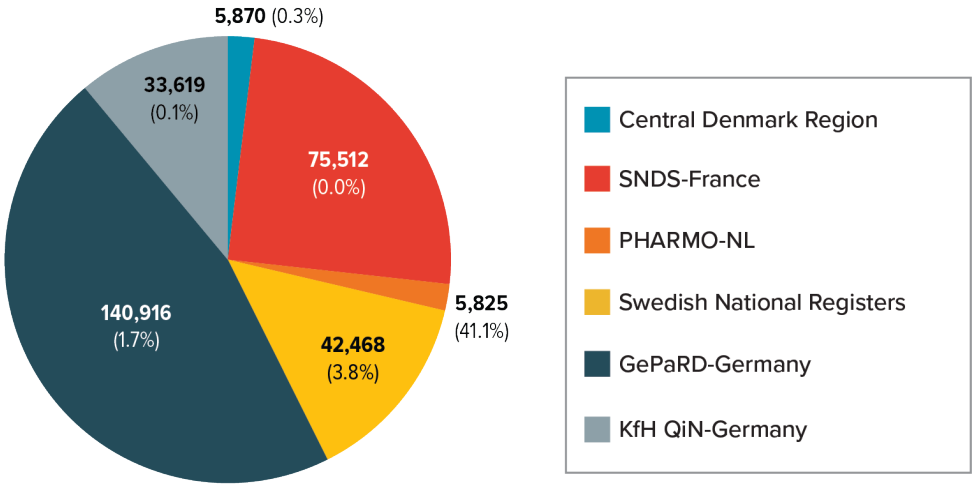
There was no comprehensive capture of all types of IV iron in any of the study data sources. Moreover, the IV iron exposure captured in this study is based on partial capture mostly reflecting IV iron treatment from ambulatory outpatient settings.

This section presents the final number of eligible IV iron exposures by ordinal number of the exposure to IV iron i.e., first exposure, second exposure, and third or subsequent exposure overall and for each data source. The percentage of IV iron dextran treatments over the total IV iron exposure is also provided.

### First Dispensing or Administration

Overall, 304,210 first IV iron treatments were identified during the study period across all data sources. The number of first IV iron exposures varied by data source from 5,825 in PHARMO-NL to 140,916 in GePaRD in Germany. Intravenous iron dextran treatments represented 2.1% of all first IV iron exposures with marked variability between data sources; notably IV iron dextran use represented 41.1% of the overall IV iron use captured in PHARMO-NL, while in the remaining data sources it ranged from 0.1% (KfH QiN, Germany) to 3.8% in the Swedish registers (Figure 10).

## Figure 10. Number of First IV Iron Treatments (Percentage of Iron Dextran)




**TOTAL TREATMENTS:** 304,210 (2.1% dextran)

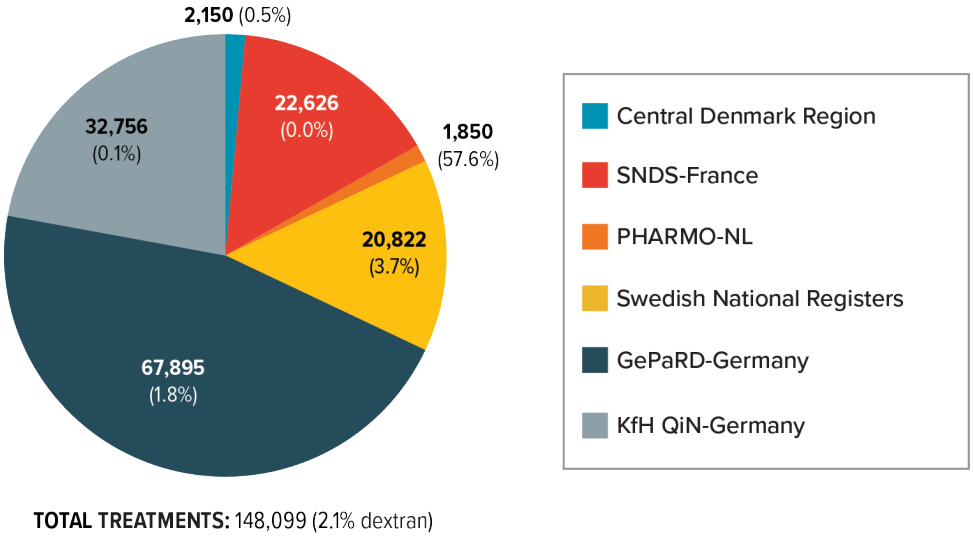
GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

Note: Numbers for the Central Denmark Region data were rounded to the nearest 10 to comply with Danish data-protection and reporting requirements rules aimed at prevention of identification of individuals.

### Second Dispensing or Administration

There were 148,099 second IV iron exposures across data sources ranging from 1,850 treatments in PHARMO-NL to 67,895 treatments in GePaRD in Germany. The overall proportion of IV iron-dextran treatments was 2.1% of all IV iron treatments and in PHARMO-NL represented 57.6% of the total PHARMO-NL IV iron exposure (Figure 11).

**Figure 11. Number of Second IV Iron Treatments (Percentage of Iron Dextran)**




**TOTAL TREATMENTS:** 148,099 (2.1% dextran)

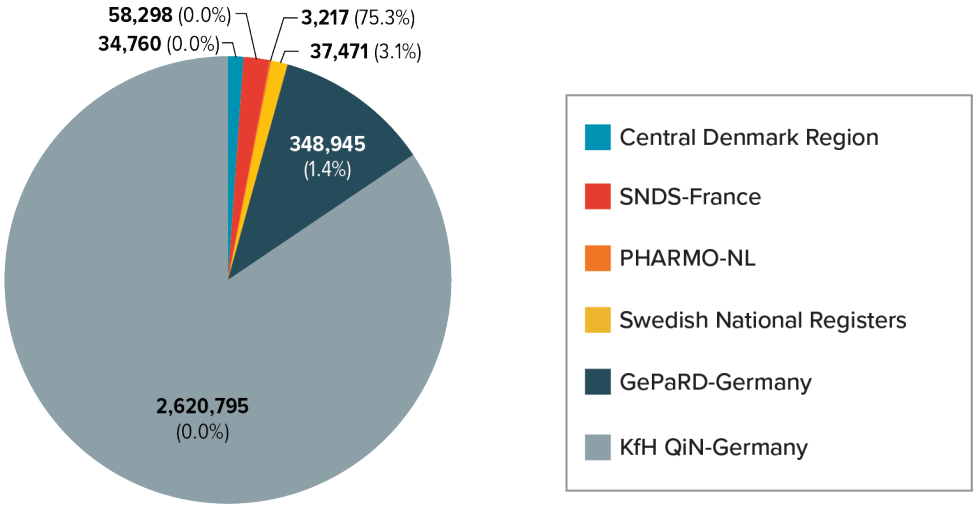
GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

Note: Numbers for the Central Denmark Region data were rounded to the nearest 10 to comply with Danish data-protection and reporting requirements rules aimed at prevention of identification of individuals.

### Third or Subsequent Dispensing or Administration

For the third or subsequent IV iron exposures, a total of 3,103,486 exposures in 105,634 patients were identified of which 2,620,795 (84.4%) IV iron treatments were contributed by the KfH QiN dialysis registry and 348,945 (11.2%) IV iron treatments came from the GePaRD, both located in Germany. The average number of IV iron treatments per patient in the KfH QiN was 80 treatments per patient whereas in the general population data sources ranged from 2 to 8 treatments per patient. IV iron dextran accounted for 0.3% of third or subsequent IV iron exposures across all data sources, however, in PHARMO-NL IV iron dextran accounted for 75.3% of third or subsequent IV iron treatments (Figure 12).

**Figure 12. Number of Third or Subsequent IV Iron Treatments (Percentage of Iron Dextran)**




**TOTAL TREATMENTS:** 3,103,486 (0.3% dextran)

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

Note: Numbers for the Danish data were rounded to the nearest 10 to comply with Danish data-protection and reporting requirements rules aimed at prevention of identification of individuals.

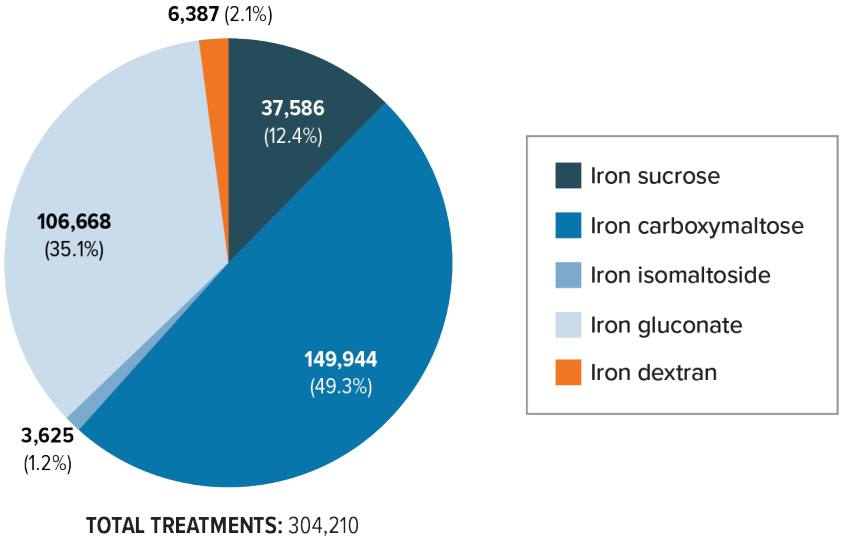
#### 10.1.1.2 Individual IV Iron Types

The distribution of the individual IV iron types differed across data sources. Iron carboxymaltose was the only IV iron product available across all data sources. Iron gluconate was available only in the GePaRD and the KfH QiN registry both located in Germany. The SNDS database in France contributed data only for iron carboxymaltose.

**First Dispensing or Administration**

Among first exposures to IV iron, iron carboxymaltose was the most frequent IV iron type (49.3% of patients) followed by iron gluconate (35.1% of patients) and iron sucrose (12.4%). The use of iron dextran and iron isomaltoside was low (Figure 13).

**Figure 13. Number of First IV Iron Treatments by Individual IV Iron Type: All Data Sources**



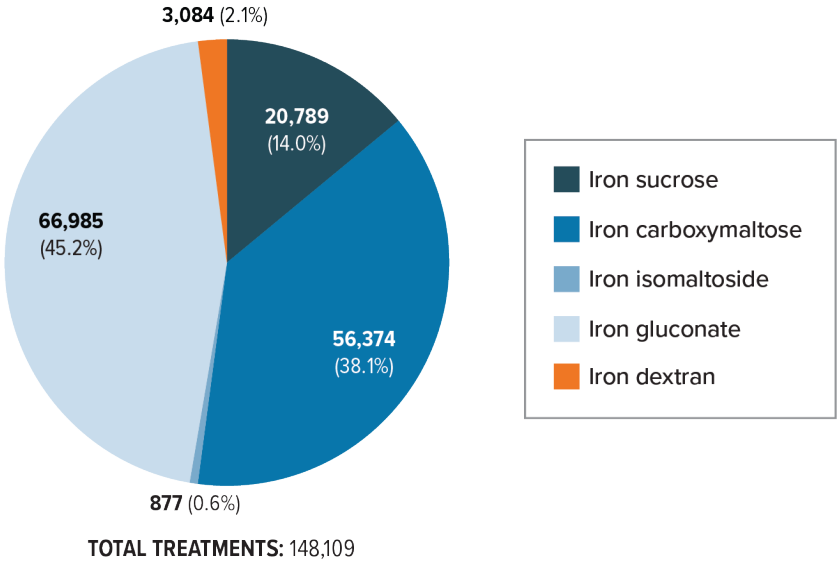

IV = intravenous.

Note: Percentages were calculated from the total number of patients with a first IV iron treatment.

**Second Dispensing or Administration**

For second IV iron exposures, iron gluconate was the product most frequently used (45.2% of treatments) followed by iron carboxymaltose in 38.1% of treatments and iron sucrose in 14.0% of all treatments. Iron dextran and iron isomaltoside were used in 2.1% and 0.6% of treatments, respectively (Figure 14).

**Figure 14. Number of Second IV Iron Treatments by Individual IV Iron Type: All Data Sources**




**TOTAL TREATMENTS:** 148,109

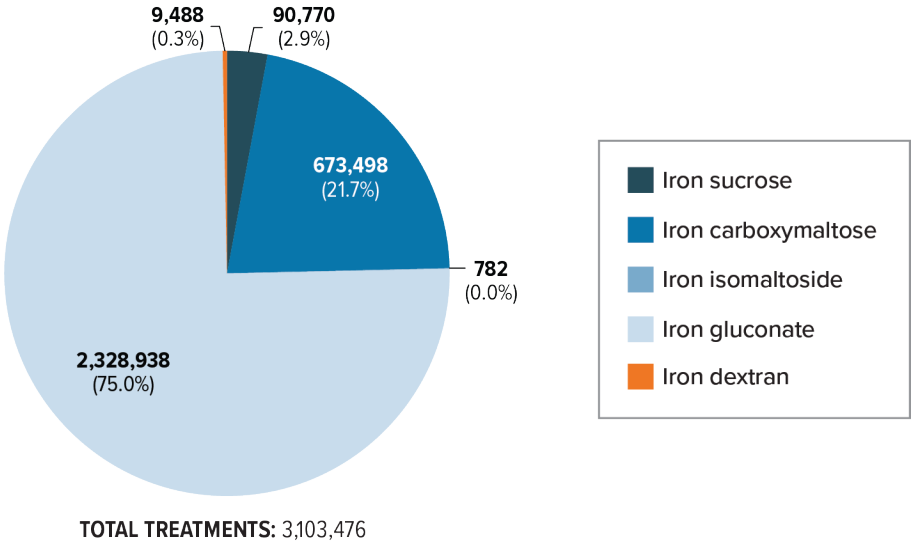
Iv = intravenous.

Note: Percentages were calculated from the total number of patients with a second IV iron treatment.

### Third or Subsequent Dispensing or Administration

For the third or subsequent IV iron treatments, 75% were iron gluconate followed by iron carboxymaltose representing 21.7% of all third or subsequent treatments and iron sucrose 2.9% (Figure 15). As previously highlighted, the KfH QiN registry in Germany contributed the largest number of all third and subsequent treatments (N = 2,620,795 [75%]).

**Figure 15. Number of Third and Subsequent Treatments by Individual IV Iron Type: All Data Sources**




**TOTAL TREATMENTS:** 3,103,476

IV = intravenous.

Note: Percentages were calculated from the total number of third or subsequent IV iron treatments.

### *10.1.2 IV Penicillin Cohort*

Data for the IV penicillins cohort was contributed by the Health Services Database of the Central Denmark Region, the SNDS in France, the PHARMO-NL, and the GePaRD in Germany databases.

Table 5 displays the final number of first exposures to parenteral penicillins (IV or intramuscular [IM]) and the number of treatments for any parenteral penicillins exposure, overall and by data source.

Overall, 231,294 first exposures to penicillins and 984,000 penicillins treatments were identified during the study period from the data sources contributing to the penicillins cohort. The Health Services Database of the Central Denmark Region contributed the largest number of first parenteral penicillins treatments (50.6%) and of any penicillins treatments (74.8%). Relevant numbers of IV penicillins treatments were also contributed by the three data sources where information on IV penicillins use was available.

**Table 5. Final Cohort Selection: IV Penicillins Cohort**

| IV Penicillins Treatments (n) | Central Denmark Region | SNDS, France | PHARMO-NL | GePaRD, Germany | Overall |
|---|---|---|---|---|---|
| Number of **first** IV penicillins treatments | 116,980[a] | 57,200 | 39,002 | 18,112 | 231,294 |
| Number of **any** IV penicillins treatments | 736,070[a] | 78,292 | 114,639 | 54,999 | 984,000 |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National Health Insurance System database, previously named SNIIRAM).

[a] Numbers were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

Note: IV penicillins use is not available in the Swedish registers and the KfH QiN dialysis registry in Germany.

## 10.2 Descriptive Data

### *10.2.1 Baseline Characteristics of Users*

The full results of the distribution of the baseline characteristics of users in each data source are included in Annex 3, Baseline Characteristics excel file, Tabs IV iron Any_by Group and IV Penicillin_Any.

#### 10.2.1.1 IV Iron Cohort

- The distributions by age and sex were similar in all study populations. The overall mean age (standard deviation [SD]) was 57 (19.3) years. For iron dextran the mean age (SD) was 58.8 (20.2) years and for non-dextrans 56.9 (19.3) years.

Across data sources, the mean (SD) age of patients among the iron-dextran group ranged from 58.5 (20.2) years in the Swedish registers to 63 (22.0) years in the Central Denmark Region. Among the iron non-dextran group, the mean (SD) age ranged from 54.2 (20.8) years in the Swedish registers to 67.5 (14.9) years in the KfH QiN dialysis registry in Germany.

- IV iron users were more frequently females, with differences across data sources by iron group; among the iron-dextran group, the proportion of females ranged from 52% in the KfH QiN dialysis registry in Germany to 78% in PHARMO-NL. For the iron non-dextran group females comprised 37% in the KfH QiN registry and 75% in the Swedish registers.

- In the general population data sources, IV iron treatment at cohort entry was mostly captured from outpatient ambulatory drug-dispensing data (ambulatory IV iron dispensings were 100% in SNDS in France, GePaRD in Germany, and the Swedish registers, and in the PHARMO-NL, 78% of iron dextran and 5% iron non-dextrans). Hospital treatment administration data were captured in the PHARMO-NL in 22% of iron dextran and 95% of iron non-dextrans and for most iron treatments in the Central Denmark Region.

- Chronic kidney disease, iron-deficiency anaemia, and gastrointestinal bleeding were among the conditions assessed as potential IV iron indications. Their prevalence varied greatly across study populations, dependent on the type of available data, i.e., outpatient diagnosis and primary care diagnoses as opposed to hospital discharge diagnoses. Overall, the highest prevalences were those from the GePaRD in Germany where diagnoses were captured from all health care settings. The following results were found in the general population data sources (not including KfH QiN dialysis registry in Germany):

  – Chronic kidney disease: among the iron-dextran group ranged from 0% in the Central Denmark Region to 45% in the GePaRD in Germany, and in the iron non-dextran group from 15% in the Swedish registers to 37% in the Health Services Database of the Central Denmark Region.

  – Iron-deficiency anaemia: among iron dextran users ranged from 2% in the Swedish registers to 40% in the GePaRD in Germany, and among iron non-dextran users from 3% in the Central Denmark Region and the Swedish registers to 47% in the GePaRD.

  – Gastrointestinal bleeding: among iron dextran users ranged from 3% in PHARMO-NL and the Swedish registers to 22% in GePaRD in Germany, and among iron non-dextrans from 4% in the Swedish registers to 20% in the GePaRD.

- The prevalence of conditions that are risk factors for hypersensitivity reactions also varied across data sources, mainly because of type of available data: the prevalence of history of anaphylaxis was low, ranging from 0% to 1%; history of asthma ranged from 0% to 11% in the iron dextran group and from 1% to 14% in the iron non-dextran group; and history of any allergies ranged from 2% in PHARMO-NL to 51% in GePaRD in Germany in the iron-dextran group and 3% in PHARMO-NL to 56% in GePaRD in the iron non-dextran group.

- The prevalence of use of antibacterials ranged from 32% to 52% (in the iron-dextran group) and from 30% to 42% (in the iron non-dextran group), with the lower ranges referring to the Swedish national registers and the highest range to the Central Denmark Region, respectively.

#### 10.2.1.2 IV Penicillins

- The mean (SD) age of patients in the IV penicillins cohort overall was 60.2 (19.6) years and ranged from 51.3 (18.0) years in the GePaRD in Germany to 61.9 (19.9) years in the SNDS in France.
- Females comprised from 39% of users in the GePaRD in Germany to 58.3% in the SNDS in France.
- History of anaphylaxis at baseline was low (0%-1%) and history of any allergies ranged from 2.0% in PHARMO-NL to 54% in the GePaRD in Germany.
- The Health Services Database of the Central Denmark Region captured the largest number of any IV penicillins treatments of which 96% where administered in hospital. In the SNDS in France and GePaRD in Germany, all penicillins use was captured through outpatient dispensing data. In the PHARMO-NL, 65% of IV penicillins treatments were captured as in-hospital treatments.

## 10.3 Outcome Data

### *10.3.1 Main Analysis*

#### 10.3.1.1 IV Iron

The following sections present the number of potential anaphylaxis events identified in the main analysis using the main case-identification algorithm and the same day or the same day and day after risk windows overall and for first, second, and third or subsequent IV iron exposure across all data sources by IV iron dextran group and by IV iron types.

Table 6 summarises the data source-specific results for the number of anaphylaxis events identified as potential study cases through the main case-identification algorithm recorded on the same day or same day and day after IV iron exposure, among patients receiving first, second, and third or subsequent IV iron treatment.

## Table 6. IV Iron Treatment and Number of Potential Anaphylaxis Events: Overall and Data Source-specific Results

| IV Iron Treatment and Potential Anaphylaxis Events (n) | Central Denmark Region | SNDS, France | PHARMO-NL | Swedish National Registers | GePaRD, Germany | KfH QiN, Germany | Overall |
|---|---|---|---|---|---|---|---|
| **First IV iron treatment** | | | | | | | |
| Patients | 5,870[a] | 75,512 | 5,825 | 42,468 | 140,916 | 33,619 | 304,210 |
| Events[b] | Min, 1; max, 4 | 0 | 0 | 3 | 9 | 0 | Min, 13; max, 16 |
| **Second IV iron treatment** | | | | | | | |
| Patients | 2,150 | 22,626 | 1,850 | 20,822 | 67,895 | 32,756 | 148,099 |
| Events | 0 | 0 | 0 | 1 | 2 | 0 | 3 |
| **Third or subsequent IV iron treatment** | | | | | | | |
| Patients (treatments) | 1,420 (34,760)[a] | 11,597 (58,298) | 913 (3,217) | 11,771 (37,471) | 47,789 (348,945) | 32,144 (2,620,795) | 105,634 (3,103,486) |
| Events | 0 | 0 | 0 | 0 | 10 | 0 | 10 |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = *S*ystème National des Données de Santé (French National Health Insurance System database, previously named SNIIRAM).

[a] Numbers were rounded to the nearest 10 because of data-protection rules aimed at prevention of identification of individuals.

[b] Number of potential anaphylaxis events reported as ranges to comply with data-protection rules aimed at prevention of identification of individuals.

### Overall and IV Iron Groups: Iron Dextran and Iron Non-dextrans

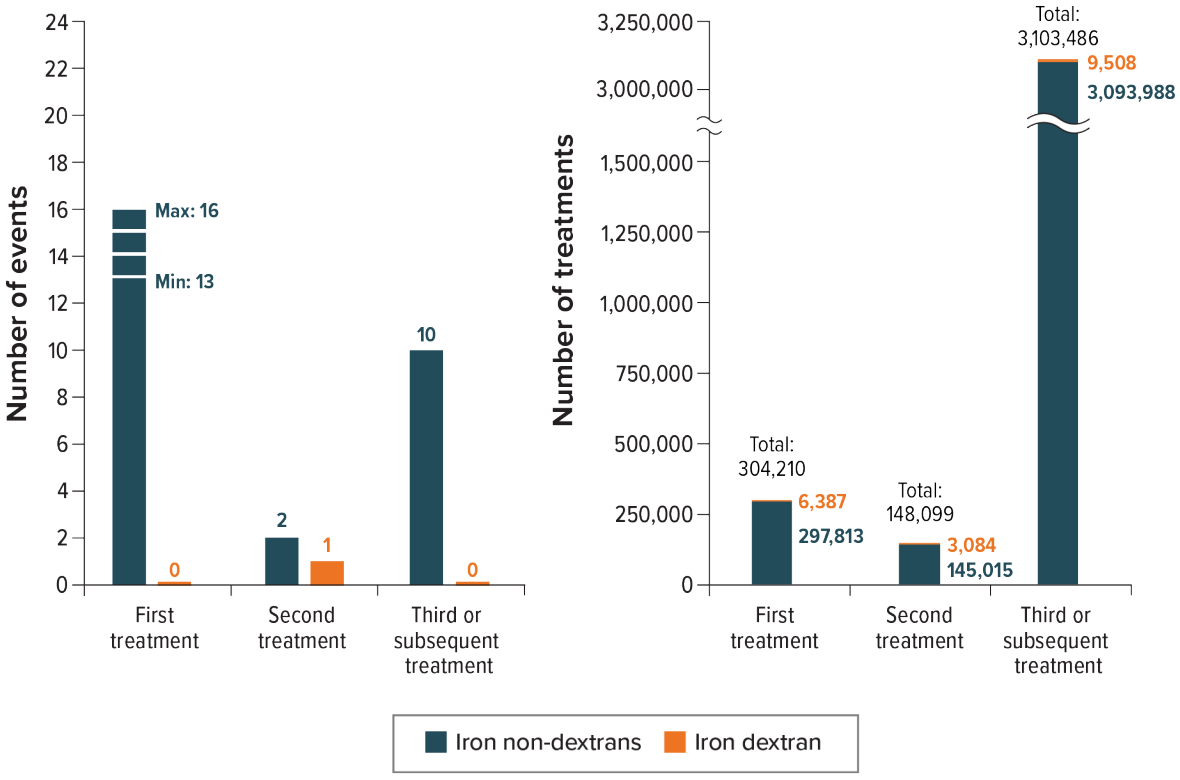
Figure 16 displays the pooled number of potential anaphylaxis events identified through the main case-identification algorithm, overall and by iron group (iron dextran and iron non-dextran) for first, second, and third or subsequent IV iron exposures across all data sources.

The number of potential anaphylaxis events among patients that had a first exposure to IV iron (N = 304,210 patients) ranged from 13 to 16 events across all data sources (numbers are reported as ranges to comply with Danish data-protection rules aimed at the prevention of identification of individuals). All events were identified in the iron non-dextran group.

Among patients with second IV iron exposures, there were three potential anaphylaxis events identified (N = 148,099 patients) across all data sources. One event was identified among the iron-dextran group and two events among the iron non-dextran group.

For third or subsequent IV iron treatments, 10 potential events were identified from a total of 3,103,486 treatments. All events were found among the iron non-dextran group. It is worth noting that in the KfH QiN dialysis registry in Germany contributing 84.4% of all third or subsequent treatments, no events were identified.

**Figure 16. Number of Potential Anaphylaxis Events and Treatments by Iron Dextran and Iron Non-dextran: First, Second, and Third or Subsequent IV Iron Treatments (Main Algorithm)**




IV = intravenous.

### By IV Iron Individual Type

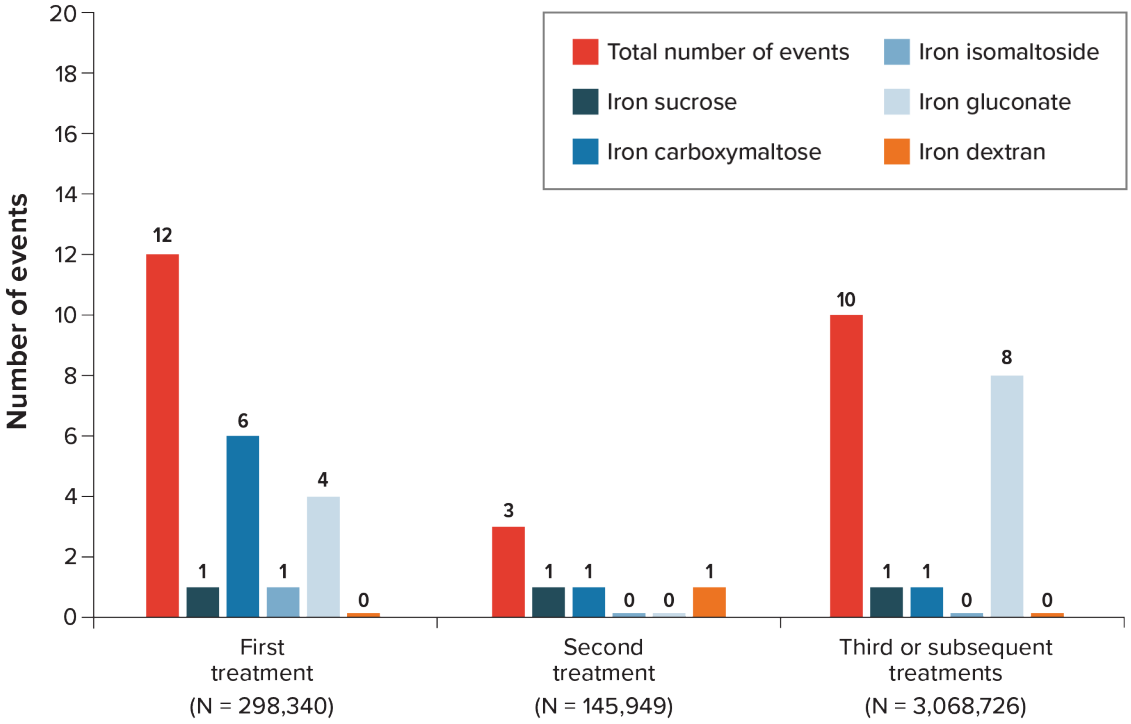
Figure 17 displays the number of potential anaphylaxis events, overall and by IV iron type in relation to IV iron at first, second, and third or subsequent exposures across all data sources but not including the Central Denmark Region. Data by individual IV iron types were not available from Denmark because of the low cell-count limits and data-protection rules aimed at prevention of identification of individuals. Therefore, the denominators and number of events by IV iron type shown here are different from those by IV iron group (iron dextran and iron non-dextran) for the first, second, and third or subsequent exposures.

Among patients with a first exposure (N = 298,340 patients), 12 potential anaphylaxis events were identified after excluding the Health Services Database of the Central Denmark Region; 6 following exposure to iron carboxymaltose, 4 for iron gluconate, and one each among those exposed to iron sucrose and to iron isomaltoside.

Among patients with a second exposure (N = 145,949), three potential events were identified: one following exposure to iron carboxymaltose, one among the iron sucrose type, and one among iron dextran.

Among the third or subsequent IV iron treatments (N = 3,068,726), 10 potential events were identified: one following exposure to iron carboxymaltose, 8 for iron gluconate, and one following exposure to iron sucrose.

**Figure 17. Number of Potential Anaphylaxis Events by IV Iron Type: First, Second, and Third or Subsequent IV Iron Treatments (Main Algorithm)**




IV = intravenous.

Note: Number of events and denominators do not match the numbers by IV iron group (iron dextran and iron non-dextran) because Danish data by individual IV iron type were not included because of Danish data-protection reporting restrictions aimed at protection of identification of individuals.

#### 10.3.1.2 IV Penicillins

In the main analysis (cases identified through the main case-identification algorithm within the "same day" or "same day and day after" IV penicillins treatment), 30 potential anaphylaxis events were identified among patients who had a first IV penicillins treatment (N = 231,294 patients) across the four data sources contributing data to the IV penicillins cohort. There were 44 potential anaphylaxis events from all 984,000 penicillins treatments (see Table 7).

**Table 7. IV Penicillins Treatment and Number of Potential Anaphylaxis Events: Overall and Data Source-specific Results**

| IV Penicillins Treatment (n) | Central Denmark Region | SNDS, France | PHARMO-NL | GePaRD, Germany | Overall |
|---|---|---|---|---|---|
| Number of **first** IV penicillins treatments | 116,980[a] | 57,200 | 39,002 | 18,112 | 231,294 |
| Events | 20[a] | 1 | 3 | 6 | 30 |
| Number of **any** IV penicillins treatments | 736,070[a] | 78,292 | 114,639 | 54,999 | 984,000 |
| Events | 30[a] | 2 | 4 | 8 | 44 |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; KfH QiN = Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme; PHARMO-NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National Health Insurance System database, previously named SNIIRAM).

[a] Numbers were rounded up to the nearest 10 because of data-protection rules aimed at prevention of identification of individuals.

Note: Data on IV penicillins use are not available in Sweden and the KfH QiN registry in Germany.

### *10.3.2 Expanded Algorithm (Sensitivity Analyses)*

#### 10.3.2.1 IV Iron

The expanded case-identification algorithm (see Section 9.4.1.1) identified nine additional potential anaphylaxis events following an IV iron exposure.

**Overall and by IV Iron Group: Iron Dextran and Iron Non-dextrans**

Figure 18 displays the pooled number of potential anaphylaxis events identified through the expanded case-identification algorithm, overall and by iron group (iron dextran and iron non-dextran) for first, second, and third or subsequent IV iron exposures across all data sources.

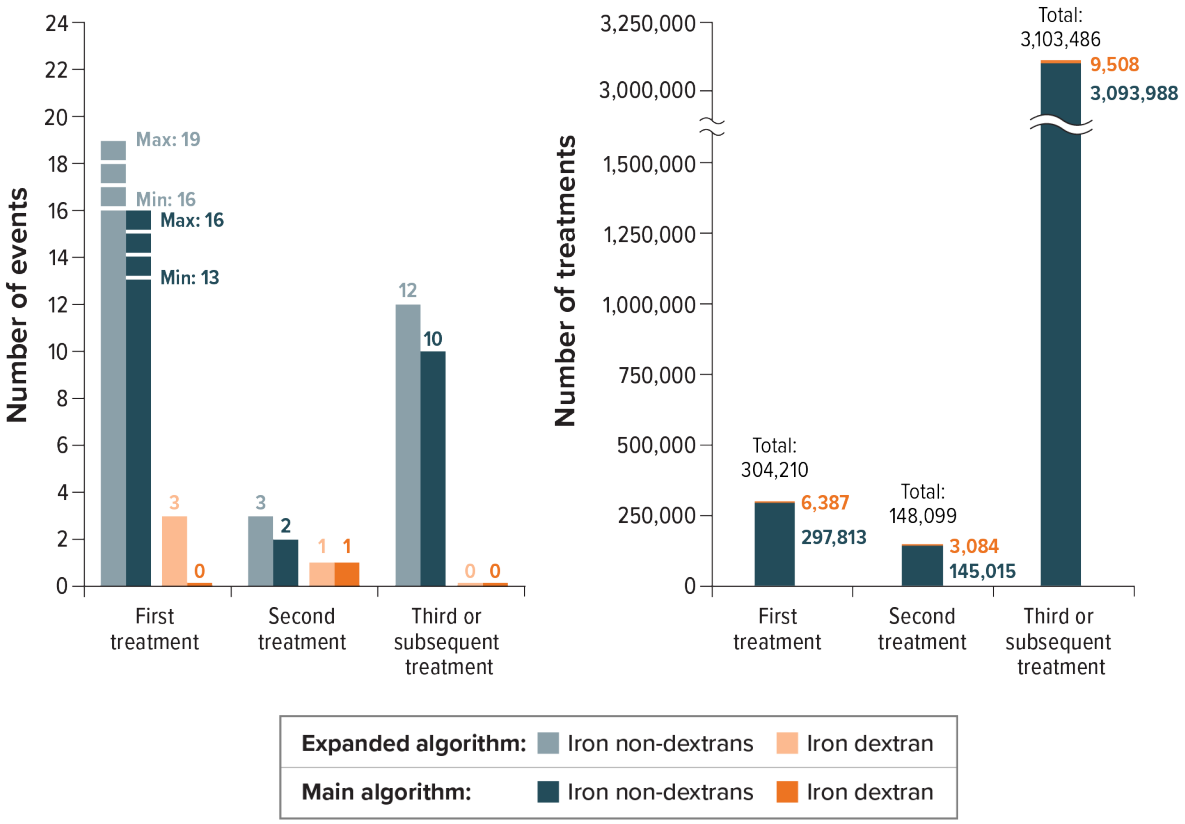
Among patients with a first exposure to IV iron (N = 304,210 patients), six additional potential events were identified through the expanded case-identification algorithm (three for iron dextran and three for iron non-dextrans) for a total number of potential anaphylaxis events ranging from 19 to 22 events across all data sources (numbers are reported as ranges to comply with Danish data-protection rules aimed at prevention of

identification of individuals). Three events were identified in the iron-dextran group and between 16 and 19 events among the iron non-dextran group.

Among patients with second IV iron exposures (148,099 patients), one additional potential event was identified among iron non-dextran users for a total of four potential anaphylaxis events (one event among the iron-dextran group and three events among the iron non-dextran group).

For third or subsequent IV iron treatments, two additional potential anaphylaxis events were identified from 3,103,486 treatments for 12 potential events. All events were found among the iron non-dextran group. As previously highlighted, in the KfH QiN dialysis registry in Germany contributing 84.4% of all third or subsequent treatments, no events were identified

**Figure 18. Number of Potential Anaphylaxis Events and Number of Treatments by Iron Dextran and Iron Non-dextran: First, Second, and Third or Subsequent IV Iron Treatments (Expanded Algorithm Compared With Main Algorithm)**




IV = intravenous.

### By IV Iron Individual Type

Figure 19 shows the results by IV iron type in relation to exposure to IV iron at first, second, and third or subsequent exposure. As previously highlighted, because of the Danish data-protection rules aimed at prevention of identification of individuals, Danish data by individual iron types could not be reported. Therefore, the denominators and

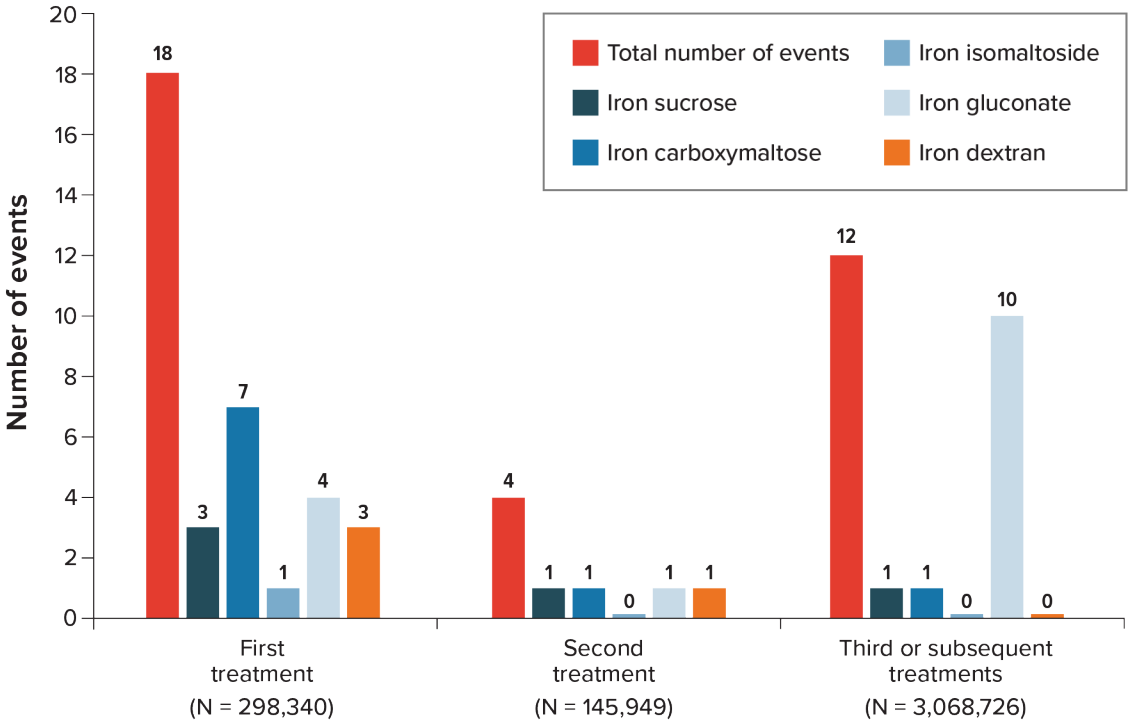
potential anaphylaxis events for the individual IV iron types in this section do not include the Danish data.

Overall, 34 potential events were identified for all ordinal IV iron exposures across all IV iron types. Among patients with a first exposure (N = 298,340 patients), 18 potential anaphylaxis events were identified through the expanded algorithm; seven following exposure to iron carboxymaltose, four for iron gluconate, three among those exposed to iron sucrose, one among an iron isomaltoside-exposed patient, and three among patients exposed to iron dextran.

Among patients with a second exposure (N = 145,949), four potential anaphylaxis events were identified: one patient each following exposure to iron carboxymaltose, iron gluconate, iron sucrose, and iron dextran.

Among the third and subsequent IV iron treatments (N = 3,068,726), 12 potential anaphylaxis events were identified: 1 following exposure to iron carboxymaltose, 10 to iron gluconate, and 1 following exposure to iron sucrose.

**Figure 19. Number of Potential Anaphylaxis Events by IV Iron Type: First, Second, and Third or Subsequent IV Iron Treatments (Expanded Algorithm)**




IV = intravenous

Note: Number of events and denominators do not match the numbers by IV iron group (iron dextran and iron non-dextran) because of Danish data-protection reporting restrictions aimed at prevention of identification of individuals.

For comparison purposes refer to number of events from the main analysis reported in Figure 17.

### 10.3.2.2 IV Penicillins

The expanded algorithm identified 259 potential anaphylaxis events among patients that had a first IV penicillins treatment (N = 231,294 patients) across the four data sources

contributing data to the IV penicillins cohort. Overall, there were 471 potential anaphylaxis events from a total of 984,000 penicillins treatments.

### *10.3.3 Seven-day Risk Window (Sensitivity Analyses)*

#### 10.3.3.1 IV Iron Cohort

**Overall and by IV Iron Group: Iron Dextran and Iron Non-dextrans**

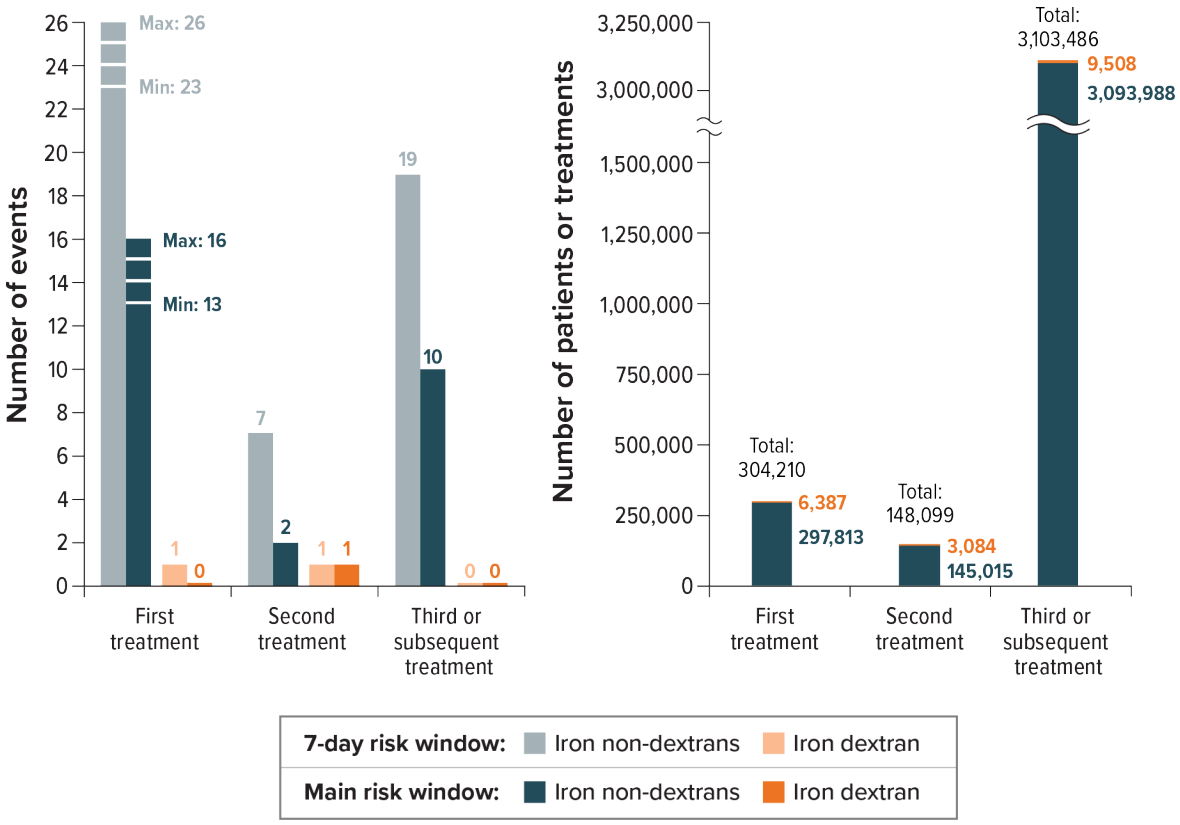
The overall number of potential anaphylaxis events identified through the main case-identification algorithm and the 7-days risk window in relation to exposure to IV iron at first, second, and third or subsequent exposure by iron-dextran group across all data sources are presented in Figure 20.

Among patients with a first exposure to IV iron (N = 304,210 patients), 11 additional potential anaphylactic events were identified through the 7-days risk window for a total number of potential events ranging from 24 to 27 events across all data sources (numbers are reported as ranges to comply with Danish data-protection rules). One event was identified among the iron-dextran group and between 23 and 26 potential events among the iron non-dextran group.

Among patients with second IV iron exposures, five additional potential events were identified for a total of eight potential anaphylaxis events identified among 148,099 patients across data sources. One event was identified among the iron-dextran group and seven events among the iron non-dextran group.

For third or subsequent IV iron treatments, 9 additional potential anaphylaxis events were identified from a total of 3,103,486 treatments for 19 potential events. All events were found among the iron non-dextran group. As previously highlighted, in the KfH QiN dialysis registry in Germany contributing 84.4% of all third or subsequent treatments, no events were sought beyond day 0 as both administration date and event date were available.

**Figure 20. Number of Potential Anaphylaxis Events and Treatments by Iron Dextran and Iron Non-dextran: First, Second, and Third or Subsequent IV Iron Treatments, Main Algorithm in 7-days Risk Window and Main Algorithm in Main Risk Window**




IV = intravenous.

### By IV Iron Individual Type

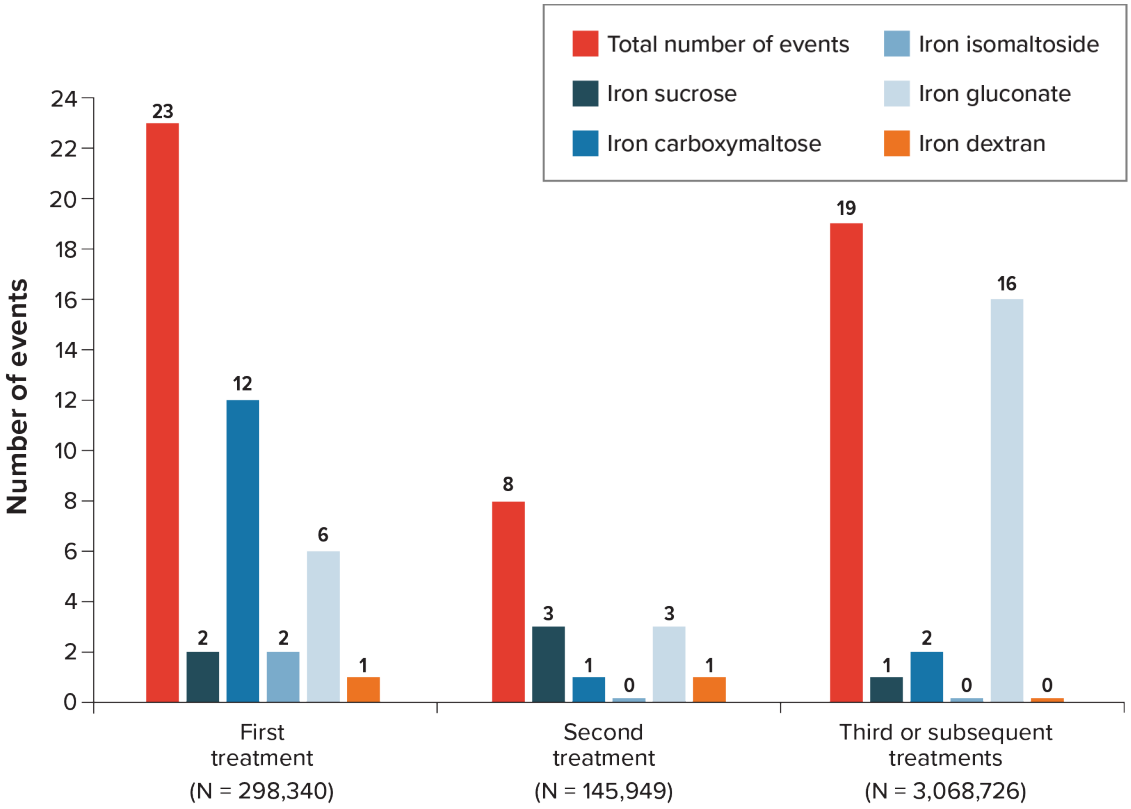
Results are shown overall and by IV iron type in relation to exposure to IV iron at first, second, and third or subsequent exposures (Figure 21). As previously highlighted, because of the Danish data-protection rules, no data by individual iron types were available from the Central Denmark Region data. Therefore, the denominators and potential anaphylaxis events for the individual IV iron types reflect numbers from all data sources except the Health Services Database of the Central Denmark Region.

Overall, 50 potential events were identified in all IV iron exposures across all IV iron types. Among patients with a first exposure (N = 298,340 patients), 23 potential anaphylaxis events were identified through the 7-days risk window across all data sources (not including Danish data); 12 following exposure to iron carboxymaltose, 6 to iron gluconate, 2 to iron sucrose, 2 to iron isomaltoside, and 1 to iron dextran.

Among patients with a second exposure (N = 145,949), eight potential anaphylaxis events were identified: one event following exposure to iron carboxymaltose, three following iron gluconate, three among the iron sucrose type, and one in the iron dextran type.

Among the third or subsequent IV iron treatments (N = 3,068,726), 19 potential anaphylaxis events were identified: 2 following exposure to iron carboxymaltose, 16 among the iron gluconate type, and 1 following exposure to iron sucrose.

**Figure 21. Number of Potential Anaphylaxis Events by IV Iron Type: First, Second, and Third or Subsequent IV Iron Treatments (7-days Risk Window)**




IV = intravenous.

Note: Number of events and denominators do not match the numbers by IV iron group (iron dextran and iron non-dextrans) because of Danish data-protection reporting restrictions aimed at prevention of identification of individuals.

For comparison purposes refer to number of events from the main analysis reported in Figure 17.

### *10.3.4 Outcome Validation*

#### 10.3.4.1 Direct Validation

**Health Services Database of the Central Denmark Region**

All potential anaphylaxis cases identified in the Central Denmark Region among IV iron-treated patients were considered for validation (N = 1-4, data-protection range). For the IV penicillins cohort, a sample of potential cases identified through the main algorithm was selected for validation.

Case validation was performed through review of medical records of potential cases in the hospital departments that granted permission to access patient records.

A total of 42 potential anaphylaxis events were targeted for validation:

- Between 1 and 4 in the IV iron cohort, identified through the main and expanded algorithms (range owing to data-protection rules aimed at preventing identification of individual patients)
- The remainder in the IV penicillin cohort, identified through the main algorithm.

Access was obtained for all 42 medical records and all underwent clinical adjudication. The PPV (95% CI) for the case-identification algorithms used to identify potential events among IV iron users is presented combined with the potential events identified among IV penicillin users because of the data-protection rules. Accordingly, the number of potential cases excluded because of insufficient information cannot be reported.

Table 8 reports an estimated PPV (95% CI) for the IV iron and IV penicillin potential cases combined of 70% (50%-86%). This PPV was calculated based on the potential cases identified through the main and expanded algorithms for the IV iron cohort and from the main algorithm for the IV penicillin cohort, while excluding potential cases with insufficient information.

When potential cases among IV penicillin users were analysed separately, the estimated PPV of the main case-identification algorithm ranged from 43%, when all potential cases for which there was insufficient information to establish case status were classified as non-cases, to 81%, when all potential cases with insufficient information were classified as cases.

The PPV for IV penicillin users excluding potential cases with insufficient information cannot be provided because of data-protection rules to prevent the back calculation of cells with less than five cases.

## Table 8. Positive Predictive Value for IV Iron and IV Penicillin (Denmark)

| | Positive Predictive Value % (95% CI) |
|---|---|
| **IV iron (main and expanded algorithm) plus IV penicillin (main algorithm)** | |
| Excluding potential cases with insufficient information | 70 (50-86) |
| **IV penicillin (main algorithm only)** | |
| Potential cases with insufficient information classified as non-cases | 43 (27-61) |
| Potential cases with insufficient information classified as cases | 81 (65-92) |

CI = confidence interval; IV = intravenous; PPV = positive predictive value.

### PHARMO Database Network

All potential events of anaphylaxis (N = 26) identified through the main and expanded algorithms among IV iron users (N = 6) and IV penicillins users (N = 20) were targeted for validation. There were no additional potential events identified through the 7-days risk window analysis.

Out of 10 hospitals where the potential anaphylaxis events were identified, 4 hospitals did not find the patients in their systems (N = 11 potential events) and 2 additional hospitals (N = 2 potential events) did not grant approval.

- The main difficulty for not finding the patient records in the hospital systems was because the hospitals switched to a different system several years previously. Not all information was transferred into the new system because this was no longer required (i.e., retention of information was expired) or patients had passed away.
- The main reason for not granting approval for access to the medical records were concerns around recent changes in patient data-protection rules (GDPR).

Four hospitals granted approval for access to the medical records of 13 potential events. The records of 13 potential events were abstracted for case adjudication (3 were captured through the main algorithm and 10 additional cases identified through the expanded algorithm). The case adjudication resulted in 9 non-cases, 3 non-evaluable cases, and 1 confirmed case.

Table 9 presents the number of potential anaphylaxis events and confirmed cases for the main algorithm and for the expanded algorithm for IV iron dextran, IV iron non-dextran, and IV penicillin treatments.

**Table 9. Positive Predictive Value by IV Iron Group and IV Penicillin: Main and Expanded Algorithm (PHARMO-NL)**

| | Main Algorithm | | | | Expanded Algorithm | | | |
|---|---|---|---|---|---|---|---|---|
| | **Potential Events (N)** | **Records Obtained (N)** | **Patients Evaluable (N)** | **Confirmed Cases (N)** | **Potential Events (N)** | **Records Obtained (N)** | **Patients Evaluable (N)** | **Confirmed Cases (N)** |
| **IV iron** | | | | | | | | |
| IV iron dextran | 0 | NA | NA | NA | 3 | 0 | NA | NA |
| IV iron non-dextrans | 0 | NA | NA | NA | 3 | 0 | NA | NA |
| IV iron (any) | 0 | NA | NA | NA | 6 | 0 | NA | NA |
| PPV (95% CI) | | | | NE | | | | NE |
| **IV penicillin** | | | | | | | | |
| IV penicillin (any) | 4 | 3 | 1 | 1 | 20 | 13 | 10 | 1 |
| PPV (%) (95% CI) | | | | 100 (2.50-100) | | | | 10 (0.25-44.5) |

CI = confidence interval; IV = intravenous; NA = not applicable; NE = not estimable; PHARMO-NL = PHARMO Database Network in the Netherlands; PPV = positive predictive value.

For the IV iron cohort, as no potential cases were identified through the main algorithm and no medical records were obtained for potential cases identified through the expanded algorithm, the IV iron-specific PPV could not be calculated. For the IV penicillin cohort the PPV of the main case-identification algorithm, based on one confirmed case, was 100.0% (95% CI, 25.0-100.0) and the PPV for the expanded algorithm was 10.0% (95% CI, 2.5-44.5).

The adjusted IPs by the PPVs are not presented due to the small number of evaluable patients identified through the main algorithm.

#### 10.3.4.2 Indirect Validation

**Validation of GePaRD, Germany, Case-Identification Algorithm Through Oldenburg Hospital**

The anaphylaxis algorithm searched the Hospital Information System data for potential anaphylaxis events recorded as admission diagnoses and primary and secondary discharge diagnoses. On the basis of 78 patients with potential anaphylaxis events identified through the algorithm Criterion A (inpatient-specific ICD codes for anaphylaxis) and 43 confirmed events, the estimated PPV was 62.3% (95% CI, 49.8%-73.7%) based on all codes in Criterion A. When non-evaluable patients with an anaphylaxis diagnosis were considered as confirmed events the PPV was 68.1% (95% CI, 55.8%-78.8%).

One potential anaphylaxis event was identified though Criterion C (inpatient ICD codes of unspecific hypersensitivity reactions) which was not confirmed by validation. For the Criterion B of the algorithm no potential events were identified in this hospital-based setting.

#### 10.3.4.3 Other Validation Activities

**KfH QiN, Germany, Medical Record Review**

In KfH QiN no events of anaphylaxis were identified during the main analysis risk window ("same day" of IV iron administration). However, there were 5 patients who had a code for angioneurotic oedema during the risk window but lacked other necessary criteria to be considered study events. The medical records of these 5 patients were accessed and their non-case status was further confirmed either by recorded evidence of continued use of IV iron after the angioneurotic event (n = 4) or by explicit confirmation by the treating doctor in 1 patient who died after the angioneurotic event.

## 10.4 Main Results

**The results presented in this section are based on the beta-binomial regression analyses since these are more appropriate for studies involving very low number of events (see Methods Section 9.9.2.2). In the tables of results in Annex 4, results based on the traditional meta-analysis approach are also presented.**

### *10.4.1 IV Iron*

Complete overall and data source-specific results for IV iron can be found by IV iron group in Tables 1.1 to 1.3 and by IV iron types in Tables 2.1a to 2.3c in Annex 4_Final Results 20Feb2020. In Annex 4 and throughout the following sections in this report, estimates are presented rounded to three digits i.e., rounding estimates to the nearest decimal place, the nearest unit, or the nearest 10. Values less than 999 are reported to three digits on the indicated scale; values greater than 999 are reported to three informative digits.

Table 10 shows, by ordinal number of IV iron treatment (i.e., first, second, and third or subsequent), the IPs (95% CI) of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and non-dextrans separately.

The resulting RRs and RDs (iron dextran vs. iron non-dextrans), with the corresponding 95% CIs are also displayed.

Table 10 displays results from the main analyses (i.e., main case-identification algorithm applied during the exposure risk window defined by “same day” or “same day and day after” after IV iron treatment).

**Table 10. Risk of Anaphylaxis After Treatment With IV Iron, Overall, by IV Iron Dextran and Iron Non-dextran Groups and Incidence by IV Iron Types. Main Analysis**

| | First Treatments | Second Treatments | Third and Subsequent Treatments |
|---|---|---|---|
| **Overall IV iron** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16* | 3 | 10 |
| Patients (n)** | 304,210 | 148,099 | 3,103,486 |
| IP (95% CI)* | Min, 0.38 (0.17-0.88); max, 0.51 (0.28-0.97) | 0.25 (0.07-0.94) | 0.02 (0.00-0.13) |
| **Iron dextran** | | | |
| Anaphylaxis events (n) | 0 | 1 | 0 |
| Patients (n)** | 6,387 | 3,084 | 9,508 |
| IP (95% CI) | 0 (0-> 9,995) | 3.33 (0.48-23.3) | 0 (0-> 9,995) |
| **Iron non-dextran** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16 | 2 | 10 |
| Patients (n)** | 297,813 | 145,015 | 3,093,988 |
| IP (95% CI) | Min, 0.44 (0.16-1.24); max, 0.55 (0.23-1.34) | 0.25 (0.06-1.06) | 0.03 (0.00-0.19) |
| RR (95% CI)*** | Min, 0 (0.00-> 9,995); max, 0 (0.00-> 9,995) | 13.1 (1.26-146) | 0 (0-> 9,995) |

| | First Treatments | Second Treatments | Third and Subsequent Treatments |
|---|---|---|---|
| RD (95% CI)*** | Min, −0.44 (−1.02 to > 9,995); max, −0.55, (−1.14 to > 9,995) | 3.08 (0.12-23.1) | -0.03 (−0.13-> 9,995) |
| **Iron types** | | | |
| *Iron sucrose* | | | |
| Anaphylaxis events (n) | 1 | 1 | 1 |
| Patients (n) | 36,306 | 19,669 | 56,840 |
| IP (95% CI) | 0.43 (0.06-3.10) | 0.59 (0.08-4.25) | 0.21 (0.03-1.50) |
| *Iron carboxymaltose* | | | |
| Anaphylaxis events (n) | 6 | 1 | 1 |
| Patients (n) | 146,674 | 55,684 | 672,948 |
| IP (95% CI) | 0.45 (0.12-1.69) | 0.22 (0.03-1.62) | 0.05 (0.01-0.33) |
| *Iron gluconate* | | | |
| Anaphylaxis events (n) | 4 | 0 | 8 |
| Patients (n) | 106,668 | 66,985 | 2,328,938 |
| IP (95% CI) | 0.46 (0.08-2.79) | 0 (0-NE) | 0.05 (0.01-0.34) |
| *Iron isomaltoside* | | | |
| Anaphylaxis events (n) | 1 | 0 | 0 |
| Patients (n) | 2,325 | 537 | 512 |
| IP (95% CI) | 4.44 (0.62-31.5) | 0 (0-NE) | 0 (0-> 9,995) |
| *Iron dextran* | | | |
| Anaphylaxis events (n) | 0 | 1 | 0 |
| Patients (n) | 6,367 | 3,074 | 9,488 |
| IP (95% CI) | 0 (0-> 9,995) | 3.31 (0.48-23.7) | 0 (0-> 9,995) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; NE = not estimable; RR = risk ratio; RD = risk difference.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed because of data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

#### 10.4.1.1 Overall IV Iron

**First Dispensing or Administration**

Overall, between 13 and 16 potential anaphylaxis events were identified in all data sources after a first treatment with IV iron which translated into an IP of anaphylaxis ranging between 0.38 and 0.51 per 10,000 first IV iron treatments (reported as range

because of Danish data-protection reporting restrictions that do not allow reporting counts between 1 and 4) (see Table 10).

**Second Dispensing or Administration**

Overall, three potential anaphylaxis events were identified in all data sources after a second treatment with IV iron, which translated into an IP of anaphylaxis of 0.25 per 10,000 second IV iron treatments (see Table 10).

**Third or Subsequent Dispensing or Administration**

Overall, 10 potential anaphylaxis events were identified in all data sources after a third or subsequent treatment with IV iron, which translated into an IP of anaphylaxis of 0.02 per 10,000 third or subsequent IV iron treatments (see Table 10).

#### 10.4.1.2 IV Iron Groups: Iron Dextran and Iron Non-dextran

**First Dispensing or Administration**

No potential anaphylaxis events were identified among first treatments with iron dextran and, consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The RD of anaphylaxis between iron dextran and non-dextrans ranged from −0.44 to −0.55 per 10,000 treatments, favouring the iron dextran. See Table 10.

**Second Dispensing or Administration**

Of the three potential anaphylaxis events identified in all data sources after a second treatment with IV iron, one was identified among iron dextran and two among iron non-dextrans. The estimated RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was 13.1 and the corresponding RD was 3.08 per 10,000 treatments, favouring the iron non-dextran group. See Table 10.

**Third or Subsequent Dispensing or Administration**

Ten potential anaphylaxis events were identified in the iron non-dextran group and no cases were identified among iron dextran. Consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The corresponding RD was −0.03 per 10,000 treatments, favouring the iron dextran. See Table 10.

#### 10.4.1.3 IV Iron Types

The main results for the individual types of IV iron are described in this section and the corresponding complete tabulated results can be found in Tab 2.1, Tab 2.2, and Tab 2.3 of the excel file Annex 3_Main Results 18Dec2919. Overall, results for individual types of IV iron are based on very small numbers.

**First Dispensing or Administration**

At first treatment, the IP of anaphylaxis ranged from 0.43 per 10,000 treatments for iron sucrose (based on one potential event of anaphylaxis) to 4.44 per 10,000 treatments for iron isomaltoside (based on one event of anaphylaxis). No events were identified for first

treatments with iron dextran. The RR and RD of anaphylaxis using iron sucrose as the common reference was highest for iron isomaltoside (RR, 10.3; 95% CI, 0.62-158; RD, 4.01; 95% CI, −0.67 to 30.6, favouring iron sucrose).

#### Second Dispensing or Administration

At second treatment, IPs ranged from 0.22 per 10,000 second treatments of iron carboxymaltose (based on one event of anaphylaxis) to 3.31 per 10,000 second treatments of iron dextran (based on one event of anaphylaxis). No events were identified for iron isomaltoside or iron gluconate second treatments. The RR and RD of anaphylaxis using iron sucrose as the common reference was highest for iron dextran (RR, 5.60; 95% CI, 0.35-86.6; RD, 2.72; 95% CI, −1.84 to 22.8, favouring iron sucrose).

#### Third or Subsequent Dispensing or Administration

At third or subsequent treatments, IPs ranged from 0.05 per 10,000 third or subsequent treatments of iron carboxymaltose and iron gluconate, respectively to 0.21 per 10,000 third treatments of iron sucrose (based on one event of anaphylaxis for iron carboxymaltose, eight events of anaphylaxis for iron gluconate and one event of anaphylaxis for iron sucrose). No events were identified for iron dextran and iron isomaltoside. The RR of anaphylaxis using iron sucrose as the common reference was highest for iron gluconate (RR, 0.24; 95% CI, 0.02-3.54) whereas the RD of anaphylaxis using iron sucrose as the common reference were highest for iron dextran (RD, −0.21; 95% CI, −1.08 to > 9,995) and iron isomaltose (RD, −0.21; 95% CI, −1.11 to > 9,995), favouring iron dextran and iron isomaltose respectively.

### *10.4.2 IV Penicillins*

Table 11 shows the risk of anaphylaxis among users of IV penicillins at first treatment and at any treatment, based on the data sources that contributed data to the IV penicillins cohort (i.e., Health Services Database of the Central Denmark Region, PHARMO-NL and the GePaRD in Germany). Complete results for IV penicillins can be found in Tables 1.1 and 1.4 in Annex 4_Final Results 20Feb2020.

At first treatment with IV penicillins, the IP of anaphylaxis, based on 30 potential events, was 1.16 per 10,000 first treatments, whereas at any treatment, the IP was 0.45 per 10,000 treatments.

**Table 11. Risk of Anaphylaxis at First Treatment and at any Treatment With IV Penicillins. Main Analysis**

| | First Treatment With IV Penicillins | Any Treatment With IV Penicillins |
|---|---|---|
| **Any IV penicillins** | | |
| Anaphylaxis events (n) | 30 | 44 |
| Treatments (n) | 231,294* | 984,000* |
| IP (95% CI) | 1.16 (0.78-1.73) | 0.45 (0.32-0.63) |

CI = confidence interval; IP = incidence proportion; IV = intravenous.

* Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

## 10.5 Other Analyses

**All sensitivity analyses were conducted using the main case-identification algorithm (see Figure 7) and the risk window defined as "same day" or "same day and day after" IV iron exposure as described in the methods Section 9.3.2 and Figure 5. Exceptions were the analyses that used the expanded case-identification algorithm and the expanded 7-day exposure risk window. For the IV penicillin exposure, sensitivity analyses focused on the expanded case-identification algorithm, the modified exposure windows, and the penicillin subtypes.**

This section presents the results of all sensitivity analyses listed in the methods Section 9.9.4. The estimated IPs per 10,000 IV iron treatments, RRs (iron dextran vs. iron non-dextrans) and RDs per 10,000 (iron dextran minus iron non-dextrans), and the corresponding 95% CIs described in this section were calculated using beta-binomial regression meta-analysis (see Section 9.9.2.2) to account for between-site variability because of the very low number of events.

For some analyses, the estimated IPs, RRs, and RDs by iron type using iron sucrose as the common reference for the individual comparisons are also presented. The analyses by IV iron type did not include data from the Health Services Database of the Central Denmark Region because of data-protection rules, aimed at prevention of identification of individuals.

Annex 4 displays the detailed results for the sensitivity analyses by order of IV iron treatments and by IV iron groups and types, including the data source-specific data as follows: Tables 3.1, 3.2, 3.3, 3.4, and 4.1, 4.2, 4.3, 4.4 (expanded algorithm by IV iron groups and types, respectively); Table 5 (penicillin subtype); Tables 6.1, 6.2, 6.3, 6.4, and 7.1, 7.2, 7.3, 7.4 (7-days risk window analysis by IV iron groups and types, respectively); Table 8 (dialysis patients only by IV iron groups), Tables 9.1, 9.2, 9.3, 9.4, and 10.1, 10.2, 10.3, 10.4 (excluding dialysis patients by IV iron groups and types, respectively), Tables 11.1, 11.2, 11.3, 11.4, and 12.1, 12.2, 12.3, 12.4 (excluding sites with zero events by IV iron groups and types, respectively), Tables 13.1 and 13.2 (any IV iron before and after 2013, respectively), and Tables 14.1, 14.2, and 15.1, 15.2 (IV iron after first switch and any switch, by IV iron groups and types, respectively). The data source and overall results for IV penicillin exposure are included in Tables 3.1 and 3.4 (expanded algorithm for first and any IV penicillin exposure) and Table 6.4 for the 7-days risk window for any IV penicillin exposure.

### *10.5.1 Expanded Case-Identification Algorithm*

#### 10.5.1.1 Overall IV Iron, IV Iron Groups, and IV Iron Types

Table 12 shows, by ordinal number of IV iron treatment (i.e., first, second, and third or subsequent), the IPs of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and non-dextrans separately using the expanded case-identification algorithm applied during the exposure risk window defined by "same day" or "same day and day after" IV iron dispensing/administration).

**Table 12. Risk of Anaphylaxis After Treatment with IV Iron, Overall and by IV Iron Dextran and Iron Non-dextran Groups. Expanded Case-Identification Algorithm**

| | First Treatments | Second Treatments | Third or Subsequent Treatments |
|---|---|---|---|
| **Overall IV irons** | | | |
| Anaphylaxis events (n) | Min, 19; max, 22* | 4 | 12 |
| Treatments (n)** | 304,210 | 148,099 | 3,103,486 |
| IP (95% CI)* | Min, 0.63 (0.38-1.05); max, 2.81 (0.60-13.8) | 0.30 (0.08-1.09) | 0.03 (0.01-0.14) |
| **IV iron dextran** | | | |
| Anaphylaxis events (n) | 3 | 1 | 0 |
| Treatments (n)** | 6,387 | 3,084 | 9,508 |
| IP (95% CI) | Min, 4.59 (1.43-14.8); max, 4.62 (1.46-14.7) | 3.35 (0.48-23.4) | 0 (0-> 9,995) |
| **IV iron non-dextrans** | | | |
| Anaphylaxis events (n) | Min, 16; max, 19 | 3 | 12 |
| Treatments (n)** | 297,813 | 145,015 | 3,093,988 |
| IP (95% CI) | Min, 0.58 (0.28-1.22); max, 0.70 (0.38-1.31) | 0.32 (0.08-1.27) | 0.03 (0.00-0.20) |
| RR (95% CI)*** | Min, 7.95 (2.05-31.8); max, 6.61 (1.83-24.6) | 10.6 (1.03-115) | 0 (0-> 9,995) |
| RD (95% CI)*** | Min, 4.02 (0.77-14.3); max, 3.92 (0.68-14.0) | 3.03 (0.02-23.1) | -0.03 (−0.14 to > 9,995) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; RR = risk ratio; RD = risk difference.

Note: Because the IV iron non-dextrans have a different number of events in the minimum and maximum scenarios, the data going into these two models are different. Thus, all regression coefficients may be affected, and IP estimates for IV iron dextran can vary slightly between scenarios even in situations where the numerators and denominators are the same in both scenarios.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### First Dispensing or Administration

When the expanded case-identification algorithm was used, between 19 and 22 potential anaphylaxis events were identified (i.e., 6 additional events compared with the number from the main algorithm), for an IP ranging from 0.63 (95% CI, 0.38-1.05) to 2.81 (95% CI, 0.60-13.8) per 10,000 first iron treatments. Of these, 3 events occurred in iron dextran and between 16 and 19 in iron non-dextrans first treatments, for a resulting RR ranging from 7.95 (95% CI, 2.05-31.8) to 6.61 (95% CI, 1.83-24.6) and a resulting RD ranging from 4.02 (95% CI, 0.77-14.3) to 3.92 (95% CI, 0.68-14.0), per 10,000 first iron treatments favouring iron non-dextrans.

When assessing IV iron types, the RR of anaphylaxis using iron sucrose as the common reference after a first IV iron treatment was highest for iron dextran, based on three potential events (RR, 4.70; 95% CI, 0.83-26.1) and iron isomaltoside, based on one potential event (RR, 4.52; 95% CI, 0.44-45.8). The largest RD using iron sucrose as the common reference was observed for iron dextran (RD, 3.58; 95% CI, −0.38 to 14.3), and iron isomaltoside (RD, 3.40; 95% CI, −1.19 to 29.7), favouring iron sucrose in both cases.

### Second Dispensing or Administration

When the expanded case-identification algorithm was used, four potential anaphylaxis events were identified (i.e., one additional event compared with the number from the main algorithm) for an IP of 0.30 (95% CI, 0.08-1.09) per 10,000 second IV iron treatments. Of these, one event occurred in iron dextran and three in iron non-dextrans, for a resulting RR of 10.6 (95% CI, 1.03-115) and a corresponding RD of 3.03 (95% CI, 0.02-23.1) per 10,000 second IV iron treatments favouring iron non-dextrans. When assessing IV iron types, the RR and RD of anaphylaxis using iron sucrose as the common reference after a second treatment with IV iron was largest for iron dextran (RR, 6.32; 95% CI, 0.39-97.8; RD, 2.74; 95% CI, −1.45 to 22.5), favouring iron sucrose.

### Third or Subsequent Dispensing or Administration

When the expanded case-identification algorithm was used, 12 potential anaphylaxis events were identified (i.e., 2 additional events compared with the number from the main algorithm) for an IP of 0.03 (95% CI, 0.01-0.14) per 10,000 third or subsequent IV iron treatments. No potential anaphylaxis events were identified among third or subsequent treatments with iron dextran and, consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The corresponding RD was −0.03 (95% CI, −0.14 to > 9,995) per 10,000 treatments, favouring the iron dextran. When assessing IV iron types, the RR of anaphylaxis using iron sucrose as the common reference after a third or subsequent treatment with IV iron was highest for iron gluconate (RR, 0.27; 95% CI, 0.02-3.83), whereas the RD using iron sucrose as the common reference after a third or subsequent treatment with IV iron

was largest for iron dextran (RD, −0.21; 95% CI, −1.09 to > 9,995) and iron isomaltoside (RD, −0.21; 95% CI, −1.12 to > 9,995), per 10,000 third or subsequent treatments with IV iron, favouring iron dextran and iron isomaltoside, respectively.

#### 10.5.1.2 IV Penicillin, First and Any Exposure

When the expanded case-identification algorithm was used, 259 potential anaphylaxis events were identified (i.e., 229 additional events) among first IV penicillin treatments and 471 potential events were identified (i.e., 427 additional potential events) among first and subsequent IV penicillin treatments. Table 13 shows, the IPs of potential anaphylaxis events per 10,000 IV penicillin treatments, for first and any treatment using the expanded case-identification algorithm applied during the exposure risk window defined by “same day” or “same day and day after” IV penicillin dispensing/administration).

**Table 13. Risk of Anaphylaxis at First Treatment and at any Treatment With IV Penicillins. Expanded Algorithm**

| | First Treatment With IV Penicillins | Any Treatment With IV Penicillins |
|---|---|---|
| **Any IV penicillins** | | |
| Anaphylaxis events (n) | 259 | 471 |
| Treatments (n) | 231,294* | 984,000* |
| IP (95% CI) | 6.45 (4.98-8.42) | 3.38 (2.81-4.09) |

CI = confidence interval; IP = incidence proportion; IV = intravenous.

* Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

### *10.5.2 Seven-day Risk Window*

#### 10.5.2.1 Overall IV Iron, IV Iron Groups, and IV Iron Types

Table 14 shows, by ordinal number of IV iron treatment (i.e., first, second, and third or subsequent), the IPs of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and iron non-dextrans separately using the main case-identification algorithm applied during the expanded exposure risk window including up to 7 days after IV iron treatment) (see Section 9.9.4).

These analyses were performed in all data sources, however, KfH QiN, Germany, contributed data to the risk window expansion analysis based on administration data and events identified during the same day (day 0) risk window applicable to this data source.

The resulting RRs and RDs (iron dextran vs. iron non-dextrans), with the corresponding 95% CIs, are also displayed.

**Table 14. Risk of Anaphylaxis After Treatment With IV Iron, Overall and by IV Iron Dextran and Iron Non-dextran Groups. 7-days Risk Window**

| | First Treatments | Second Treatments | Third or Subsequent Treatments |
|---|---|---|---|
| **Overall IV irons** | | | |
| Anaphylaxis events (n) | Min, 24; max, 27* | 8 | 19 |
| Treatments (n)** | 304,210 | 148,099 | 3,103,486 |
| IP (95% CI)* | Min, 0.74 (0.43-1.29); max, 0.88 (0.56-1.39) | 0.46 (0.15-1.45) | 0.05 (0.02-0.15) |
| **IV iron dextran** | | | |
| Anaphylaxis events (n) | 1 | 1 | 0 |
| Treatments (n)** | 6,387 | 3,084 | 9,508 |
| IP (95% CI) | Min, 1.62 (0.23-11.3); max, 1.61 (0.23-11.2) | 3.39 (0.49-23.6) | 0 (0-> 9,995) |
| **IV iron non-dextrans** | | | |
| Anaphylaxis events (n) | Min, 23; max, 26 | 7 | 19 |
| Treatments (n)** | 297,813 | 145,015 | 3,093,988 |
| IP (95% CI) | Min, 0.77 (0.37-1.62); max, 0.93 (0.50-1.75) | 0.50 (0.14-1.86) | 0.06 (0.02-0.22) |
| RR (95% CI)*** | Min, 2.11 (0.27-17.0); max, 1.74 (0.23-13.4) | 6.76 (0.69-70.1) | 0 (0-> 9,995) |
| RD (95% CI)*** | Min, 0.85 (−0.80 to 10.6); max, 0.68 (−0.95 to 10.4) | 2.88 (−0.30 to 23.2) | −0.06(−0.17 to > 9,995) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; RR = risk ratio; RD = risk difference.

Note: Because the IV iron non-dextrans have a different number of events in the minimum and maximum scenarios, the data going into these two models are different. Thus, all regression coefficients may be affected, and IP estimates for IV iron dextran can vary slightly between scenarios even in situations where the numerators and denominators are the same in both scenarios.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at the prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at the prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### First Dispensing or Administration

When the main algorithm was used in conjunction with the 7-day risk window in all data sources except KfH QiN dialysis registry in Germany, where dates of IV iron administration and anaphylaxis diagnoses were captured, between 24 and 27 anaphylaxis events were identified (i.e., 11 additional events compared with the number from the main algorithm) for an IP ranging from 0.74 (95% CI, 0.43-1.29) to 0.88 (95% CI, 0.56-1.39) per 10,000 first iron treatments. Of these, 1 event occurred in iron

dextran and between 23 and 26 in iron non-dextrans first treatments, for a resulting RR ranging from 2.11 (95% CI, 0.27-17.0) to 1.74 (95% CI, 0.23-13.4) and a resulting RD ranging from 0.85 (95% CI, −0.80 to 10.6) to 0.68 (95% CI, −0.95 to 10.4), per 10,000 first iron treatments favouring iron non-dextrans. When assessing IV iron types, the RR and RD of anaphylaxis using iron sucrose as the common reference after a first treatment with IV iron were highest for iron isomaltoside (RR, 15.2; 95% CI, 1.63-133; RD, 8.18; 95% CI, 1.07-33.8, favouring iron sucrose).

**Second Dispensing or Administration**

In the 7-day risk window sensitivity analysis conducted using all data sources, except the KfH QiN dialysis registry in Germany, eight potential anaphylaxis events were identified (i.e., five additional events), for an IP of 0.46 (95% CI, 0.15-1.45) per 10,000 second IV iron treatments. Of these, one event occurred in iron dextran and seven in iron non-dextrans, for a resulting RR of 6.76 (95% CI, 0.69-70.1) and a corresponding RD of 2.88 (95% CI, −0.30 to 23.2) per 10,000 second IV iron treatments favouring IV iron non-dextrans. The RR and RD of anaphylaxis using IV iron sucrose as the common reference was highest for iron dextran (RR, 2.04; 95% CI, 0.20-19.7; RD, 1.67; 95% CI, −3.02 to 21.7), favouring iron sucrose.

**Third or Subsequent Dispensing or Administration**

In the 7-day risk window sensitivity analysis conducted using all data sources except the KfH QiN dialysis registry in Germany, 19 potential anaphylaxis events were identified (i.e., 9 additional events), for an IP of 0.05 (95% CI, 0.02-0.15) per 10,000 third or subsequent IV iron treatments. No potential events of anaphylaxis were identified among iron dextran and, consequently, the RR comparing the IP of anaphylaxis between iron dextran and non-dextrans was estimated to be 0. The corresponding RD was −0.06 (95% CI, −0.17 to > 9,995) per 10,000 treatments, favouring the iron dextran. The RR of anaphylaxis using iron sucrose as the common reference was highest for iron carboxymaltose (RR, 0.45; 95% CI, 0.04-4.99). The largest RD using iron sucrose as the common reference was seen for iron dextran (RD, −0.21; 95% CI, −1.09 to > 9,995) and iron isomaltoside (RD, −0.21; 95% CI, −1.12 to > 9,995), favouring iron dextran and iron isomaltoside, respectively.

#### 10.5.2.2 IV Penicillin, any Exposure

Table 15 shows the IPs of potential anaphylaxis events per 10,000 IV penicillin treatments, for any treatment using the main case-identification algorithm applied during the 7-days exposure risk window. This analysis was conducted in the data sources that contributed data to the IV penicillins cohort (i.e., Central Denmark Region, the SNDS in France, PHARMO-NL, and the GePaRD in Germany).

**Table 15. Risk of Anaphylaxis at First Treatment and at any Treatment With IV Penicillins. 7-days Risk Window**

| | Any Treatment With IV Penicillins |
|---|---|
| **Any IV penicillins** | |
| Anaphylaxis events (n) | 48 |
| Treatments (n) | 984,000* |
| IP (95% CI) | 0.53 (0.40-0.71) |

CI = confidence interval; IP = incidence proportion; IV = intravenous.

* Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

### *10.5.3 Before 1 January 2013 and After 31 December 2013*

Owing to the low number of events, this stratified analysis was conducted among users of IV iron irrespective of the number of exposures (i.e., first, second, and third or subsequent exposures confounded). Only GePaRD in Germany and the Swedish National Registers contributed events to this analysis. The Central Denmark Region did not contribute data to this analysis. Data from 2013 were not included.

This analysis was conducted using the main case-identification algorithm applied during the exposure risk window defined by “same day” or “same day and day after” IV iron treatment.

Table 16 shows, for both periods of interest, the IPs of potential anaphylaxis events per 10,000 IV iron treatments, overall for all IV irons and for iron dextran and non-dextrans, separately. The resulting RRs and RDs (iron dextran vs. iron non-dextrans), with the corresponding 95% CIs, are also displayed.

**Table 16. Risk of Anaphylaxis at any Treatment With IV Irons, Before and After 2013. Main Analysis**

| | Before 2013 | After 2013 |
|---|---|---|
| **Any IV iron** | | |
| Anaphylaxis events (n) | 12 | 10 |
| Treatments (n)* | 1,775,379 | 1,331,988 |
| IP (95% CI) | 0.06 (0.03-0.17) | 0.09 (0.04-0.24) |
| **IV iron dextran** | | |
| Anaphylaxis events (n) | 0 | 1 |
| Treatments (n)* | 14,908 | 2,753 |
| IP (95% CI) | 0 (0.00 to > 9,995) | 3.64 (0.53-25.4) |
| **IV iron non-dextrans** | | |
| Anaphylaxis events (n) | 12 | 9 |
| Treatments (n)* | 1,760,471 | 1,329,235 |
| IP (95% CI) | 0.07 (0.02-0.24) | 0.11 (0.04-0.34) |
| RR (95% CI)** | 0 (0.00 to > 9,995)) | 33.2 (3.76-317) |
| RD (95% CI)** | −0.07 (−0.19 to > 9,995) | 3.53 (0.39-25.4) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; RR = risk ratio; RD = risk difference.

*Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

**RRs calculated for iron dextran vs. iron non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

On the basis of a comparable number of IV iron treatments in both periods, the IP of anaphylaxis remained similar at 0.06 per 10,000 IV iron treatments and 0.09 per 10,000 IV iron treatments from the period before 2013 to the period after 2013. No events of anaphylaxis were observed for iron dextran in the period before 2013. The RD changed from slightly favouring iron dextran in the before 2013 period (RD, −0.07; 95% CI, −0.19 to > 9,995 per 10,000 iron treatments) to favouring iron non-dextrans in the after 2013 period (RD, 3.53; 95% CI, 0.39-25.4 per 10,000 iron treatments).

### *10.5.4 Exclusion of Data Sources with Zero Events*

#### 10.5.4.1 Overall IV Iron, IV Iron Groups, and IV Iron Types

This section presents the resulting estimates after excluding data sources with zero events for each ordinal IV iron exposure i.e., first, second, and third or subsequent events.

**First Dispensing or Administration**

There were zero events identified among patients with a first IV iron dispensing/administration in three data sources: the SNDS in France, PHARMO-NL, and

the KfH QiN dialysis registry in Germany. After excluding these data sources, based on 189,254 first IV iron users and between 13 and 16 anaphylaxis events, the overall IPs ranged from 0.69 (95% CI, 0.40-1.19) to 1.92 (95% CI, 0.79-4.77) per 10,000 first iron treatments. There were no events in the iron dextran group and, thus, the resulting RRs (min, max) were 0 (95% CI, 0.00 to > 9,995). Risk differences ranged from −0.85 (95% CI, −1.63 to > 9,995) to −1.03 (95% CI, −1.70 to > 9,995) per 10,000 first iron treatments favouring iron dextran.

When assessing IV iron types, the RRs and RDs of anaphylaxis using iron sucrose as the common reference were highest for iron isomaltoside, based on one potential event (RR, 16.2; 95% CI, 0.97-248; RD, 5.11; 95% CI, −0.04 to 37.9, favouring iron sucrose).

**Second Dispensing or Administration**

There were no anaphylaxis events among patients with a second IV iron treatment in the Health Services Database of the Central Denmark Region, SNDS in France, PHARMO-NL, and the KfH QiN dialysis registry in Germany. Exclusion of these data sources resulted in 88,717 patients with a second IV iron treatment for an overall IP of 0.34 (95% CI, 0.11-1.07) per 10,000 second IV iron treatments. On the basis of one potential anaphylaxis event among iron dextran and two events in the iron non-dextrans, the estimated RR was 21.9 (95% CI, 2.09-243) corresponding to a RD of 4.81 (95% CI, 0.41-35.1) per 10,000 second IV iron treatments favouring the iron non-dextrans.

Results by IV iron types showed highest IPs (5.17; 95% CI, 0.75-36.9), highest RRs (8.02; 95% CI, 0.50-124) and RDs (4.53; 95% CI, −51.35 to 36.0, favouring iron sucrose) for the iron dextran type.

**Third or Subsequent Dispensing or Administration**

The GePaRD database in Germany was the only data source identifying potential cases among 348,945 third or subsequent IV iron treatments. The beta-binomial meta-analysis IPs, RRs, and RDs were not estimable because the model failed to converge when there was only one data point.

### *10.5.5 Exclusion of Dialysis Patients*

The patterns of IV iron treatment among dialysis patients differ from those among patients with other conditions. Therefore, an analysis excluding patients undergoing dialysis, in data sources where these patients could be identified, was considered of relevance. Furthermore, in the US studies assessing the risk of anaphylaxis associated with IV iron treatment, dialysis patients were excluded.

#### 10.5.5.1 Overall IV Iron, IV Iron Groups and IV Iron Types

Table 17 summarises the IPs, RRs, and RDs estimates for each ordinal IV iron exposure i.e., first, second, and third or subsequent overall and by iron group after excluding dialysis patients in each data source except in the SNDS in France, where dialysis patients could not be identified.

**Table 17. Risk of Anaphylaxis After Treatment With IV Iron Excluding Dialysis Patients, Overall, and by IV Iron-dextran and Non-dextran Groups**

| | First Treatments | Second Treatments | Third and Subsequent Treatments |
|---|---|---|---|
| **Overall IV iron** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16* | 3 | 6 |
| Treatments (n)** | 176,261 | 76,224 | 144,717 |
| IPs per 10,000 (95% CI) | Min, 0.77 (0.41-1.47); max, 1.75 (0.71-4.46) | 0.46 (0.14-1.59) | 0.34 (0.08-1.63) |
| **Iron dextran** | | | |
| Anaphylaxis events (n) | 0 | 1 | 0 |
| Treatments (n)** | 5,804 | 2,604 | 4,915 |
| IPs per 10,000 (95% CI) | 0 (0.00 to > 9,995) | 3.91 (0.56-27.3) | 0.0 (0.00-NE) |
| **Iron non-dextrans** | | | |
| Anaphylaxis events (n) | Min, 13; max, 16* | 2 | 6 |
| Treatments (n)** | 170,457 | 73,620 | 139,802 |
| IPs per 10,000 (95% CI) | Min, 1.00 (0.42-2.42); max, 1.24 (0.62-2.53) | 0.45 (0.11-1.87) | 0.38 (0.10-1.42) |
| RRs (95% CI)*** | Min, 0.00 (0.00-NE); max, 0 (0.00 to > 9,995) | 8.72 (0.83-96.8) | 0 (0.00-NE) |
| RDs (95% CI)*** | Min, −1.00 (NE52-NE); max, −1.24 (−2.22 to > 9,995) | 3.46 (−0.15 to 27.0) | −0.38 (NE-NE) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; NE = not estimable; RR = risk ratio; RD = risk difference.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

***RRs calculated for iron dextran vs. non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### First Dispensing or Administration

After excluding dialysis patients, based on 176,261 patients with a first IV iron treatment and between 13 and 16 potential anaphylaxis events (all occurring among the iron non-dextran group), the overall IPs ranged from 0.77 (95% CI, 0.41-1.47) to 1.75 (95% CI, 0.71-4.46) per 10,000 first iron treatments. The RD ranged from −1.00 (95% CI, NE-NE) to −1.24 (95% CI, −2.22 to > 9,995), favouring iron dextran in both scenarios.

Results by IV iron type (using iron sucrose as the common reference) showed the highest RR and the largest RD of anaphylaxis after a first treatment for iron isomaltoside although based on one potential event each for iron sucrose and iron isomaltoside (RR, 13.2; 95% CI, 0.79-202; RD, 4.21; 95% CI, −0.27 to 31.6).

### Second Dispensing or Administration

There were 76,224 non-dialysis patients with second IV iron treatments; one potential anaphylaxis event in the iron-dextran and two potential events in the iron non-dextran group. The IP of anaphylaxis per 10,000 second treatments was higher in the iron-dextran group than in the iron non-dextran group. The resulting RR of 8.72 (95% CI, 0.83-96.8) and RD of 3.46 (95% CI, −0.15 to 27.0) favoured the iron non-dextran group.

Results by IV iron type (using iron sucrose as the common reference) showed the highest RR and largest RD of anaphylaxis after second treatments for iron dextran, although based on one potential event (RR, 6.37; 95% CI, 0.40-98.5; RD, 3.25; 95% CI, −1.69 to 26.7).

### Third or Subsequent Dispensing or Administration

There were 144,717 third or subsequent IV iron treatments and six potential anaphylaxis events (all among the iron non-dextran group).

Results by IV iron type showed that all potential anaphylaxis events occurred among the iron gluconate type, thus resulting in a RR of 0; 95% CI, 0-NE, and a RD, −0.38; 95% CI, NE-NE.

## *10.5.6 Risk in Patients Switching Between IV Iron Types*

We conducted an analysis on the risk of anaphylaxis after switching from an iron non-dextran to an iron dextran (and vice versa). The analysis was conducted after a first switch and after any switch. Results are shown in Table 18.

**Table 18. Risk of Anaphylaxis After Switching Between IV Iron Groups, After a First Switch and After any Subsequent Switch**

| | Anaphylaxis After a First Switch | | Anaphylaxis After any Switch | |
|---|---|---|---|---|
| | From Dextrans to Non-dextrans | From Non-dextrans to Dextrans | From Dextrans to Non-dextrans | From Non-dextrans to Dextrans |
| Anaphylaxis events (n) | 0 | 2 | 0 | 2 |
| Switches (n) | 332 | 608 | 619 | 702 |
| IPs per 10,000 (95% CI) | 0 (0-0) | 32.9 (8.26-136) | 0 (NE-NE) | 29.0 (NE-NE) |

CI = confidence interval; IP = incidence proportion, IV = intravenous; NE = not estimable.

Overall, no anaphylaxis occurred after a switch from an iron dextran to an iron non-dextran.

However, two potential anaphylaxis events occurred after a first switch from an iron non-dextran to an iron dextran for an IP of 32.9 per 10,000 first switches. No additional events occurred in subsequent switches from an iron dextran to an iron non-dextran.

### *10.5.7 All First and Subsequent Treatments With IV Iron Combined*

The risk estimates for anaphylaxis (identified through the main case-identification algorithm and the same day and day after exposure risk window) among all users of IV iron captured by the study, are presented in Table 19. Similar to the analyses focusing on third or subsequent treatments, the low IPs found in this analysis can be largely attributed to the high number of IV iron treatments in the KfH QiN dialysis registry network in Germany.

Overall, between 26 and 29 potential anaphylaxis events were identified that resulted in a range of IPs from 0.07 to 0.09 per 10,000 IV iron treatments. The IP for iron dextran was 0.53 per 10,000 iron-dextran treatments (based on one event). For iron non-dextrans the IPs ranged from 0.08 to 0.10 per 10,000 iron non-dextrans treatments. The RR for iron dextran versus iron non-dextrans ranged from 5.45 to 7.03 and the RD ranged from 0.44 to 0.45 anaphylaxis per 10,000 iron treatments, favouring iron non-dextrans.

**Table 19. Risk of Anaphylaxis After Treatment With IV Iron Irrespective of Number of Treatments, Overall, and by IV Iron-dextran and Iron Non-dextran Groups**

| | **Any Treatments** |
|---|---|
| **Overall IV iron** | |
| Anaphylaxis events (n) | Min, 26; max, 29* |
| Treatments (n)** | 3,555,795 |
| IPs per 10,000 (95% CI) | Min, 0.07 (0.04-0.15); max, 0.09 (0.05-0.16) |
| **Iron dextran** | |
| Anaphylaxis events (n) | 1 |
| Treatments (n)** | 18,979 |
| IPs per 10,000 (95% CI)*** | 0.53 (0.08-3.74) |
| **Iron non-dextrans** | |
| Anaphylaxis events (n) | Min, 25; max, 28* |
| Treatments (n)** | 3,536,816 |
| IPs per 10,000 (95% CI) | Min, 0.08 (0.03-0.19); max, 0.10 (0.05-0.21) |
| RRs (95% CI)**** | Min, 5.45 (0.70-44.2); max, 7.03 (0.85-59.9) |
| RDs (95% CI)**** | Min, 0.44 (−0.04 to 3.65); max, 0.45 (−0.01 to 2.91) |

CI = confidence interval; IP = incidence proportion; IV = intravenous; Max = maximum; Min = minimum; RD = risk difference; RR = risk ratio.

*The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed due to data-protection rules aimed at prevention of identification of individuals. Therefore, IPs per 10,000 first treatments are reported as minimum and maximum range.

** Treatments included the Danish data which were rounded to the nearest 10 to comply with data-protection rules aimed at prevention of identification of individuals.

*** The IP for iron dextran was calculated using a pooled crude approach because the beta-binomial model did not converge due to the sparsity of data.

****RRs calculated for iron dextran vs. iron non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

### *10.5.8 Description of Number of Potential Events Outside the Main Risk Window up to 21 Days After Treatment*

#### 10.5.8.1 IV Iron

To evaluate the possibility of a delayed administration of a dispensed IV iron, the occurrence of potential anaphylaxis events from day 2 to 21 days after treatment was assessed. This analysis was performed in data sources not capturing the date of administration of IV iron or the precise date of diagnosis of anaphylaxis.

Table 20 shows the additional potential events identified from day 2 up to 21 days after IV iron exposure. Overall, 70 additional potential events were identified of which 46% occurred during the 2 to 7 days after IV iron treatment.

**Table 20. Number of Potential Anaphylaxis Occurrences (Main Algorithm) Identified After the Risk Window Among New Users of Intravenous Iron Compounds at any Treatment**

| Number of Days After IV Iron Treatment | SNDS, France | PHARMO-NL | Swedish National Registers | GePaRD, Germany |
|---|---|---|---|---|
| 2-4 | 2 | 0 | 2 | 7 |
| 5-7 | 2 | 0 | 1 | 18 |
| 8-10 | 1 | 0 | 2 | 5 |
| 11-13 | 2 | 0 | 0 | 9 |
| 14-16 | 1 | 0 | 1 | 6 |
| 17-19 | 2 | 0 | 0 | 1 |
| 20-21 | 2 | 0 | 0 | 6* |

GePaRD = German Pharmacoepidemiological Research Database; IV = intravenous; PHARMO NL = PHARMO Database Network in the Netherlands; SNDS = Système National des Données de Santé (French National health care insurance system database, previously named SNIIRAM).

*In GePaRD the number refers to potential occurrences of anaphylaxis from day 20 to day 22 after IV iron treatment.

This analysis was not performed in the Central Denmark Region due to data-protection rules aimed at preventing identification of individuals.

#### 10.5.8.2 IV Penicillin

Overall, there were 15 additional potential anaphylaxis events among IV penicillin users identified in GePaRD in Germany and SNDS in France outside the risk window. Overall, 33% of all potential events occurred from day 2 to day 7 after IV penicillin treatment.

### *10.5.9 Risk of Anaphylaxis by IV Penicillins Subtypes*

We conducted an analysis of the risk of anaphylaxis among penicillins users by subtype of penicillins. The groups considered a priori were natural penicillins, betalactamase-resistant penicillins, aminopenicillins, carboxypenicillins, ureidopenicillins, and other penicillins.

Ureidopenicillins were associated with a higher IP of anaphylaxis, ranging from 3.40 to 3.48 per 10,000 first treatments. Aminopenicillins were associated with a lower risk of anaphylaxis; IP ranged from 0.43 to 0.49 per 10,000 first treatments based on one event.

### *10.5.10 Risk Among Dialysis Patients*

The analysis among patients undergoing dialysis was performed in patients receiving any first or subsequent IV iron treatment. Two potential anaphylaxis events were identified, both among IV iron non-dextrans–treated patients. The resulting IP was 0.01 (95% CI, 0.00-0.09) per 10,000 IV iron exposures. Table 8 in Annex 4 presents data source-specific results.

## 10.6 Adverse Events/Adverse Reactions

This study followed the EMA guideline on the requirements for reporting of adverse events, "*EMA's GVP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (Rev 2)"* (EMA, 2014; EMA, 2017b) and the ISPE guideline (ISPE, 2015). The guideline indicates that the reporting of suspected adverse reactions in the form of individual case safety reports is not required for non-interventional, postauthorisation studies such as the study described here that is based on secondary use of data.

# 11 Discussion

## 11.1 Key Results

### *11.1.1 Main Analyses*

#### 11.1.1.1 IV Iron

- The study identified 304,210 patients with a first-recorded IV iron dispensing/administration of whom 6,367 (2.1%) were for iron dextran. For the second IV iron treatments, there were 148,099 patients of whom iron dextran users represented 2.1%; for the third and subsequent treatments, 3,103,486 treatments in 105,634 patients were captured with iron dextran accounting for 0.3% of all third or subsequent treatments. Eighty-four percent of all third or subsequent IV iron treatments were driven by treatments from the KfH QiN dialysis registry in Germany. This finding reflects the repeated treatments required for the management of dialysis patients.
- IV iron treatment in this study reflects only partial use in each country, mostly from ambulatory drug-dispensing data. The study only captures hospital use in the Central Denmark Region (full capture) and the Netherlands (partial capture). Likewise, the study captures IV iron types as used in each of the settings covered in each country.

- Chronic kidney disease, iron-deficiency anaemia, and gastrointestinal bleeding were the most frequent conditions related to potential IV iron indications. The prevalence of these conditions varied greatly across study populations dependent on the type of available data i.e., outpatient diagnosis, primary care diagnoses versus hospital discharge diagnoses. The prevalence of conditions that are risk factors for hypersensitivity reactions also varied across data sources: history of anaphylaxis ranged from 0% to 1% and history of any allergies ranged from 2% to 51%.

- At first IV iron treatment, between 13 and 16 potential cases of anaphylaxis were identified. The resulting IP ranged from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97) per 10,000 first treatments. No events among iron dextran users were identified in this group. Therefore, the RR of iron dextran versus iron non-dextrans was 0. The corresponding risk difference ranged from -0.44 to -0.55 events per 10,000 first treatments. IPs and RDs estimates presented as ranges owing to the data protection rules aimed at preventing the identification of individual patients.

- The IPs of anaphylaxis were generally higher for the first treatment. Among second IV iron treatments, from a total of three potential anaphylaxis cases, a single case was identified in the iron-dextran group.

- There were no anaphylaxis events identified in three populations i.e., the SNDS in France, PHARMO-NL, and KfH QiN dialysis registry in Germany.

- Risk estimates by groups and types of IV iron were estimated but are based on a very small number of events.

- No adjusted analyses could be performed because of the small number of events.

- The study case-identification algorithm as used in GePaRD in Germany has been validated in the Oldenburg University Hospital showing a PPV of 62.3% (95% CI, 49.8-73.7).

- There were no potential anaphylaxis events among IV iron users in PHARMO-NL. In the Central Denmark Region, owing to the data-protection rules aimed at preventing identification of individual patients, the results of the validation of potential events among IV iron users (1-4 events) could only be reported as a combined PPV for potential anaphylaxis events among the IV iron users and IV penicillin users (PPV 70; 95% CI, 50-86).

#### 11.1.1.2 IV Penicillins

- The study identified 231,294 first treatments and 984,000 total treatments of IV penicillins overall.

- At first IV penicillins treatment, 30 potential cases of anaphylaxis were identified. The resulting IP was 1.16 (95% CI, 0.78-1.73) per 10,000 treatments.

- The Central Denmark Region contributed the majority of parenteral penicillins patients (50.6%) and treatments (74.8%) because it was the only study data source that comprehensively captured in-hospital administration of drugs.

- Two data sources did not contribute data for IV penicillins i.e., KfH QiN dialysis registry in Germany, and the Swedish registers.
- The only evaluable case identified through the main algorithm in PHARMO-NL was confirmed resulting in a PPV of 100%. In the Central Denmark Region, the estimated PPV combining the potential events from IV iron and IV penicillin users was 70% based on potential cases with sufficient information.

### *11.1.2 Sensitivity Analyses*

#### 11.1.2.1 IV Iron

The sensitivity analyses conducted were intended to assess whether the main case-identification algorithm and the exposure risk window applied in the main analysis were adequately identifying the study outcome.

- Expanding the case-identification algorithm to include adrenaline administration as a proxy of anaphylaxis, six additional potential events were identified among first IV iron treatment in PHARMO-NL. However, direct validation of these potential events suggested that most adrenaline use in these patients was not intended to treat an anaphylactic reaction. In the Central Denmark Region, the data were too sparse to evaluate meaningfully the impact of this algorithm expansion.
- Expanding the exposure risk window up to 7 days to identify events in data sources using dispensing data or where the exact date of the potential event was not known identified 11 additional potential events. All these additional events were identified in data sources where case validation was not possible. The analysis of potential events occurring from day 2 up to day 21 did not provide strong evidence of delayed administration of IV iron.
- Dialysis patients were excluded based on the different pattern (i.e., chronic) of use of IV iron among these patients and the impossibility of ascertaining new-user status (especially in the KfH QiN dialysis registry in Germany). This analysis showed an increase in the IP of anaphylaxis among first IV iron treatments (IPs ranged from 0.77 to 1.75 per 10,000 first treatments).
- When anaphylaxis occurring after a switch from iron non-dextrans to iron dextran was assessed, two additional potential anaphylaxis events were identified after a first switch from an iron non-dextran to an iron dextran. No additional potential events were identified after further switches between the iron non-dextran and iron-dextran groups.
- Similar to the analyses focusing on third or subsequent treatments, the results assessing all treatments with IV iron combined were largely driven by the large number of IV iron treatments in the KfH QiN dialysis registry in Germany.

#### 11.1.2.2 IV Penicillin

- Expanding the case-identification algorithm to include adrenaline administration as a proxy of anaphylaxis, 427 additional potential events were identified among

first and subsequent IV penicillin treatments across all sites with IV penicillin data.

- Direct validation of the additional potential events in PHARMO-NL suggested that most adrenaline use in these patients was not intended to treat an anaphylactic reaction.

- Expanding the exposure risk window up to 7 days to identify events in data sources using dispensing data or where the exact date of the potential event was not known identified four additional potential events. Since there were no cases identified in PHARMO-NL or the Central Denmark Region direct validation was not possible.

## 11.2 Limitations

The 2014 and 2016 feasibility evaluations identified a large number of important challenges that have been confirmed upon conduct of the study (the study feasibility reports are included in Annex 5).

The following are the main limitations encountered:

- A very low number of potential anaphylaxis events has been identified despite the use of multiple, large, population-based data sources. This low number of events was identified in the descriptive analysis (March 2019). This prompted a modification of the methods as reflected in the amended protocol endorsed by EMA-PRAC on September 2019. Among others, this precluded the conduct of the originally planned propensity score-adjusted analyses. Estimates from beta-binomial regression meta-analyses have been provided. While they take into account site variability, estimates may be subject to confounding. Section 9.4.3 shows the variables initially considered for the propensity score models.

- Assessment of a differential risk of anaphylaxis by groups or types of IV iron has been limited by the very small number of users of some types of IV iron and its variability across countries. There is substantial capture only for iron sucrose, iron gluconate, and iron carboxymaltose. However, capture of iron dextran and iron isomaltoside in this study was marginal. This limited the comparison of iron dextran with iron non-dextrans and of individual IV iron types based on an appropriate number of exposures and events. Of interest, iron dextran represented a large proportion of all IV iron treatments captured in the PHARMO-NL. This finding was further assessed by verifying that all treatments originally identified as iron dextran from all PHARMO-NL sources (Outpatient Pharmacy, Inpatient Pharmacy and GP Database) contained the description “Cosmofer”, the brand name for iron dextran.

- Full validation was not possible in any data source and therefore the degree of outcome misclassification is unknown. Validation of potential events was conducted in PHARMO-NL and the Central Denmark Region for hospitals that allowed access to the medical records. The approvals and access requests took longer than originally envisioned. Some hospitals did not grant access to their records. In Denmark, the data-protection rules compounded by lack of sufficient

information available from the reviewed records precluded detailed analysis of the validation data.

- There was important heterogeneity in the type of information available across data sources, notably only the Health Services Database of the Central Denmark Region captured in-hospital use of the medications of interest comprehensively and the PHARMO-NL captured partial in-hospital use. In France, only one IV iron preparation (iron carboxymaltose) was available for outpatients and captured in the SNDS, while all other IV iron preparations were available in hospital and included in the Diagnosis Related Group cost and were not identifiable. In addition, some data sources have relied on dispensed drug data rather than on actual administration of the drugs. This introduced a degree of uncertainty around the actual date of exposure and some degree of exposure misclassification may exist.

- New-user status has also been challenging to determine because of the limited capture of in-hospital use, likely the most common setting where the study drugs are administered often for the first time. According to whole-sales statistics from the Swedish eHealth Agency (Swedish Pharmaceutical Statistics, 2020), approximately 50% to 80% of IV iron treatments were administered in the inpatient setting (i.e., recorded as requisitions for IV iron treatments bought by hospitals and administered directly to the patient) during the study period. The same limitation applies to the ascertainment of second and third or subsequent treatments and analysis in all countries.

- Patients diagnosed with chronic kidney disease are likely to have received IV iron treatment before registration into the KfH QiN dialysis registry in Germany. Therefore, this may have introduced a depletion of susceptible patients because patients who had experienced a prior hypersensitivity reaction after treatment with IV iron would be less likely to be treated again.

- In most data sources it has been difficult to distinguish between IV and IM iron administration, which is of relevance for iron dextran, the IV iron compound that can be administered IV or IM. 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 mostly refers to IV use. This may also have applied to IV penicillins.

- Although beta-binomial regression was recommended for meta-analyses of rare events, the model was not able to estimate CIs in certain situations where at least one treatment group had zero events. In other situations, variance estimates were orders of magnitude larger than regression coefficient estimates, yielding CIs bounded by minimum and maximum possible values. Additionally, model convergence was not always stable. When beta-binomial regression was implemented using the non-linear mixed (NLMIXED) procedure in SAS, the model would converge to slightly different parameter estimates or not converge at all depending on the user-specified initial starting values. To standardise regression models, the FMM procedure in SAS was implemented, which does not depend on user-specified initial starting values. However, within the FMM procedure, slightly different parameter estimates could be obtained by changing the default convergence criteria, maximum number of iterations, or optimisation technique.

- Despite all efforts and the commitment and engagement of the principal investigator at DIMDI, the DIMDI-DaTraV data source was not able to contribute data to the study because of the lack of resources at DIMDI to perform the study activities. DIMDI-DaTraV would have likely been the database with the largest contribution of IV iron exposure data to the study because of its coverage of the whole German population. However, the major limitations identified during feasibility evaluation have persisted. Most relevant is the lack of a recorded exact date for all diagnoses (only one quarter is available) which would have jeopardised the establishment of a plausible temporal relationship between the exposure to IV iron and the diagnosis of a potential anaphylaxis event. Also, the systematic lack of data for the year before a patient's death would have effectively excluded all fatal cases from the study.

## 11.3 Interpretation

This study found an IP of anaphylaxis ranging from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97) per 10,000 first IV iron treatments (IP, 0.77-1.75 per 10,000 first IV iron treatment in the non-dialysis populations). These estimates are lower than the estimates of 2.4 to 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in Wang et al. (2015) or those reported by Walsh et al. (2016): 2 to 4 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively). For the resulting RRs and RDs by IV iron groups and types the interpretation was limited due to the small number of events underlying these estimates.

The following potential reasons for the differences in the incidence of anaphylaxis between our study and the US studies exist:

- Potential underascertainment of anaphylaxis events.
  - This study adapted the case-identification algorithm from the US study by Walsh et al. (2016) that used ICD, ATC, procedure and other types of codes to identify anaphylaxis events. Had the case-identification algorithm not been adapted to the type of data available in the participating data sources, an underascertainment of events would have occurred. The inclusion in the study of a cohort of new users of penicillins was intended to assess the performance of the algorithm and address this potential limitation. The IP of anaphylaxis among new users of penicillins was 1.16 per 10,000 first treatments which is in the lower range of published estimates (ranging from 0.1 to 5 per 10,000). This provides evidence supporting the adequateness of the case-identification algorithm used in the study.
- The validation of potential events in Denmark and PHARMO-NL.

  Although based on a single confirmed case (PHARMO-NL), direct validation of the main algorithm suggests that the PPV is in line with other studies. The direct validation of the expanded algorithm in PHARMO-NL suggests that the addition of adrenaline to the algorithm was not helpful; a similar finding was suggested by the validation in the Central Denmark Region. In Denmark, the direct validation of the case-identification algorithms, despite the limitations imposed by compliance with data-protection rules, resulted in a PPV of 70% for the combined potential events among IV iron and IV penicillin users.

The validation of the study case-identification algorithm used in GePaRD in Germany in the Oldenburg University Hospital also supports that the case-identification algorithm can detect cases of anaphylaxis. The estimated PPV of the case-identification algorithm was similar to that of the algorithm used in the US Sentinel study (Walsh et al., 2013).

Therefore, even if a certain degree of misclassification of the outcomes is likely to exist, the study has provided evidence supporting the notion that the results are unlikely to have been driven by a major misclassification of the outcome status of participating patients.

- Underascertainment of exposure to IV iron.

  This study captured limited data on in-hospital use of IV iron, the setting where most use of this drug is likely to happen. Moreover, the data sources capturing inpatient use, Health Services Database of the Central Denmark Region, and PHARMO-NL, covered only a subset of the countries' population: about 25% of the total Danish population in the Health Services Database of the Central Denmark Region and 20% of the Dutch population in PHARMO-NL. In contrast, the US studies captured use of IV iron drugs comprehensively irrespective of administration setting.

  Nevertheless, this study was able to capture a substantial amount of IV iron treatments (i.e., 304,210 first treatments) thanks to the use of multiple large data sources. This use of IV iron was in line with that observed in the US Sentinel study by Walsh et al. (2016) (70,866 first treatments) and the US Medicare study by Wang et al. (2015) (688,183 first treatments).

  Therefore, the small number of events identified in the study does not appear driven by a poor capture of the use of IV iron in Europe.

- Misclassification of IV iron new-user status.

  The correct ascertainment of first use of IV iron may have been limited by the lack of data on in-hospital (or specialty clinics) use of IV iron. For instance, it is conceivable that a patient may have received the first doses of IV iron while in hospital and later received follow-up doses in an outpatient setting. The former treatments will have been missed by our study (except in the Central Denmark Region and PHARMO-NL) and the latter will have been captured but incorrectly considered as initial treatments. Indeed, data from Sweden suggests that between 50% and 80% of IV iron treatments occur in an in-hospital setting. A similar situation may have occurred with IV penicillins.

  In contrast, the US studies by Walsh et al. (2016) and Wang et al. (2015) had ascertainment of exposure to IV iron, irrespective of administration setting, and could therefore determine new-user status more precisely. Interestingly, both US studies excluded dialysis patients.

  It is known that the risk of anaphylaxis decreases with the increasing number of exposures to a drug because of the nature of anaphylactic reactions and to the depletion of susceptible patients. Therefore, the lower than expected number of events observed may, at least in part, be due to a misclassification of the new-user status of patients in our study. The sensitivity analysis excluding dialysis

patients is consistent with this hypothesis. Indeed, patients undergoing dialysis are regularly treated with IV iron to compensate for the increased losses of iron during dialysis and a decreased production of red blood cells. The main contributor of IV treatments in dialysis patients in this study, the KfH QiN in Germany, was unable to ascertain use of IV iron before registration in the registry network. It is likely that patients who undergo dialysis will have received IV iron doses before joining the dialysis speciality clinics in the KfH QiN registry network. Therefore, the misclassification of the new-user status of IV iron may be particularly important among dialysis patients. The analysis excluding dialysis patients was intended to reduce the new-user status misclassification and, as expected, showed an increase of the IP of anaphylaxis, from 0.38 to 0.51 per 10,000 first IV iron treatments when dialysis patients were included to 0.77 to 1.75 per 10,000 first IV iron treatments when dialysis patients were excluded.

- Results by group and type of IV iron.

  The main aim of this study was to compare the risk of anaphylaxis among iron dextran users with iron non-dextrans users. This analysis has been jeopardised by the small number of users of iron dextran and only one event in the second iron-dextran treatment. In contrast, iron-dextran use was common in the US studies.

  The evaluation of type of IV iron was targeted to identify anaphylaxis among users of the first type of IV iron, irrespective of the number of treatments with the specific IV iron type. However, the sensitivity analyses looking at the risk of anaphylaxis after a switch between IV iron groups identified two events after a first switch from an iron non-dextran to an iron dextran, for a high IP of anaphylaxis after such switches (i.e., IP, 32.9; 95% CI, 8.26-136 per 10,000 first switches). This finding is based on a low number of events.

## 11.4 Generalisability

The study provided a wide array of patient characteristics, health systems, drug use, and medical practice patterns, most of which were from outpatient settings across populations in different European countries. Generalisations from these findings depend on the category of the finding (Rothman et al., 2013; Rothman, 2014). Findings that relate to drug use and patient characterisation, or to risk minimisation evaluation apply to the specific patient population in the participating countries (i.e., Denmark, France, Germany, The Netherlands, and Sweden). The results that relate to endpoint validation should be generalisable to database or medical record systems using data collection and data linkage approaches similar to those used in Denmark and The Netherlands. The risk of events among those using IV iron products should be generalisable to all patients using this medication, apart from the effect of any as yet unidentified biological mediators.

# 12 Other Information

None.

# 13 Conclusion

This study was based on 304,210 patients with a first-recorded IV iron treatment in five European countries. However, there were only 6,387 first treatments of iron dextran.

Overall, the study found an overall IP of anaphylaxis, ranging from 0.38 (95% CI, 0.17-0.88) to 0.51 (95% CI, 0.28-0.97) per 10,000 first treatments; for iron non-dextrans from 0.44 to 0.55 and not assessable for iron dextran. The range stemmed from the masking of the exact number of events mandated by current data-protection Danish regulations to prevent identification of individual patients. These IPs were lower than the estimates of 2 and 6.8 per 10,000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in the US studies by Walsh et al. (2016) and Wang et al. (2015).

The low number of events precluded the conduct of the originally planned adjusted analyses and thus limits the interpretation of the results based on groups and types of IV iron.

The risk of anaphylaxis among IV penicillins users was within the expected range of IPs based on the literature, suggesting that the main case-identification algorithm used by the study was adequate. The results from the sensitivity analyses and from the available data of validation of cases, and the study case-identifying algorithm also supported this view.

The limitations of the study were identified by the feasibility evaluations conducted in 2014 and 2016 and reflected in the submitted reports. Most notably, the likely misclassification of repeated users of IV iron as first users, due to the impossibility of capturing use in hospital and specialty clinics in most data sources, may have resulted in an underestimation of the IPs of anaphylaxis.

Due to methodological limitations, the study cannot exclude the possibility of a high risk of anaphylaxis associated with the administration of injectable iron and whether there are differences in the risk between the different types of IV iron. Some sensitivity analyses yielded risk ratios above the unity when comparing the risk of anaphylaxis for iron dextran versus iron non-dextrans; however, these analyses were based on very few cases, all of which had important validity concerns, and therefore conclusions cannot be drawn.

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# Appendices

# Annex 1.
# List of Stand-alone Documents

None.

# Annex 2
# IV Iron Marketing Authorisation Holders Consortium

**Table 2 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 |
| Acino AG | Am Windfeld 35, 83714 Miesbach, Germany | [redacted]@primevigilance.com |
| Arrow Génériques | 26 Avenue Tony Garnier F-69007 Lyon, France | [redacted]@arrow-generiques.com |
| Baxter | Baxter Medical AB,Torshamnsgatan 48, 164 40 Kista, Sweden | [redacted]@baxter.com |
| Generis Farmacéutica SA | Rua João de Deus, 19 P-2700-487 Amadora, Portugal | [redacted]@generis.pt |
| Altan Pharmaceuticals SAU | Calle Cólquide 6, Portal 2-1ª planta Edificio Prisma ES-28230 Las Rozas Madrid, Spain | [redacted]@altanpharma.com |
| Laboratoires Sterop SA | Avenue de Scheut 46-50, 1070 Bruxelles, Belgium | [redacted]@infarama.be |
| Medice Arzneimittel Pütter GmbH & Co. KG | Kuhloweg 37, DE-58638 Iserlohn, Germany | [redacted]@medice.de |
| Mylan SAS | 117, allée des Parcs 69800 Saint-Priest, France | [redacted]@mylan.in |
| Orifarm Generics A/S | Energivej 15 / POB 69 DK-5260 Odense S, Denmark | [redacted]@orifarm.com |
| Panmedica (Panpharma SA), | 69/71 Avenue Pierre Grenier F-92100 Boulogne-Billancourt, France | [redacted]@panpharma.fr |
| Pharmachemie BV (Teva) | Sweensweg 5, 2031 GA Haarlem, The Netherlands | [redacted]@teva.co.il |
| Pharmacosmos A/S | Roervangsvei 30 Holbaek DK-4300, Denmark | [redacted]@pharmacosmos.com |
| Rafarm SA | 12 Korinthou 15451, Neo Psychiko, Attiki, Greece | [redacted]@rafarm.gr<br>[redacted]@rafarm.gr |

| Name | Address | Contact Details |
|---|---|---|
| Sandoz SAS | 49 avenue Georges Pompidou 92593 Levallois-Perret, France | [redacted] sandoz.com |
| Sanofi Aventis Groupe | 1, avenue Pierre Brossolette 91380 Chilly-Mazaarin, France | [redacted] sanofi.com |
| Vifor France | 100-101 Terrasse Boieldieu, France<br>Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, France | [redacted]@viforpharma.com |

# Annex 3. Cohort Attrition and Baseline Characteristics: Data Source-specific Tables of Results

Annex 3_Cohorts Attrition.xlsx

Annex 3_Baseline Characteristics.xlsx

# Annex 4. Main and Sensitivity Analysis: Tables of Results

**Table 1.1 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.71 (20 / 116,980) | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | -1.71 |
| | 95% CI | 1.11, 2.64 | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | -5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | 1.71 (20 / 116,980) | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | -6.85 |
| | 95% CI | 1.11, 2.64 | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | -13.6, -0.14 |
| SNDS Database, France | Estimate | 0.17 (1 / 57,200) | 0 (0 / 75,512) | NE | 0 (0 / 75,512) | NE | NE |
| | 95% CI | 0.03, 0.99 | 0, 0.51 | NE, NE | 0, 0.51 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.77 (3 / 39,002) | 0 (0 / 5,825) | 0 (0 / 2,393) | 0 (0 / 3,432) | NE | 0 |
| | 95% CI | 0.26, 2.26 | 0, 6.59 | 0, 16.0 | 0, 11.2 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.71 (3 / 42,468) | 0 (0 / 1,599) | 0.73 (3 / 40,869) | 0 | -0.73 |
| | 95% CI | NA | 0.24, 2.08 | 0, 24.0 | 0.25, 2.16 | 0, 32.7 | -1.56, 0.10 |
| GePaRD, Germany | Estimate | 3.31 (6 / 18,112) | 0.64 (9 / 140,916) | 0 (0 / 2,346) | 0.65 (9 / 138,570) | 0 | -0.65 |
| | 95% CI | 1.52, 7.23 | 0.34, 1.21 | 0, 16.3 | 0.34, 1.23 | 0, 25.2 | -1.07, -0.23 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 33,619) | 0 (0 / 29) | 0 (0 / 33,590) | NE | 0 |
| | 95% CI | NA | 0, 1.14 | 0, 1170 | 0, 1.14 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 1.17 (30 / 231,294) | 0.43 (13 / 304,210) | 0 (0 / 6,387) | 0.44 (13 / 297,813) | 0 | -0.44 |
| | 95% CI | 0.80, 1.70 | 0.25, 0.73 | 0, 6.01 | 0.26, 0.75 | 0, 13.8 | -0.75, 5.57 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 1.16 | 0.38 | 0 | 0.44 | 0 | -0.44 |
| | 95% CI | 0.78, 1.73 | 0.17, 0.88 | 0, >9995 | 0.16, 1.24 | 0, >9995 | -1.02, >9995 |
| Pooled (Crude) Analysis (Max) | Estimate | 1.17 (30 / 231,294) | 0.53 (16 / 304,210) | 0 (0 / 6,387) | 0.54 (16 / 297,813) | 0 | -0.54 |
| | 95% CI | 0.80, 1.70 | 0.32, 0.85 | 0, 6.01 | 0.33, 0.87 | 0, 11.2 | -0.87, 5.47 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Beta-Binomial Meta-Analysis (Max) | Estimate | 1.16 | 0.51 | 0 | 0.55 | 0 | -0.55 |
| | 95% CI | 0.78, 1.73 | 0.28, 0.97 | 0, >9995 | 0.23, 1.34 | 0, >9995 | -1.14, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 1.2 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 2,150) | 0 (0 / 10) | 0 (0 / 2,140) | NE | 0 |
| | 95% CI | NA | 0, 17.8 | 0, 3540 | 0, 17.9 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 22,626) | NE | 0 (0 / 22,626) | NE | NE |
| | 95% CI | NA | 0, 1.70 | NE, NE | 0, 1.70 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 1,850) | 0 (0 / 1,066) | 0 (0 / 784) | NE | 0 |
| | 95% CI | NA | 0, 20.7 | 0, 35.9 | 0, 48.8 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.48 (1 / 20,822) | 0 (0 / 760) | 0.50 (1 / 20,062) | 0 | -0.50 |
| | 95% CI | NA | 0.08, 2.72 | 0, 50.3 | 0.09, 2.82 | 0, 101 | -1.48, 0.48 |
| GePaRD, Germany | Estimate | NA | 0.29 (2 / 67,895) | 8.18 (1 / 1,223) | 0.15 (1 / 66,672) | 54.5 | 8.03 |
| | 95% CI | NA | 0.08, 1.07 | 1.44, 46.2 | 0.03, 0.85 | 5.69, 522 | -8.00, 24.0 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 32,756) | 0 (0 / 25) | 0 (0 / 32,731) | NE | 0 |
| | 95% CI | NA | 0, 1.17 | 0, 1330 | 0, 1.17 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.20 (3 / 148,099) | 3.25 (1 / 3,084) | 0.14 (2 / 145,015) | 23.5 | 3.11 |
| | 95% CI | NA | 0.07, 0.60 | 0.57, 18.4 | 0.04, 0.50 | 3.08, 180 | 0.42, 18.2 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.25 | 3.33 | 0.25 | 13.1 | 3.08 |
| | 95% CI | NA | 0.07, 0.94 | 0.48, 23.3 | 0.06, 1.06 | 1.26, 146 | 0.12, 23.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 1.3 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 34,760) | 0 (0 / 20) | 0 (0 / 34,750) | NE | 0 |
| | 95% CI | NA | 0, 1.10 | 0, 2040 | 0, 1.11 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 58,298) | NE | 0 (0 / 58,298) | NE | NE |
| | 95% CI | NA | 0, 0.66 | NE, NE | 0, 0.66 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 3,217) | 0 (0 / 2,421) | 0 (0 / 796) | NE | 0 |
| | 95% CI | NA | 0, 11.9 | 0, 15.8 | 0, 48.0 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0 (0 / 37,471) | 0 (0 / 1,148) | 0 (0 / 36,323) | NE | 0 |
| | 95% CI | NA | 0, 1.03 | 0, 33.4 | 0, 1.06 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NA | 0.29 (10 / 348,945) | 0 (0 / 5,015) | 0.29 (10 / 343,930) | 0 | -0.29 |
| | 95% CI | NA | 0.16, 0.53 | 0, 7.65 | 0.16, 0.54 | 0, 26.3 | -0.47, -0.11 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 2,620,795) | 0 (0 / 904) | 0 (0 / 2,619,891) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 42.3 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.03 (10 / 3,103,486) | 0 (0 / 9,508) | 0.03 (10 / 3,093,988) | 0 | -0.03 |
| | 95% CI | NA | 0.02, 0.06 | 0, 4.04 | 0.02, 0.06 | 0, 125 | -0.06, 4.01 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.02 | 0 | 0.03 | 0 | -0.03 |
| | 95% CI | NA | 0.00, 0.13 | 0, >9995 | 0.00, 0.19 | 0, >9995 | -0.13, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 1.4 Combined Analysis Across Research Partner Databases By Dextran Category - Main Algorithm - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.41 (30 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | -0.23 |
| | 95% CI | 0.29, 0.58 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | -0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 0.41 (30 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | -0.94 |
| | 95% CI | 0.29, 0.58 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | -1.85, -0.02 |
| SNDS Database, France | Estimate | 0.26 (2 / 78,292) | 0 (0 / 156,436) | NE | 0 (0 / 156,436) | NE | NE |
| | 95% CI | 0.07, 0.93 | 0, 0.25 | NE, NE | 0, 0.25 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.35 (4 / 114,639) | 0 (0 / 10,892) | 0 (0 / 5,880) | 0 (0 / 5,012) | NE | 0 |
| | 95% CI | 0.14, 0.90 | 0, 3.53 | 0, 6.53 | 0, 7.66 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.40 (4 / 100,761) | 0 (0 / 3,507) | 0.41 (4 / 97,254) | 0 | -0.41 |
| | 95% CI | NA | 0.15, 1.02 | 0, 10.9 | 0.16, 1.06 | 0, 26.6 | -0.81, -0.01 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.38 (21 / 557,756) | 1.16 (1 / 8,584) | 0.36 (20 / 549,172) | 3.20 | 0.80 |
| | 95% CI | 0.74, 2.87 | 0.25, 0.58 | 0.21, 6.60 | 0.24, 0.56 | 0.55, 18.7 | -1.49, 3.09 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.44 (44 / 984,000) | 0.07 (26 / 3,555,795) | 0.53 (1 / 18,979) | 0.07 (25 / 3,536,816) | 7.46 | 0.46 |
| | 95% CI | 0.32, 0.59 | 0.05, 0.11 | 0.09, 2.99 | 0.05, 0.10 | 1.28, 43.4 | 0.02, 2.91 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 0.45 | 0.07 | 0.53 | 0.08 | 7.03 | 0.46 |
| | 95% CI | 0.32, 0.63 | 0.04, 0.15 | 0.08, 3.74 | 0.03, 0.19 | 0.85, 59.9 | -0.01, 3.68 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.44 (44 / 984,000) | 0.08 (29 / 3,555,795) | 0.53 (1 / 18,979) | 0.08 (28 / 3,536,816) | 6.66 | 0.45 |
| | 95% CI | 0.32, 0.59 | 0.06, 0.12 | 0.09, 2.99 | 0.05, 0.11 | 1.15, 38.6 | 0.01, 2.91 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 0.45 | 0.09 | 0.53 | 0.10 | 5.45 | 0.44 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.32, 0.63 | 0.05, 0.16 | 0.08, 3.73 | 0.05, 0.21 | 0.70, 44.2 | -0.04, 3.65 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.1a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 75,512) | NE | NE | NE | NE |
| | 95% CI | 0, 0.51 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,594) | 0 (0 / 456) | NE | 0 (0 / 2,393) | 0 (0 / 1,382) |
| | 95% CI | 0, 24.0 | 0, 83.5 | NE, NE | 0, 16.0 | 0, 27.7 |
| Swedish National Registries | Estimate | 0.51 (1 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.49 (1 / 20,316) |
| | 95% CI | 0.09, 2.91 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.09, 2.79 |
| GePaRD, Germany | Estimate | 1.31 (5 / 38,101) | 0 (0 / 784) | 0.47 (4 / 85,282) | 0 (0 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.56, 3.07 | 0, 48.8 | 0.18, 1.21 | 0, 16.3 | 0, 2.67 |
| KfH-QiN, Germany | Estimate | 0 (0 / 11,982) | 0 (0 / 17) | 0 (0 / 21,386) | 0 (0 / 29) | 0 (0 / 205) |
| | 95% CI | 0, 3.20 | 0, 1840 | 0, 1.80 | 0, 1170 | 0, 184 |
| Pooled (Crude) Analysis | Estimate | 0.41 (6 / 146,674) | 4.30 (1 / 2,325) | 0.37 (4 / 106,668) | 0 (0 / 6,367) | 0.28 (1 / 36,306) |
| | 95% CI | 0.19, 0.89 | 0.76, 24.3 | 0.15, 0.96 | 0, 6.03 | 0.05, 1.56 |
| Beta-Binomial Meta-Analysis | Estimate | 0.45 | 4.44 | 0.46 | 0 | 0.43 |
| | 95% CI | 0.12, 1.69 | 0.62, 31.5 | 0.08, 2.79 | 0, >9995 | 0.06, 3.10 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.1b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.04 | 19.0 | NE | 0 |
| | 95% CI | 0.11, 9.99 | 1.99, 182 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.49, Inf | NE, NE | 0.18, Inf | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.49 | 15.6 | 1.36 | 0 |
| | 95% CI | 0.23, 9.39 | 1.63, 150 | 0.20, 9.06 | 0, 21.9 |
| Beta-Binomial Meta-Analysis | Estimate | 1.04 | 10.3 | 1.06 | 0 |
| | 95% CI | 0.10, 11.1 | 0.62, 158 | 0.08, 14.7 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.1c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.02 | 8.87 | NE | -0.49 |
| | 95% CI | -1.37, 1.41 | -9.50, 27.2 | NE, NE | -1.46, 0.47 |
| GePaRD, Germany | Estimate | 1.31 | 0 | 0.47 | 0 |
| | 95% CI | 0.16, 2.46 | NE, NE | 0.01, 0.93 | NE, NE |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.13 | 4.03 | 0.10 | -0.28 |
| | 95% CI | -1.16, 0.68 | 0.39, 24.1 | -1.20, 0.74 | -1.56, 5.75 |
| Beta-Binomial Meta-Analysis | Estimate | 0.02 | 4.01 | 0.03 | -0.43 |
| | 95% CI | -2.55, 1.26 | -0.67, 30.6 | -2.52, 2.24 | -2.23, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.2a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 22,626) | NE | NE | NE | NE |
| | 95% CI | 0, 1.70 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 364) | 0 (0 / 82) | NE | 0 (0 / 1,066) | 0 (0 / 338) |
| | 95% CI | 0, 104 | 0, 448 | NE, NE | 0, 35.9 | 0, 112 |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0 (0 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0, 3.21 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0 (0 / 46,021) | 8.18 (1 / 1,223) | 1.38 (1 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0, 0.83 | 1.44, 46.2 | 0.24, 7.84 |
| KfH-QiN, Germany | Estimate | 0 (0 / 11,616) | 0 (0 / 13) | 0 (0 / 20,964) | 0 (0 / 25) | 0 (0 / 138) |
| | 95% CI | 0, 3.31 | 0, 2280 | 0, 1.83 | 0, 1330 | 0, 271 |
| Pooled (Crude) Analysis | Estimate | 0.18 (1 / 55,684) | 0 (0 / 537) | 0 (0 / 66,985) | 3.25 (1 / 3,074) | 0.51 (1 / 19,669) |
| | 95% CI | 0.03, 1.02 | 0, 71.0 | 0, 0.57 | 0.57, 18.4 | 0.09, 2.88 |
| Beta-Binomial Meta-Analysis | Estimate | 0.22 | 0 | 0 | 3.31 | 0.59 |
| | 95% CI | 0.03, 1.62 | 0, NE | 0, NE | 0.48, 23.7 | 0.08, 4.25 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.2b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.40, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0 | 5.90 |
| | 95% CI | 0, 2.10 | 0, 142 | 0, 0.60 | 0.62, 56.5 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.35 | 0 | 0 | 6.40 |
| | 95% CI | 0.04, 3.38 | 0, 141 | 0, 1.13 | 0.67, 61.3 |
| Beta-Binomial Meta-Analysis | Estimate | 0.38 | 0 | 0 | 5.60 |
| | 95% CI | 0.03, 6.03 | 0, NE | 0, NE | 0.35, 86.6 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.2c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.28 | 0 | NE | 0 |
| | 95% CI | -1.22, 3.77 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | -1.38 | -1.38 | -1.38 | 6.79 |
| | 95% CI | -4.10, 1.33 | -4.10, 1.33 | -4.10, 1.33 | -9.46, 23.0 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.33 | -0.51 | -0.51 | 2.74 |
| | 95% CI | -2.71, 0.58 | -2.88, 70.5 | -2.88, 0.07 | -0.56, 17.9 |
| Beta-Binomial Meta-Analysis | Estimate | -0.37 | -0.59 | -0.59 | 2.72 |
| | 95% CI | -3.87, 1.03 | NE, NE | NE, NE | -1.84, 22.8 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.3a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 58,298) | NE | NE | NE | NE |
| | 95% CI | 0, 0.66 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 31) | NE | 0 (0 / 2,421) | 0 (0 / 412) |
| | 95% CI | 0, 108 | 0, 1100 | NE, NE | 0, 15.8 | 0, 92.4 |
| Swedish National Registries | Estimate | 0 (0 / 8,562) | 0 (0 / 149) | NE | 0 (0 / 1,148) | 0 (0 / 27,612) |
| | 95% CI | 0, 4.48 | 0, 251 | NE, NE | 0, 33.4 | 0, 1.39 |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.27 (8 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.14, 0.53 | 0, 7.65 | 0.06, 2.08 |
| KfH-QiN, Germany | Estimate | 0 (0 / 588,840) | 0 (0 / 84) | 0 (0 / 2,029,405) | 0 (0 / 904) | 0 (0 / 1,562) |
| | 95% CI | 0, 0.07 | 0, 437 | 0, 0.02 | 0, 42.3 | 0, 24.5 |
| Pooled (Crude) Analysis | Estimate | 0.01 (1 / 672,948) | 0 (0 / 512) | 0.03 (8 / 2,328,938) | 0 (0 / 9,488) | 0.18 (1 / 56,840) |
| | 95% CI | 0.00, 0.08 | 0, 74.5 | 0.02, 0.07 | 0, 4.05 | 0.03, 1.00 |
| Beta-Binomial Meta-Analysis | Estimate | 0.05 | 0 | 0.05 | 0 | 0.21 |
| | 95% CI | 0.01, 0.33 | 0, >9995 | 0.01, 0.34 | 0, >9995 | 0.03, 1.50 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.3b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.61 | 0 | 0.73 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.12, 4.48 | 0, 20.9 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.08 | 0 | 0.20 | 0 |
| | 95% CI | 0.01, 0.81 | 0, 426 | 0.03, 1.20 | 0, 23.0 |
| Beta-Binomial Meta-Analysis | Estimate | 0.22 | 0 | 0.24 | 0 |
| | 95% CI | 0.01, 3.53 | 0, >9995 | 0.02, 3.54 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.3c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.22 | -0.37 | -0.10 | -0.37 |
| | 95% CI | -1.14, 1.59 | -1.09, 0.35 | -0.84, 0.64 | -1.09, 0.35 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.16 | -0.18 | -0.14 | -0.18 |
| | 95% CI | -0.98, -0.01 | -1.00, 74.3 | -0.96, 0.01 | -1.00, 3.87 |
| Beta-Binomial Meta-Analysis | Estimate | -0.16 | -0.21 | -0.16 | -0.21 |
| | 95% CI | -1.44, 0.17 | -1.11, >9995 | -1.41, 0.16 | -1.08, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.4a Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 156,436) | NE | NE | NE | NE |
| | 95% CI | 0, 0.25 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 2,311) | 0 (0 / 569) | NE | 0 (0 / 5,880) | 0 (0 / 2,132) |
| | 95% CI | 0, 16.6 | 0, 67.1 | NE, NE | 0, 6.53 | 0, 18.0 |
| Swedish National Registries | Estimate | 0.56 (2 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.17 (1 / 59,900) |
| | 95% CI | 0.15, 2.03 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.03, 0.95 |
| GePaRD, Germany | Estimate | 0.88 (6 / 68,232) | 0 (0 / 1,226) | 0.28 (12 / 430,836) | 1.16 (1 / 8,584) | 0.41 (2 / 48,878) |
| | 95% CI | 0.40, 1.92 | 0, 31.2 | 0.16, 0.49 | 0.21, 6.60 | 0.11, 1.49 |
| KfH-QiN, Germany | Estimate | 0 (0 / 612,438) | 0 (0 / 114) | 0 (0 / 2,071,755) | 0 (0 / 958) | 0 (0 / 1,905) |
| | 95% CI | 0, 0.06 | 0, 326 | 0, 0.02 | 0, 39.9 | 0, 20.1 |
| Pooled (Crude) Analysis | Estimate | 0.09 (8 / 875,306) | 2.96 (1 / 3,374) | 0.05 (12 / 2,502,591) | 0.53 (1 / 18,929) | 0.27 (3 / 112,815) |
| | 95% CI | 0.05, 0.18 | 0.52, 16.8 | 0.03, 0.08 | 0.09, 2.99 | 0.09, 0.78 |
| Beta-Binomial Meta-Analysis | Estimate | 0.10 | 2.97 | 0.04 | 0.54 | 0.29 |
| | 95% CI | 0.03, 0.31 | 0.41, 21.1 | 0.01, 0.23 | 0.08, 3.86 | 0.09, 0.98 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.4b Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 3.34 | 40.9 | NE | 0 |
| | 95% CI | 0.44, 25.5 | 4.27, 391 | NE, NE | 0, 65.6 |
| GePaRD, Germany | Estimate | 2.15 | 0 | 0.68 | 2.85 |
| | 95% CI | 0.50, 9.31 | 0, 76.5 | 0.17, 2.72 | 0.37, 21.7 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.34 | 11.1 | 0.18 | 1.99 |
| | 95% CI | 0.10, 1.19 | 1.60, 77.7 | 0.05, 0.59 | 0.28, 13.9 |
| Beta-Binomial Meta-Analysis | Estimate | 0.35 | 10.2 | 0.14 | 1.85 |
| | 95% CI | 0.07, 1.77 | 1.02, 102 | 0.02, 1.10 | 0.18, 18.2 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 2.4c Combined Analysis Across Research Partner Databases By Individual Category - Main Algorithm - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.39 | 6.66 | NE | -0.17 |
| | 95% CI | -0.45, 1.23 | -6.72, 20.0 | NE, NE | -0.49, 0.16 |
| GePaRD, Germany | Estimate | 0.47 | -0.41 | -0.13 | 0.76 |
| | 95% CI | -0.43, 1.37 | -0.98, 0.16 | -0.72, 0.46 | -1.60, 3.11 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.17 | 2.70 | -0.22 | 0.26 |
| | 95% CI | -0.69, 0.02 | 0.22, 16.5 | -0.73, -0.04 | -0.41, 2.73 |
| Beta-Binomial Meta-Analysis | Estimate | -0.19 | 2.68 | -0.25 | 0.25 |
| | 95% CI | -0.86, 0.10 | 0.01, 20.7 | -0.91, 0.01 | -0.59, 3.53 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.1 Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 20.5 (240 / 116,980) | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | -1.71 |
| | 95% CI | 18.1, 23.3 | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | -5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | 20.5 (240 / 116,980) | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | -6.85 |
| | 95% CI | 18.1, 23.3 | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | -13.6, -0.14 |
| SNDS Database, France | Estimate | 0.35 (2 / 57,200) | 0 (0 / 75,512) | NE | 0 (0 / 75,512) | NE | NE |
| | 95% CI | 0.10, 1.27 | 0, 0.51 | NE, NE | 0, 0.51 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 2.82 (11 / 39,002) | 10.3 (6 / 5,825) | 12.5 (3 / 2,393) | 8.74 (3 / 3,432) | 1.43 | 3.80 |
| | 95% CI | 1.57, 5.05 | 4.72, 22.5 | 4.26, 36.8 | 2.97, 25.7 | 0.33, 6.21 | -13.5, 21.1 |
| Swedish National Registries | Estimate | NA | 0.71 (3 / 42,468) | 0 (0 / 1,599) | 0.73 (3 / 40,869) | 0 | -0.73 |
| | 95% CI | NA | 0.24, 2.08 | 0, 24.0 | 0.25, 2.16 | 0, 32.7 | -1.56, 0.10 |
| GePaRD, Germany | Estimate | 3.31 (6 / 18,112) | 0.64 (9 / 140,916) | 0 (0 / 2,346) | 0.65 (9 / 138,570) | 0 | -0.65 |
| | 95% CI | 1.52, 7.23 | 0.34, 1.21 | 0, 16.3 | 0.34, 1.23 | 0, 25.2 | -1.07, -0.23 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 33,619) | 0 (0 / 29) | 0 (0 / 33,590) | NE | 0 |
| | 95% CI | NA | 0, 1.14 | 0, 1170 | 0, 1.14 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 11.2 (259 / 231,294) | 0.62 (19 / 304,210) | 4.69 (3 / 6,387) | 0.54 (16 / 297,813) | 8.74 | 4.16 |
| | 95% CI | 9.92, 12.6 | 0.40, 0.98 | 1.60, 13.8 | 0.33, 0.87 | 2.72, 28.0 | 1.04, 13.3 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 6.45 | 0.63 | 4.59 | 0.58 | 7.95 | 4.02 |
| | 95% CI | 4.98, 8.42 | 0.38, 1.05 | 1.43, 14.8 | 0.28, 1.22 | 2.05, 31.8 | 0.77, 14.3 |
| Pooled (Crude) Analysis (Max) | Estimate | 11.2 (259 / 231,294) | 0.72 (22 / 304,210) | 4.69 (3 / 6,387) | 0.64 (19 / 297,813) | 7.36 | 4.06 |
| | 95% CI | 9.92, 12.6 | 0.48, 1.10 | 1.60, 13.8 | 0.41, 1.00 | 2.32, 23.3 | 0.94, 13.2 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 6.45 | 2.81 | 4.62 | 0.70 | 6.61 | 3.92 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 4.98, 8.42 | 0.60, 13.8 | 1.46, 14.7 | 0.38, 1.31 | 1.83, 24.6 | 0.68, 14.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.2: Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 2,150) | 0 (0 / 10) | 0 (0 / 2,140) | NE | 0 |
| | 95% CI | NA | 0, 17.8 | 0, 3540 | 0, 17.9 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 22,626) | NE | 0 (0 / 22,626) | NE | NE |
| | 95% CI | NA | 0, 1.70 | NE, NE | 0, 1.70 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 1,850) | 0 (0 / 1,066) | 0 (0 / 784) | NE | 0 |
| | 95% CI | NA | 0, 20.7 | 0, 35.9 | 0, 48.8 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.48 (1 / 20,822) | 0 (0 / 760) | 0.50 (1 / 20,062) | 0 | -0.50 |
| | 95% CI | NA | 0.08, 2.72 | 0, 50.3 | 0.09, 2.82 | 0, 101 | -1.48, 0.48 |
| GePaRD, Germany | Estimate | NA | 0.44 (3 / 67,895) | 8.18 (1 / 1,223) | 0.30 (2 / 66,672) | 27.3 | 7.88 |
| | 95% CI | NA | 0.15, 1.30 | 1.44, 46.2 | 0.08, 1.09 | 3.57, 208 | -8.15, 23.9 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 32,756) | 0 (0 / 25) | 0 (0 / 32,731) | NE | 0 |
| | 95% CI | NA | 0, 1.17 | 0, 1330 | 0, 1.17 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.27 (4 / 148,099) | 3.25 (1 / 3,084) | 0.21 (3 / 145,015) | 15.7 | 3.04 |
| | 95% CI | NA | 0.11, 0.69 | 0.57, 18.4 | 0.07, 0.61 | 2.25, 109 | 0.35, 18.2 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.30 | 3.35 | 0.32 | 10.6 | 3.03 |
| | 95% CI | NA | 0.08, 1.09 | 0.48, 23.4 | 0.08, 1.27 | 1.03, 115 | 0.02, 23.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.3: Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 34,760) | 0 (0 / 20) | 0 (0 / 34,750) | NE | 0 |
| | 95% CI | NA | 0, 1.10 | 0, 2040 | 0, 1.11 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 58,298) | NE | 0 (0 / 58,298) | NE | NE |
| | 95% CI | NA | 0, 0.66 | NE, NE | 0, 0.66 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 3,217) | 0 (0 / 2,421) | 0 (0 / 796) | NE | 0 |
| | 95% CI | NA | 0, 11.9 | 0, 15.8 | 0, 48.0 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0 (0 / 37,471) | 0 (0 / 1,148) | 0 (0 / 36,323) | NE | 0 |
| | 95% CI | NA | 0, 1.03 | 0, 33.4 | 0, 1.06 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NA | 0.34 (12 / 348,945) | 0 (0 / 5,015) | 0.35 (12 / 343,930) | 0 | -0.35 |
| | 95% CI | NA | 0.20, 0.60 | 0, 7.65 | 0.20, 0.61 | 0, 21.9 | -0.55, -0.15 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 2,620,795) | 0 (0 / 904) | 0 (0 / 2,619,891) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 42.3 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.04 (12 / 3,103,486) | 0 (0 / 9,508) | 0.04 (12 / 3,093,988) | 0 | -0.04 |
| | 95% CI | NA | 0.02, 0.07 | 0, 4.04 | 0.02, 0.07 | 0, 104 | -0.07, 4.00 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.03 | 0 | 0.03 | 0 | -0.03 |
| | 95% CI | NA | 0.01, 0.14 | 0, >9995 | 0.00, 0.20 | 0, >9995 | -0.14, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 3.4: Combined Analysis Across Research Partner Databases By Dextran Category - Expanded Algorithm - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 5.98 (440 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | -0.23 |
| | 95% CI | 5.44, 6.56 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | -0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 5.98 (440 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | -0.94 |
| | 95% CI | 5.44, 6.56 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | -1.85, -0.02 |
| SNDS Database, France | Estimate | 0.38 (3 / 78,292) | 0 (0 / 156,436) | NE | 0 (0 / 156,436) | NE | NE |
| | 95% CI | 0.13, 1.13 | 0, 0.25 | NE, NE | 0, 0.25 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 1.74 (20 / 114,639) | 5.51 (6 / 10,892) | 5.10 (3 / 5,880) | 5.99 (3 / 5,012) | 0.85 | -0.88 |
| | 95% CI | 1.13, 2.69 | 2.52, 12.0 | 1.74, 15.0 | 2.04, 17.6 | 0.20, 3.69 | -9.78, 8.01 |
| Swedish National Registries | Estimate | NA | 0.40 (4 / 100,761) | 0 (0 / 3,507) | 0.41 (4 / 97,254) | 0 | -0.41 |
| | 95% CI | NA | 0.15, 1.02 | 0, 10.9 | 0.16, 1.06 | 0, 26.6 | -0.81, -0.01 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.43 (24 / 557,756) | 1.16 (1 / 8,584) | 0.42 (23 / 549,172) | 2.78 | 0.75 |
| | 95% CI | 0.74, 2.87 | 0.29, 0.64 | 0.21, 6.60 | 0.28, 0.63 | 0.48, 16.2 | -1.54, 3.04 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 4.79 (471 / 984,000) | 0.10 (35 / 3,555,795) | 2.11 (4 / 18,979) | 0.09 (31 / 3,536,816) | 24.1 | 2.02 |
| | 95% CI | 4.37, 5.24 | 0.07, 0.14 | 0.82, 5.42 | 0.06, 0.12 | 8.86, 65.3 | 0.73, 5.33 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 3.38 | 0.11 | 2.11 | 0.11 | 19.5 | 2.00 |
| | 95% CI | 2.81, 4.09 | 0.07, 0.18 | 0.79, 5.63 | 0.06, 0.22 | 6.06, 65.1 | 0.67, 5.54 |
| Pooled (Crude) Analysis (Max) | Estimate | 4.79 (471 / 984,000) | 0.11 (38 / 3,555,795) | 2.11 (4 / 18,979) | 0.10 (34 / 3,536,816) | 21.9 | 2.01 |
| | 95% CI | 4.37, 5.24 | 0.08, 0.15 | 0.82, 5.42 | 0.07, 0.13 | 8.11, 59.3 | 0.72, 5.32 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Beta-Binomial Meta-Analysis (Max) | Estimate | 3.38 | 0.12 | 2.11 | 0.13 | 16.3 | 1.98 |
| | 95% CI | 2.81, 4.09 | 0.08, 0.19 | 0.79, 5.62 | 0.07, 0.23 | 5.34, 51.5 | 0.65, 5.51 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.1a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 75,512) | NE | NE | NE | NE |
| | 95% CI | 0, 0.51 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 6.27 (1 / 1,594) | 0 (0 / 456) | NE | 12.5 (3 / 2,393) | 14.5 (2 / 1,382) |
| | 95% CI | 1.11, 35.5 | 0, 83.5 | NE, NE | 4.26, 36.8 | 3.97, 52.6 |
| Swedish National Registries | Estimate | 0.51 (1 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.49 (1 / 20,316) |
| | 95% CI | 0.09, 2.91 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.09, 2.79 |
| GePaRD, Germany | Estimate | 1.31 (5 / 38,101) | 0 (0 / 784) | 0.47 (4 / 85,282) | 0 (0 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.56, 3.07 | 0, 48.8 | 0.18, 1.21 | 0, 16.3 | 0, 2.67 |
| KfH-QiN, Germany | Estimate | 0 (0 / 11,982) | 0 (0 / 17) | 0 (0 / 21,386) | 0 (0 / 29) | 0 (0 / 205) |
| | 95% CI | 0, 3.20 | 0, 1840 | 0, 1.80 | 0, 1170 | 0, 184 |
| Pooled (Crude) Analysis | Estimate | 0.48 (7 / 146,674) | 4.30 (1 / 2,325) | 0.37 (4 / 106,668) | 4.71 (3 / 6,367) | 0.83 (3 / 36,306) |
| | 95% CI | 0.23, 0.99 | 0.76, 24.3 | 0.15, 0.96 | 1.60, 13.8 | 0.28, 2.43 |
| Beta-Binomial Meta-Analysis | Estimate | 0.54 | 4.37 | 0.39 | 4.54 | 0.97 |
| | 95% CI | 0.20, 1.50 | 0.60, 31.0 | 0.08, 2.05 | 1.37, 15.4 | 0.28, 3.35 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.1b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.43 | 0 | NE | 0.87 |
| | 95% CI | 0.06, 3.31 | 0, 5.81 | NE, NE | 0.17, 4.33 |
| Swedish National Registries | Estimate | 1.04 | 19.0 | NE | 0 |
| | 95% CI | 0.11, 9.99 | 1.99, 182 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.49, Inf | NE, NE | 0.18, Inf | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.58 | 5.21 | 0.45 | 5.70 |
| | 95% CI | 0.16, 2.05 | 0.75, 36.3 | 0.11, 1.81 | 1.32, 24.7 |
| Beta-Binomial Meta-Analysis | Estimate | 0.56 | 4.52 | 0.41 | 4.70 |
| | 95% CI | 0.12, 2.76 | 0.44, 45.8 | 0.05, 3.10 | 0.83, 26.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.1c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - First Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | -8.20 | -14.5 | NE | -1.94 |
| | 95% CI | -31.7, 15.3 | -34.5, 5.57 | NE, NE | -26.5, 22.6 |
| Swedish National Registries | Estimate | 0.02 | 8.87 | NE | -0.49 |
| | 95% CI | -1.37, 1.41 | -9.50, 27.2 | NE, NE | -1.46, 0.47 |
| GePaRD, Germany | Estimate | 1.31 | 0 | 0.47 | 0 |
| | 95% CI | 0.16, 2.46 | NE, NE | 0.01, 0.93 | NE, NE |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.35 | 3.47 | -0.45 | 3.89 |
| | 95% CI | -1.97, 0.40 | -0.34, 23.5 | -2.07, 0.34 | 0.49, 13.0 |
| Beta-Binomial Meta-Analysis | Estimate | -0.43 | 3.40 | -0.57 | 3.58 |
| | 95% CI | -2.75, 0.74 | -1.19, 29.7 | -2.88, 1.12 | -0.38, 14.3 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.2a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 22,626) | NE | NE | NE | NE |
| | 95% CI | 0, 1.70 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 364) | 0 (0 / 82) | NE | 0 (0 / 1,066) | 0 (0 / 338) |
| | 95% CI | 0, 104 | 0, 448 | NE, NE | 0, 35.9 | 0, 112 |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0 (0 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0, 3.21 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0.22 (1 / 46,021) | 8.18 (1 / 1,223) | 1.38 (1 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0.04, 1.23 | 1.44, 46.2 | 0.24, 7.84 |
| KfH-QiN, Germany | Estimate | 0 (0 / 11,616) | 0 (0 / 13) | 0 (0 / 20,964) | 0 (0 / 25) | 0 (0 / 138) |
| | 95% CI | 0, 3.31 | 0, 2280 | 0, 1.83 | 0, 1330 | 0, 271 |
| Pooled (Crude) Analysis | Estimate | 0.18 (1 / 55,684) | 0 (0 / 537) | 0.15 (1 / 66,985) | 3.25 (1 / 3,074) | 0.51 (1 / 19,669) |
| | 95% CI | 0.03, 1.02 | 0, 71.0 | 0.03, 0.85 | 0.57, 18.4 | 0.09, 2.88 |
| Beta-Binomial Meta-Analysis | Estimate | 0.18 | 0 | 0.16 | 3.26 | 0.52 |
| | 95% CI | 0.03, 1.32 | 0, NE | 0.02, 1.15 | 0.47, 23.3 | 0.07, 3.70 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.2b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Second Dispensing or Administration - Relative Risk**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.28 | 0 | NE | 0 |
| | 95% CI | -1.22, 3.77 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | -1.38 | -1.38 | -1.17 | 6.79 |
| | 95% CI | -4.10, 1.33 | -4.10, 1.33 | -3.91, 1.58 | -9.46, 23.0 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.33 | -0.51 | -0.36 | 2.74 |
| | 95% CI | -2.71, 0.58 | -2.88, 70.5 | -2.73, 0.42 | -0.56, 17.9 |
| Beta-Binomial Meta-Analysis | Estimate | -0.33 | -0.52 | -0.36 | 2.74 |
| | 95% CI | -3.40, 0.82 | NE, NE | -3.40, 0.64 | -1.45, 22.5 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.2c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Second Dispensing or Administration - Risk Difference**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.40, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0.16 | 5.90 |
| | 95% CI | 0, 2.10 | 0, 142 | 0.02, 1.50 | 0.62, 56.5 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.35 | 0 | 0.29 | 6.40 |
| | 95% CI | 0.04, 3.38 | 0, 141 | 0.03, 2.81 | 0.67, 61.3 |
| Beta-Binomial Meta-Analysis | Estimate | 0.36 | 0 | 0.30 | 6.32 |
| | 95% CI | 0.02, 5.66 | 0, NE | 0.02, 4.72 | 0.39, 97.8 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.3a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 58,298) | NE | NE | NE | NE |
| | 95% CI | 0, 0.66 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 31) | NE | 0 (0 / 2,421) | 0 (0 / 412) |
| | 95% CI | 0, 108 | 0, 1100 | NE, NE | 0, 15.8 | 0, 92.4 |
| Swedish National Registries | Estimate | 0 (0 / 8,562) | 0 (0 / 149) | NE | 0 (0 / 1,148) | 0 (0 / 27,612) |
| | 95% CI | 0, 4.48 | 0, 251 | NE, NE | 0, 33.4 | 0, 1.39 |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.33 (10 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.18, 0.61 | 0, 7.65 | 0.06, 2.08 |
| KfH-QiN, Germany | Estimate | 0 (0 / 588,840) | 0 (0 / 84) | 0 (0 / 2,029,405) | 0 (0 / 904) | 0 (0 / 1,562) |
| | 95% CI | 0, 0.07 | 0, 437 | 0, 0.02 | 0, 42.3 | 0, 24.5 |
| Pooled (Crude) Analysis | Estimate | 0.01 (1 / 672,948) | 0 (0 / 512) | 0.04 (10 / 2,328,938) | 0 (0 / 9,488) | 0.18 (1 / 56,840) |
| | 95% CI | 0.00, 0.08 | 0, 74.5 | 0.02, 0.08 | 0, 4.05 | 0.03, 1.00 |
| Beta-Binomial Meta-Analysis | Estimate | 0.05 | 0 | 0.06 | 0 | 0.21 |
| | 95% CI | 0.01, 0.34 | 0, >9995 | 0.01, 0.37 | 0, >9995 | 0.03, 1.52 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.3b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.61 | 0 | 0.91 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.15, 5.51 | 0, 20.9 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.08 | 0 | 0.24 | 0 |
| | 95% CI | 0.01, 0.81 | 0, 426 | 0.04, 1.48 | 0, 23.0 |
| Beta-Binomial Meta-Analysis | Estimate | 0.23 | 0 | 0.27 | 0 |
| | 95% CI | 0.02, 3.59 | 0, >9995 | 0.02, 3.83 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.3c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.22 | -0.37 | -0.03 | -0.37 |
| | 95% CI | -1.14, 1.59 | -1.09, 0.35 | -0.78, 0.72 | -1.09, 0.35 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.16 | -0.18 | -0.13 | -0.18 |
| | 95% CI | -0.98, -0.01 | -1.00, 74.3 | -0.95, 0.02 | -1.00, 3.87 |
| Beta-Binomial Meta-Analysis | Estimate | -0.16 | -0.21 | -0.16 | -0.21 |
| | 95% CI | -1.45, 0.17 | -1.12, >9995 | -1.41, 0.18 | -1.09, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.4a: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 156,436) | NE | NE | NE | NE |
| | 95% CI | 0, 0.25 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 4.33 (1 / 2,311) | 0 (0 / 569) | NE | 5.10 (3 / 5,880) | 9.38 (2 / 2,132) |
| | 95% CI | 0.76, 24.5 | 0, 67.1 | NE, NE | 1.74, 15.0 | 2.57, 34.1 |
| Swedish National Registries | Estimate | 0.56 (2 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.17 (1 / 59,900) |
| | 95% CI | 0.15, 2.03 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.03, 0.95 |
| GePaRD, Germany | Estimate | 0.88 (6 / 68,232) | 0 (0 / 1,226) | 0.35 (15 / 430,836) | 1.16 (1 / 8,584) | 0.41 (2 / 48,878) |
| | 95% CI | 0.40, 1.92 | 0, 31.2 | 0.21, 0.57 | 0.21, 6.60 | 0.11, 1.49 |
| KfH-QiN, Germany | Estimate | 0 (0 / 612,438) | 0 (0 / 114) | 0 (0 / 2,071,755) | 0 (0 / 958) | 0 (0 / 1,905) |
| | 95% CI | 0, 0.06 | 0, 326 | 0, 0.02 | 0, 39.9 | 0, 20.1 |
| Pooled (Crude) Analysis | Estimate | 0.10 (9 / 875,306) | 2.96 (1 / 3,374) | 0.06 (15 / 2,502,591) | 2.11 (4 / 18,929) | 0.44 (5 / 112,815) |
| | 95% CI | 0.05, 0.20 | 0.52, 16.8 | 0.04, 0.10 | 0.82, 5.43 | 0.19, 1.04 |
| Beta-Binomial Meta-Analysis | Estimate | 0.13 | 2.97 | 0.04 | 2.11 | 0.48 |
| | 95% CI | 0.05, 0.31 | 0.41, 21.1 | 0.01, 0.23 | 0.79, 5.74 | 0.19, 1.21 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.4b: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.46 | 0 | NE | 0.54 |
| | 95% CI | 0.06, 3.52 | 0, 7.18 | NE, NE | 0.11, 2.72 |
| Swedish National Registries | Estimate | 3.34 | 40.9 | NE | 0 |
| | 95% CI | 0.44, 25.5 | 4.27, 391 | NE, NE | 0, 65.6 |
| GePaRD, Germany | Estimate | 2.15 | 0 | 0.85 | 2.85 |
| | 95% CI | 0.50, 9.31 | 0, 76.5 | 0.22, 3.34 | 0.37, 21.7 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.23 | 6.69 | 0.14 | 4.77 |
| | 95% CI | 0.08, 0.66 | 1.04, 43.1 | 0.05, 0.36 | 1.39, 16.4 |
| Beta-Binomial Meta-Analysis | Estimate | 0.26 | 6.16 | 0.09 | 4.37 |
| | 95% CI | 0.07, 0.94 | 0.70, 53.0 | 0.01, 0.56 | 1.13, 16.6 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 4.4c: Combined Analysis Across Research Partner Databases By Individual Category - Expanded Algorithm - Any Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | -5.05 | -9.38 | NE | -4.28 |
| | 95% CI | -20.6, 10.5 | -22.4, 3.61 | NE, NE | -18.5, 9.94 |
| Swedish National Registries | Estimate | 0.39 | 6.66 | NE | -0.17 |
| | 95% CI | -0.45, 1.23 | -6.72, 20.0 | NE, NE | -0.49, 0.16 |
| GePaRD, Germany | Estimate | 0.47 | -0.41 | -0.06 | 0.76 |
| | 95% CI | -0.43, 1.37 | -0.98, 0.16 | -0.65, 0.53 | -1.60, 3.11 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.34 | 2.52 | -0.38 | 1.67 |
| | 95% CI | -0.94, -0.07 | 0.02, 16.3 | -0.98, -0.13 | 0.27, 5.00 |
| Beta-Binomial Meta-Analysis | Estimate | -0.36 | 2.49 | -0.44 | 1.63 |
| | 95% CI | -1.07, -0.01 | -0.20, 20.5 | -1.14, -0.11 | 0.11, 5.21 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 5: Combined Analysis Across Research Partner Databases By IV Penicillin Subtype - Main Algorithm - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 Natural Penicillins | IP per 10,000 Betalactamase Resistant Penicillins | IP per 10,000 Aminopenicillins | IP per 10,000 Carboxypenicillins | IP per 10,000 Ureidopenicillins | IP per 10,000 Other Penicillins |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.27 (1 / 36,510) | 0.26 (1 / 38,730) | 0 (0 / 6,220) | 0 (0 / 4) | 3.50 (10 / 28,560) | 1.44 (1 / 6,970) |
| | 95% CI | 0.05, 1.55 | 0.05, 1.46 | 0, 6.17 | 0, 4900 | 1.90, 6.45 | 0.25, 8.13 |
| Danish Central Region EMR Database (Max) | Estimate | 1.10 (4 / 36,510) | 1.03 (4 / 38,730) | 0 (0 / 6,220) | 0 (0 / 1) | 3.50 (10 / 28,560) | 5.74 (4 / 6,970) |
| | 95% CI | 0.43, 2.82 | 0.40, 2.66 | 0, 6.17 | 0, 7930 | 1.90, 6.45 | 2.23, 14.8 |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 11,739) | 2.35 (2 / 8,508) | 0.64 (1 / 15,583) | NE | 0 (0 / 2,935) | NE |
| | 95% CI | 0, 3.27 | 0.64, 8.57 | 0.11, 3.63 | NE, NE | 0, 13.1 | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 4.18 (5 / 11,950) | 0 (0 / 310) | 0 (0 / 4,581) | NE | 8.05 (1 / 1,243) | NE |
| | 95% CI | 1.79, 9.79 | 0, 122 | 0, 8.38 | NE, NE | 1.42, 45.4 | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 1.00 (6 / 60,199) | 0.63 (3 / 47,548) | 0.38 (1 / 26,384) | 0 (0 / 4) | 3.36 (11 / 32,738) | 1.44 (1 / 6,970) |
| | 95% CI | 0.46, 2.17 | 0.21, 1.86 | 0.07, 2.15 | 0, 4900 | 1.88, 6.02 | 0.25, 8.13 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 1.00 | 0.97 | 0.49 | NE | 3.48 | NE |
| | 95% CI | 0.32, 3.30 | 0.27, 3.49 | 0.07, 3.49 | NE, NE | 1.44, 8.37 | NE, NE |
| Pooled (Crude) Analysis (Max) | Estimate | 1.50 (9 / 60,199) | 1.26 (6 / 47,548) | 0.38 (1 / 26,384) | 0 (0 / 1) | 3.36 (11 / 32,738) | 5.74 (4 / 6,970) |
| | 95% CI | 0.79, 2.84 | 0.58, 2.75 | 0.07, 2.15 | 0, 7930 | 1.88, 6.02 | 2.23, 14.8 |

| Database | Statistic | IP per 10,000 Natural Penicillins | IP per 10,000 Betalactamase Resistant Penicillins | IP per 10,000 Aminopenicillins | IP per 10,000 Carboxypenicillins | IP per 10,000 Ureidopenicillins | IP per 10,000 Other Penicillins |
|---|---|---|---|---|---|---|---|
| Beta-Binomial Meta-Analysis (Max) | Estimate | 1.54 | 1.46 | 0.43 | NE | 3.40 | NE |
| | 95% CI | 0.69, 3.50 | 0.58, 3.74 | 0.06, 3.04 | NE, NE | 1.61, 7.17 | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.1: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | NA | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | -1.71 |
| | 95% CI | NA | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | -5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | NA | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | -6.85 |
| | 95% CI | NA | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | -13.6, -0.14 |
| SNDS Database, France | Estimate | NA | 0.40 (3 / 75,512) | NE | 0.40 (3 / 75,512) | NE | NE |
| | 95% CI | NA | 0.14, 1.17 | NE, NE | 0.14, 1.17 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 5,825) | 0 (0 / 2,393) | 0 (0 / 3,432) | NE | 0 |
| | 95% CI | NA | 0, 6.59 | 0, 16.0 | 0, 11.2 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 1.18 (5 / 42,468) | 0 (0 / 1,599) | 1.22 (5 / 40,869) | 0 | -1.22 |
| | 95% CI | NA | 0.50, 2.76 | 0, 24.0 | 0.52, 2.86 | 0, 19.6 | -2.30, -0.15 |
| GePaRD, Germany | Estimate | NA | 1.06 (15 / 140,916) | 4.26 (1 / 2,346) | 1.01 (14 / 138,570) | 4.22 | 3.25 |
| | 95% CI | NA | 0.65, 1.76 | 0.75, 24.1 | 0.60, 1.70 | 0.71, 25.1 | -5.12, 11.6 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 33,619) | 0 (0 / 29) | 0 (0 / 33,590) | NE | 0 |
| | 95% CI | NA | 0, 1.14 | 0, 1170 | 0, 1.14 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | NA | 0.79 (24 / 304,210) | 1.56 (1 / 6,387) | 0.77 (23 / 297,813) | 2.03 | 0.79 |
| | 95% CI | NA | 0.53, 1.17 | 0.28, 8.86 | 0.51, 1.16 | 0.35, 11.8 | -0.57, 8.09 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | NA | 0.74 | 1.62 | 0.77 | 2.11 | 0.85 |
| | 95% CI | NA | 0.43, 1.29 | 0.23, 11.3 | 0.37, 1.62 | 0.27, 17.0 | -0.80, 10.6 |
| Pooled (Crude) Analysis (Max) | Estimate | NA | 0.89 (27 / 304,210) | 1.56 (1 / 6,387) | 0.87 (26 / 297,813) | 1.79 | 0.69 |
| | 95% CI | NA | 0.61, 1.29 | 0.28, 8.86 | 0.60, 1.28 | 0.31, 10.4 | -0.67, 7.99 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | NA | 0.88 | 1.61 | 0.93 | 1.74 | 0.68 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | NA | 0.56, 1.39 | 0.23, 11.2 | 0.50, 1.75 | 0.23, 13.4 | -0.95, 10.4 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.2: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 2,150) | 0 (0 / 10) | 0 (0 / 2,140) | NE | 0 |
| | 95% CI | NA | 0, 17.8 | 0, 3540 | 0, 17.9 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0 (0 / 22,626) | NE | 0 (0 / 22,626) | NE | NE |
| | 95% CI | NA | 0, 1.70 | NE, NE | 0, 1.70 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 1,850) | 0 (0 / 1,066) | 0 (0 / 784) | NE | 0 |
| | 95% CI | NA | 0, 20.7 | 0, 35.9 | 0, 48.8 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0.96 (2 / 20,822) | 0 (0 / 760) | 1.00 (2 / 20,062) | 0 | -1.00 |
| | 95% CI | NA | 0.26, 3.50 | 0, 50.3 | 0.27, 3.63 | 0, 50.6 | -2.38, 0.38 |
| GePaRD, Germany | Estimate | NA | 0.88 (6 / 67,895) | 8.18 (1 / 1,223) | 0.75 (5 / 66,672) | 10.9 | 7.43 |
| | 95% CI | NA | 0.41, 1.93 | 1.44, 46.2 | 0.32, 1.76 | 1.69, 70.3 | -8.61, 23.5 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 32,756) | 0 (0 / 25) | 0 (0 / 32,731) | NE | 0 |
| | 95% CI | NA | 0, 1.17 | 0, 1330 | 0, 1.17 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.54 (8 / 148,099) | 3.25 (1 / 3,084) | 0.48 (7 / 145,015) | 6.72 | 2.76 |
| | 95% CI | NA | 0.27, 1.07 | 0.57, 18.4 | 0.23, 1.00 | 1.08, 41.9 | 0.05, 17.9 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.46 | 3.39 | 0.50 | 6.76 | 2.88 |
| | 95% CI | NA | 0.15, 1.45 | 0.49, 23.6 | 0.14, 1.86 | 0.69, 70.1 | -0.30, 23.2 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.3: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | 0 (0 / 34,760) | 0 (0 / 20) | 0 (0 / 34,750) | NE | 0 |
| | 95% CI | NA | 0, 1.10 | 0, 2040 | 0, 1.11 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NA | 0.17 (1 / 58,298) | NE | 0.17 (1 / 58,298) | NE | NE |
| | 95% CI | NA | 0.03, 0.97 | NE, NE | 0.03, 0.97 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NA | 0 (0 / 3,217) | 0 (0 / 2,421) | 0 (0 / 796) | NE | 0 |
| | 95% CI | NA | 0, 11.9 | 0, 15.8 | 0, 48.0 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NA | 0 (0 / 37,471) | 0 (0 / 1,148) | 0 (0 / 36,323) | NE | 0 |
| | 95% CI | NA | 0, 1.03 | 0, 33.4 | 0, 1.06 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NA | 0.52 (18 / 348,945) | 0 (0 / 5,015) | 0.52 (18 / 343,930) | 0 | -0.52 |
| | 95% CI | NA | 0.33, 0.82 | 0, 7.65 | 0.33, 0.83 | 0, 14.6 | -0.77, -0.28 |
| KfH-QiN, Germany | Estimate | NA | 0 (0 / 2,620,795) | 0 (0 / 904) | 0 (0 / 2,619,891) | NE | 0 |
| | 95% CI | NA | 0, 0.01 | 0, 42.3 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NA | 0.06 (19 / 3,103,486) | 0 (0 / 9,508) | 0.06 (19 / 3,093,988) | 0 | -0.06 |
| | 95% CI | NA | 0.04, 0.10 | 0, 4.04 | 0.04, 0.10 | 0, 65.8 | -0.10, 3.98 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.05 | 0 | 0.06 | 0 | -0.06 |
| | 95% CI | NA | 0.02, 0.15 | 0, >9995 | 0.02, 0.22 | 0, >9995 | -0.17, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 6.4: Combined Analysis Across Research Partner Databases By Dextran Category - 7 Day Risk Window - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.41 (30 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | -0.23 |
| | 95% CI | 0.29, 0.58 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | -0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 0.41 (30 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | -0.94 |
| | 95% CI | 0.29, 0.58 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | -1.85, -0.02 |
| SNDS Database, France | Estimate | 0.77 (6 / 78,292) | 0.26 (4 / 156,436) | NE | 0.26 (4 / 156,436) | NE | NE |
| | 95% CI | 0.35, 1.67 | 0.10, 0.66 | NE, NE | 0.10, 0.66 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0.35 (4 / 114,639) | 0 (0 / 10,892) | 0 (0 / 5,880) | 0 (0 / 5,012) | NE | 0 |
| | 95% CI | 0.14, 0.90 | 0, 3.53 | 0, 6.53 | 0, 7.66 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | 0.69 (7 / 100,761) | 0 (0 / 3,507) | 0.72 (7 / 97,254) | 0 | -0.72 |
| | 95% CI | NE, NE | 0.34, 1.43 | 0, 10.9 | 0.35, 1.49 | 0, 15.2 | -1.25, -0.19 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.70 (39 / 557,756) | 2.33 (2 / 8,584) | 0.67 (37 / 549,172) | 3.46 | 1.66 |
| | 95% CI | 0.74, 2.87 | 0.51, 0.96 | 0.64, 8.49 | 0.49, 0.93 | 0.92, 13.0 | -1.58, 4.89 |
| KfH-QiN, Germany | Estimate | NE | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | NE, NE | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.52 (48 / 984,000) | 0.14 (51 / 3,555,795) | 1.05 (2 / 18,979) | 0.14 (49 / 3,536,816) | 7.61 | 0.92 |
| | 95% CI | 0.39, 0.68 | 0.11, 0.19 | 0.29, 3.84 | 0.10, 0.18 | 2.04, 28.4 | 0.15, 3.70 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 0.53 | 0.15 | 1.05 | 0.16 | 6.68 | 0.89 |
| | 95% CI | 0.40, 0.71 | 0.09, 0.24 | 0.26, 4.26 | 0.08, 0.30 | 1.47, 31.0 | 0.09, 4.11 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.52 (48 / 984,000) | 0.15 (54 / 3,555,795) | 1.05 (2 / 18,979) | 0.15 (52 / 3,536,816) | 7.17 | 0.91 |
| | 95% CI | 0.39, 0.68 | 0.12, 0.20 | 0.29, 3.84 | 0.11, 0.19 | 1.92, 26.7 | 0.14, 3.70 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 0.53 | 0.17 | 1.05 | 0.19 | 5.66 | 0.86 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.40, 0.71 | 0.11, 0.25 | 0.26, 4.25 | 0.11, 0.32 | 1.29, 25.5 | 0.06, 4.07 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.1a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0.40 (3 / 75,512) | NE | NE | NE | NE |
| | 95% CI | 0.14, 1.17 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,594) | 0 (0 / 456) | NE | 0 (0 / 2,393) | 0 (0 / 1,382) |
| | 95% CI | 0, 24.0 | 0, 83.5 | NE, NE | 0, 16.0 | 0, 27.7 |
| Swedish National Registries | Estimate | 1.03 (2 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.98 (2 / 20,316) |
| | 95% CI | 0.28, 3.74 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.27, 3.59 |
| GePaRD, Germany | Estimate | 1.84 (7 / 38,101) | 12.8 (1 / 784) | 0.70 (6 / 85,282) | 4.26 (1 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.89, 3.79 | 2.25, 71.9 | 0.32, 1.54 | 0.75, 24.1 | 0, 2.67 |
| KfH-QiN, Germany | Estimate | 0 (0 / 11,982) | 0 (0 / 17) | 0 (0 / 21,386) | 0 (0 / 29) | 0 (0 / 205) |
| | 95% CI | 0, 3.20 | 0, 1840 | 0, 1.80 | 0, 1170 | 0, 184 |
| Pooled (Crude) Analysis | Estimate | 0.82 (12 / 146,674) | 8.60 (2 / 2,325) | 0.56 (6 / 106,668) | 1.57 (1 / 6,367) | 0.55 (2 / 36,306) |
| | 95% CI | 0.47, 1.43 | 2.36, 31.3 | 0.26, 1.23 | 0.28, 8.89 | 0.15, 2.01 |
| Beta-Binomial Meta-Analysis | Estimate | 0.91 | 8.76 | 0.52 | 1.65 | 0.58 |
| | 95% CI | 0.39, 2.15 | 2.17, 35.0 | 0.11, 2.52 | 0.24, 11.8 | 0.10, 3.22 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.1b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.04 | 9.51 | NE | 0 |
| | 95% CI | 0.18, 5.91 | 1.25, 72.5 | NE, NE | 0, 24.4 |
| GePaRD, Germany | Estimate | Inf | Inf | Inf | Inf |
| | 95% CI | 0.69, Inf | 4.78, Inf | 0.26, Inf | 1.60, Inf |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.49 | 15.6 | 1.02 | 2.85 |
| | 95% CI | 0.37, 5.93 | 2.76, 88.4 | 0.24, 4.42 | 0.37, 21.8 |
| Beta-Binomial Meta-Analysis | Estimate | 1.58 | 15.2 | 0.90 | 2.85 |
| | 95% CI | 0.24, 10.6 | 1.63, 133 | 0.09, 8.89 | 0.21, 37.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 7.1c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - First Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.04 | 8.38 | NE | -0.98 |
| | 95% CI | -1.93, 2.01 | -10.0, 26.8 | NE, NE | -2.35, 0.38 |
| GePaRD, Germany | Estimate | 1.84 | 12.8 | 0.70 | 4.26 |
| | 95% CI | 0.48, 3.20 | -12.2, 37.7 | 0.14, 1.27 | -4.09, 12.6 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.27 | 8.05 | 0.01 | 1.02 |
| | 95% CI | -1.22, 1.02 | 1.72, 30.8 | -1.47, 0.80 | -0.87, 8.35 |
| Beta-Binomial Meta-Analysis | Estimate | 0.33 | 8.18 | -0.06 | 1.07 |
| | 95% CI | -2.25, 1.64 | 1.07, 33.8 | -2.61, 1.86 | -1.86, 11.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.2a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 22,626) | NE | NE | NE | NE |
| | 95% CI | 0, 1.70 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 364) | 0 (0 / 82) | NE | 0 (0 / 1,066) | 0 (0 / 338) |
| | 95% CI | 0, 104 | 0, 448 | NE, NE | 0, 35.9 | 0, 112 |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0.84 (1 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0.15, 4.73 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0.65 (3 / 46,021) | 8.18 (1 / 1,223) | 2.77 (2 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0.22, 1.92 | 1.44, 46.2 | 0.76, 10.1 |
| KfH-QiN, Germany | Estimate | 0 (0 / 11,616) | 0 (0 / 13) | 0 (0 / 20,964) | 0 (0 / 25) | 0 (0 / 138) |
| | 95% CI | 0, 3.31 | 0, 2280 | 0, 1.83 | 0, 1330 | 0, 271 |
| Pooled (Crude) Analysis | Estimate | 0.18 (1 / 55,684) | 0 (0 / 537) | 0.45 (3 / 66,985) | 3.25 (1 / 3,074) | 1.53 (3 / 19,669) |
| | 95% CI | 0.03, 1.02 | 0, 71.0 | 0.15, 1.32 | 0.57, 18.4 | 0.52, 4.48 |
| Beta-Binomial Meta-Analysis | Estimate | 0.21 | 0 | 0.44 | 3.29 | 1.61 |
| | 95% CI | 0.03, 1.50 | 0, NE | 0.10, 2.02 | 0.48, 23.5 | 0.50, 5.26 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.2b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.53 | 0 | NE | 0 |
| | 95% CI | 0.16, 14.6 | 0, 185 | NE, NE | 0, 60.5 |
| GePaRD, Germany | Estimate | 0 | 0 | 0.24 | 2.95 |
| | 95% CI | 0, 1.05 | 0, 71.0 | 0.05, 1.18 | 0.39, 22.5 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.12 | 0 | 0.29 | 2.13 |
| | 95% CI | 0.02, 0.82 | 0, 46.8 | 0.07, 1.27 | 0.31, 14.9 |
| Beta-Binomial Meta-Analysis | Estimate | 0.13 | 0 | 0.27 | 2.04 |
| | 95% CI | 0.01, 1.28 | 0, NE | 0.04, 1.81 | 0.20, 19.7 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.2c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.44 | -0.84 | NE | -0.84 |
| | 95% CI | -2.55, 3.43 | -2.47, 0.80 | NE, NE | -2.47, 0.80 |
| GePaRD, Germany | Estimate | -2.77 | -2.77 | -2.12 | 5.41 |
| | 95% CI | -6.61, 1.07 | -6.61, 1.07 | -6.03, 1.79 | -11.1, 21.9 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -1.35 | -1.53 | -1.08 | 1.73 |
| | 95% CI | -4.31, -0.15 | -4.48, 69.5 | -4.05, 0.21 | -2.23, 16.9 |
| Beta-Binomial Meta-Analysis | Estimate | -1.41 | -1.61 | -1.17 | 1.67 |
| | 95% CI | -4.92, 0.24 | NE, NE | -4.69, 0.65 | -3.02, 21.7 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.3a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0.17 (1 / 58,298) | NE | NE | NE | NE |
| | 95% CI | 0.03, 0.97 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 31) | NE | 0 (0 / 2,421) | 0 (0 / 412) |
| | 95% CI | 0, 108 | 0, 1100 | NE, NE | 0, 15.8 | 0, 92.4 |
| Swedish National Registries | Estimate | 0 (0 / 8,562) | 0 (0 / 149) | NE | 0 (0 / 1,148) | 0 (0 / 27,612) |
| | 95% CI | 0, 4.48 | 0, 251 | NE, NE | 0, 33.4 | 0, 1.39 |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.53 (16 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.33, 0.87 | 0, 7.65 | 0.06, 2.08 |
| KfH-QiN, Germany | Estimate | 0 (0 / 588,840) | 0 (0 / 84) | 0 (0 / 2,029,405) | 0 (0 / 904) | 0 (0 / 1,562) |
| | 95% CI | 0, 0.07 | 0, 437 | 0, 0.02 | 0, 42.3 | 0, 24.5 |
| Pooled (Crude) Analysis | Estimate | 0.03 (2 / 672,948) | 0 (0 / 512) | 0.07 (16 / 2,328,938) | 0 (0 / 9,488) | 0.18 (1 / 56,840) |
| | 95% CI | 0.01, 0.11 | 0, 74.5 | 0.04, 0.11 | 0, 4.05 | 0.03, 1.00 |
| Beta-Binomial Meta-Analysis | Estimate | 0.10 | 0 | 0.07 | 0 | 0.21 |
| | 95% CI | 0.02, 0.39 | 0, >9995 | 0.01, 0.42 | 0, >9995 | 0.03, 1.52 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.3b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 1.61 | 0 | 1.46 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.25, 8.61 | 0, 20.9 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.17 | 0 | 0.39 | 0 |
| | 95% CI | 0.02, 1.29 | 0, 426 | 0.07, 2.31 | 0, 23.0 |
| Beta-Binomial Meta-Analysis | Estimate | 0.45 | 0 | 0.31 | 0 |
| | 95% CI | 0.04, 4.99 | 0, >9995 | 0.02, 4.43 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.3c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.22 | -0.37 | 0.17 | -0.37 |
| | 95% CI | -1.14, 1.59 | -1.09, 0.35 | -0.60, 0.93 | -1.09, 0.35 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.15 | -0.18 | -0.11 | -0.18 |
| | 95% CI | -0.97, 0.01 | -1.00, 74.3 | -0.93, 0.04 | -1.00, 3.87 |
| Beta-Binomial Meta-Analysis | Estimate | -0.12 | -0.21 | -0.15 | -0.21 |
| | 95% CI | -1.41, 0.23 | -1.12, >9995 | -1.40, 0.23 | -1.09, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.4a: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0.26 (4 / 156,436) | NE | NE | NE | NE |
| | 95% CI | 0.10, 0.66 | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 2,311) | 0 (0 / 569) | NE | 0 (0 / 5,880) | 0 (0 / 2,132) |
| | 95% CI | 0, 16.6 | 0, 67.1 | NE, NE | 0, 6.53 | 0, 18.0 |
| Swedish National Registries | Estimate | 0.84 (3 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.50 (3 / 59,900) |
| | 95% CI | 0.28, 2.46 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.17, 1.47 |
| GePaRD, Germany | Estimate | 1.17 (8 / 68,232) | 8.16 (1 / 1,226) | 0.58 (25 / 430,836) | 2.33 (2 / 8,584) | 0.61 (3 / 48,878) |
| | 95% CI | 0.59, 2.31 | 1.44, 46.1 | 0.39, 0.86 | 0.64, 8.49 | 0.21, 1.80 |
| KfH-QiN, Germany | Estimate | 0 (0 / 612,438) | 0 (0 / 114) | 0 (0 / 2,071,755) | 0 (0 / 958) | 0 (0 / 1,905) |
| | 95% CI | 0, 0.06 | 0, 326 | 0, 0.02 | 0, 39.9 | 0, 20.1 |
| Pooled (Crude) Analysis | Estimate | 0.17 (15 / 875,306) | 5.93 (2 / 3,374) | 0.10 (25 / 2,502,591) | 1.06 (2 / 18,929) | 0.53 (6 / 112,815) |
| | 95% CI | 0.10, 0.28 | 1.63, 21.6 | 0.07, 0.15 | 0.29, 3.85 | 0.24, 1.16 |
| Beta-Binomial Meta-Analysis | Estimate | 0.22 | 5.95 | 0.06 | 1.05 | 0.56 |
| | 95% CI | 0.11, 0.46 | 1.47, 23.8 | 0.01, 0.29 | 0.26, 4.39 | 0.23, 1.36 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 7.4b: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.67 | 13.6 | NE | 0 |
| | 95% CI | 0.39, 7.23 | 1.95, 95.0 | NE, NE | 0, 21.9 |
| GePaRD, Germany | Estimate | 1.91 | 13.3 | 0.95 | 3.80 |
| | 95% CI | 0.55, 6.63 | 1.90, 92.6 | 0.30, 2.94 | 0.76, 19.0 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.32 | 11.1 | 0.19 | 1.99 |
| | 95% CI | 0.13, 0.80 | 2.57, 48.2 | 0.08, 0.45 | 0.46, 8.60 |
| Beta-Binomial Meta-Analysis | Estimate | 0.39 | 10.7 | 0.10 | 1.88 |
| | 95% CI | 0.13, 1.25 | 2.04, 55.2 | 0.02, 0.62 | 0.35, 9.94 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 7.4c: Combined Analysis Across Research Partner Databases By Individual Category - 7 Day Risk Window - Any Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.34 | 6.33 | NE | -0.50 |
| | 95% CI | -0.77, 1.44 | -7.06, 19.7 | NE, NE | -1.07, 0.07 |
| GePaRD, Germany | Estimate | 0.56 | 7.54 | -0.03 | 1.72 |
| | 95% CI | -0.51, 1.63 | -8.45, 23.5 | -0.76, 0.70 | -1.59, 5.02 |
| KfH-QiN, Germany | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.36 | 5.40 | -0.43 | 0.52 |
| | 95% CI | -0.99, -0.05 | 1.06, 21.1 | -1.06, -0.14 | -0.46, 3.33 |
| Beta-Binomial Meta-Analysis | Estimate | -0.34 | 5.39 | -0.50 | 0.49 |
| | 95% CI | -1.12, 0.07 | 0.81, 23.1 | -1.27, -0.11 | -0.65, 3.77 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 8: Combined Analysis Across Research Partner Databases By Dextran Category - Dialysis Patients Only - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | 0 (0 / 34,700) | NE | 0 (0 / 34,700) | NE | NE |
| | 95% CI | 0, 1.11 | NE, NE | 0, 1.11 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 303) | 0 (0 / 89) | 0 (0 / 214) | NE | 0 |
| | 95% CI | 0, 125 | 0, 414 | 0, 176 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 6,041) | 0 (0 / 185) | 0 (0 / 5,856) | NE | 0 |
| | 95% CI | 0, 6.35 | 0, 203 | 0, 6.56 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.20 (2 / 101,808) | 0 (0 / 1,573) | 0.20 (2 / 100,235) | 0 | -0.20 |
| | 95% CI | 0.05, 0.72 | 0, 24.4 | 0.05, 0.73 | 0, 122 | -0.48, 0.08 |
| KfH-QiN, Germany | Estimate | 0 (0 / 2,687,170) | 0 (0 / 958) | 0 (0 / 2,686,212) | NE | 0 |
| | 95% CI | 0, 0.01 | 0, 39.9 | 0, 0.01 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.01 (2 / 2,830,022) | 0 (0 / 2,805) | 0.01 (2 / 2,827,217) | 0 | -0.01 |
| | 95% CI | 0.00, 0.03 | 0, 13.7 | 0.00, 0.03 | 0, 1940 | -0.03, 13.7 |
| Beta-Binomial Meta-Analysis | Estimate | 0.01 | 0 | 0.02 | 0 | -0.02 |
| | 95% CI | 0.00, 0.09 | 0, >9995 | 0.00, 0.16 | 0, >9995 | -0.11, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.1: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.96 (1 / 5,090) | 0 (0 / 20) | 1.97 (1 / 5,070) | 0 | -1.97 |
| | 95% CI | 0.35, 11.1 | 0, 1430 | 0.35, 11.2 | 0, 819 | -5.84, 1.89 |
| Danish Central Region EMR Database (Max) | Estimate | 7.86 (4 / 5,090) | 0 (0 / 20) | 7.89 (4 / 5,070) | 0 | -7.89 |
| | 95% CI | 3.06, 20.2 | 0, 1430 | 3.07, 20.3 | 0, 195 | -15.6, -0.16 |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 5,689) | 0 (0 / 2,366) | 0 (0 / 3,323) | NE | 0 |
| | 95% CI | 0, 6.75 | 0, 16.2 | 0, 11.5 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.73 (3 / 41,196) | 0 (0 / 1,533) | 0.76 (3 / 39,663) | 0 | -0.76 |
| | 95% CI | 0.25, 2.14 | 0, 25.0 | 0.26, 2.22 | 0, 33.1 | -1.61, 0.10 |
| GePaRD, Germany | Estimate | 0.72 (9 / 124,286) | 0 (0 / 1,885) | 0.74 (9 / 122,401) | 0 | -0.74 |
| | 95% CI | 0.38, 1.38 | 0, 20.3 | 0.39, 1.40 | 0, 27.7 | -1.22, -0.25 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.74 (13 / 176,261) | 0 (0 / 5,804) | 0.76 (13 / 170,457) | 0 | -0.76 |
| | 95% CI | 0.43, 1.26 | 0, 6.61 | 0.45, 1.30 | 0, 8.67 | -1.30, 5.85 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 0.77 | 0 | 1.00 | 0 | -1.00 |
| | 95% CI | 0.41, 1.47 | 0, NE | 0.42, 2.42 | 0, NE | NE, NE |
| Pooled (Crude) Analysis (Max) | Estimate | 0.91 (16 / 176,261) | 0 (0 / 5,804) | 0.94 (16 / 170,457) | 0 | -0.94 |
| | 95% CI | 0.56, 1.47 | 0, 6.61 | 0.58, 1.52 | 0, 7.04 | -1.52, 5.67 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 1.75 | 0 | 1.24 | 0 | -1.24 |
| | 95% CI | 0.71, 4.46 | 0, >9995 | 0.62, 2.53 | 0, >9995 | -2.22, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.2: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | 0 (0 / 1,390) | 0 (0 / 10) | 0 (0 / 1,380) | NE | 0 |
| | 95% CI | 0, 27.7 | 0, 3540 | 0, 27.8 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,802) | 0 (0 / 1,054) | 0 (0 / 748) | NE | 0 |
| | 95% CI | 0, 21.3 | 0, 36.3 | 0, 51.1 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.50 (1 / 20,023) | 0 (0 / 724) | 0.52 (1 / 19,299) | 0 | -0.52 |
| | 95% CI | 0.09, 2.83 | 0, 52.8 | 0.09, 2.93 | 0, 102 | -1.53, 0.50 |
| GePaRD, Germany | Estimate | 0.38 (2 / 53,009) | 12.3 (1 / 816) | 0.19 (1 / 52,193) | 64.0 | 12.1 |
| | 95% CI | 0.10, 1.38 | 2.16, 69.1 | 0.03, 1.09 | 6.68, 612 | -11.9, 36.1 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.39 (3 / 76,224) | 3.84 (1 / 2,604) | 0.27 (2 / 73,620) | 14.2 | 3.57 |
| | 95% CI | 0.13, 1.16 | 0.68, 21.7 | 0.07, 0.99 | 1.85, 108 | 0.36, 21.5 |
| Beta-Binomial Meta-Analysis | Estimate | 0.46 | 3.91 | 0.45 | 8.72 | 3.46 |
| | 95% CI | 0.14, 1.59 | 0.56, 27.3 | 0.11, 1.87 | 0.83, 96.8 | -0.15, 27.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.3: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | 0 (0 / 1,600) | 0 (0 / 20) | 0 (0 / 1,580) | NE | 0 |
| | 95% CI | 0, 24.0 | 0, 2040 | 0, 24.2 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 3,098) | 0 (0 / 2,371) | 0 (0 / 727) | NE | 0 |
| | 95% CI | 0, 12.4 | 0, 16.2 | 0, 52.6 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 33,501) | 0 (0 / 1,065) | 0 (0 / 32,436) | NE | 0 |
| | 95% CI | 0, 1.15 | 0, 35.9 | 0, 1.18 | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0.56 (6 / 106,518) | 0 (0 / 1,459) | 0.57 (6 / 105,059) | 0 | -0.57 |
| | 95% CI | 0.26, 1.23 | 0, 26.3 | 0.26, 1.25 | 0, 46.0 | -1.03, -0.11 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.41 (6 / 144,717) | 0 (0 / 4,915) | 0.43 (6 / 139,802) | 0 | -0.43 |
| | 95% CI | 0.19, 0.90 | 0, 7.82 | 0.20, 0.94 | 0, 18.2 | -0.94, 7.39 |
| Beta-Binomial Meta-Analysis | Estimate | 0.34 | 0 | 0.38 | 0 | -0.38 |
| | 95% CI | 0.08, 1.63 | 0, NE | 0.10, 1.42 | 0, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 9.4: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Dialysis - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.24 (1 / 8,080) | 0 (0 / 50) | 1.25 (1 / 8,030) | 0 | -1.25 |
| | 95% CI | 0.22, 7.01 | 0, 787 | 0.22, 7.05 | 0, 674 | -3.69, 1.20 |
| Danish Central Region EMR Database (Max) | Estimate | 4.95 (4 / 8,080) | 0 (0 / 50) | 4.98 (4 / 8,030) | 0 | -4.98 |
| | 95% CI | 1.93, 12.7 | 0, 787 | 1.94, 12.8 | 0, 164 | -9.86, -0.10 |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 10,589) | 0 (0 / 5,791) | 0 (0 / 4,798) | NE | 0 |
| | 95% CI | 0, 3.63 | 0, 6.63 | 0, 8.00 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.42 (4 / 94,720) | 0 (0 / 3,322) | 0.44 (4 / 91,398) | 0 | -0.44 |
| | 95% CI | 0.16, 1.09 | 0, 11.6 | 0.17, 1.13 | 0, 26.4 | -0.87, -0.01 |
| GePaRD, Germany | Estimate | 0.60 (17 / 283,813) | 2.40 (1 / 4,160) | 0.57 (16 / 279,653) | 4.20 | 1.83 |
| | 95% CI | 0.37, 0.96 | 0.42, 13.6 | 0.35, 0.93 | 0.71, 24.8 | -2.89, 6.55 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis (Min) | Estimate | 0.55 (22 / 397,202) | 0.75 (1 / 13,323) | 0.55 (21 / 383,879) | 1.37 | 0.20 |
| | 95% CI | 0.37, 0.84 | 0.13, 4.25 | 0.36, 0.84 | 0.23, 8.03 | -0.49, 3.71 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 0.56 | 0.79 | 0.64 | 1.24 | 0.15 |
| | 95% CI | 0.32, 0.99 | 0.11, 5.49 | 0.29, 1.41 | 0.16, 10.2 | -0.88, 4.88 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.63 (25 / 397,202) | 0.75 (1 / 13,323) | 0.63 (24 / 383,879) | 1.20 | 0.13 |
| | 95% CI | 0.43, 0.93 | 0.13, 4.25 | 0.42, 0.93 | 0.21, 7.00 | -0.58, 3.63 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 0.65 | 0.78 | 0.79 | 0.99 | -0.01 |
| | 95% CI | 0.42, 1.03 | 0.11, 5.43 | 0.42, 1.51 | 0.13, 7.64 | -1.01, 4.68 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 10.1a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - First Dispensing or Administration - Incidence Proportion

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 1,567) | 0 (0 / 451) | NE | 0 (0 / 2,366) | 0 (0 / 1,305) |
| | 95% CI | 0, 24.5 | 0, 84.5 | NE, NE | 0, 16.2 | 0, 29.4 |
| Swedish National Registries | Estimate | 0.52 (1 / 19,126) | 9.61 (1 / 1,041) | NE | 0 (0 / 1,533) | 0.51 (1 / 19,496) |
| | 95% CI | 0.09, 2.96 | 1.70, 54.2 | NE, NE | 0, 25.0 | 0.09, 2.91 |
| GePaRD, Germany | Estimate | 1.35 (5 / 36,991) | 0 (0 / 718) | 0.55 (4 / 73,007) | 0 (0 / 1,885) | 0 (0 / 11,685) |
| | 95% CI | 0.58, 3.16 | 0, 53.2 | 0.21, 1.41 | 0, 20.3 | 0, 3.29 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 1.04 (6 / 57,684) | 4.52 (1 / 2,210) | 0.55 (4 / 73,007) | 0 (0 / 5,784) | 0.31 (1 / 32,486) |
| | 95% CI | 0.48, 2.27 | 0.80, 25.6 | 0.21, 1.41 | 0, 6.64 | 0.05, 1.74 |
| Beta-Binomial Meta-Analysis | Estimate | 1.04 | 4.55 | 0.63 | 0 | 0.35 |
| | 95% CI | 0.41, 2.74 | 0.63, 32.3 | 0.18, 2.26 | 0, NE | 0.05, 2.48 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.1b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - First Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.02 | 18.7 | NE | 0 |
| | 95% CI | 0.11, 9.76 | 1.96, 179 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.41, Inf | NE, NE | 0.17, Inf | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 3.38 | 14.7 | 1.78 | 0 |
| | 95% CI | 0.53, 21.4 | 1.53, 141 | 0.27, 11.8 | 0, 21.6 |
| Beta-Binomial Meta-Analysis | Estimate | 3.02 | 13.2 | 1.81 | 0 |
| | 95% CI | 0.35, 26.5 | 0.79, 202 | 0.18, 18.7 | 0, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 10.1c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - First Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.01 | 9.09 | NE | -0.51 |
| | 95% CI | -1.43, 1.45 | -9.75, 27.9 | NE, NE | -1.52, 0.49 |
| GePaRD, Germany | Estimate | 1.35 | 0 | 0.55 | 0 |
| | 95% CI | 0.17, 2.54 | NE, NE | 0.01, 1.08 | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.73 | 4.22 | 0.24 | -0.31 |
| | 95% CI | -0.76, 2.01 | 0.37, 25.3 | -1.22, 1.16 | -1.74, 6.33 |
| Beta-Binomial Meta-Analysis | Estimate | 0.70 | 4.21 | 0.28 | -0.35 |
| | 95% CI | -1.42, 2.33 | -0.27, 31.6 | -1.79, 1.84 | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.2a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 353) | 0 (0 / 82) | NE | 0 (0 / 1,054) | 0 (0 / 313) |
| | 95% CI | 0, 108 | 0, 448 | NE, NE | 0, 36.3 | 0, 121 |
| Swedish National Registries | Estimate | 1.30 (1 / 7,705) | 0 (0 / 241) | NE | 0 (0 / 724) | 0 (0 / 11,353) |
| | 95% CI | 0.23, 7.35 | 0, 157 | NE, NE | 0, 52.8 | 0, 3.38 |
| GePaRD, Germany | Estimate | 0 (0 / 12,613) | 0 (0 / 156) | 0 (0 / 34,501) | 12.3 (1 / 816) | 2.03 (1 / 4,923) |
| | 95% CI | 0, 3.04 | 0, 240 | 0, 1.11 | 2.16, 69.1 | 0.36, 11.5 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.48 (1 / 20,671) | 0 (0 / 479) | 0 (0 / 34,501) | 3.86 (1 / 2,594) | 0.60 (1 / 16,589) |
| | 95% CI | 0.09, 2.74 | 0, 79.6 | 0, 1.11 | 0.68, 21.8 | 0.11, 3.41 |
| Beta-Binomial Meta-Analysis | Estimate | 0.49 | 0 | 0 | 3.86 | 0.61 |
| | 95% CI | 0.07, 3.50 | 0, NE | 0, NE | 0.56, 27.5 | 0.08, 4.34 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.2b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.38, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0 | 6.03 |
| | 95% CI | 0, 1.50 | 0, 121 | 0, 0.55 | 0.63, 57.7 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.80 | 0 | 0 | 6.40 |
| | 95% CI | 0.08, 7.69 | 0, 133 | 0, 1.85 | 0.67, 61.2 |
| Beta-Binomial Meta-Analysis | Estimate | 0.80 | 0 | 0 | 6.37 |
| | 95% CI | 0.05, 12.8 | 0, NE | 0, NE | 0.40, 98.5 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.2c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.30 | 0 | NE | 0 |
| | 95% CI | -1.25, 3.84 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | -2.03 | -2.03 | -2.03 | 10.2 |
| | 95% CI | -6.01, 1.95 | -6.01, 1.95 | -6.01, 1.95 | -14.1, 34.6 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | -0.12 | -0.60 | -0.60 | 3.25 |
| | 95% CI | -2.96, 2.19 | -3.41, 79.0 | -3.41, 0.51 | -0.67, 21.2 |
| Beta-Binomial Meta-Analysis | Estimate | -0.12 | -0.61 | -0.61 | 3.25 |
| | 95% CI | -3.68, 2.80 | NE, NE | NE, NE | -1.69, 26.7 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.3a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 341) | 0 (0 / 31) | NE | 0 (0 / 2,371) | 0 (0 / 355) |
| | 95% CI | 0, 111 | 0, 1100 | NE, NE | 0, 16.2 | 0, 107 |
| Swedish National Registries | Estimate | 0 (0 / 8,393) | 0 (0 / 146) | NE | 0 (0 / 1,065) | 0 (0 / 23,897) |
| | 95% CI | 0, 4.57 | 0, 256 | NE, NE | 0, 35.9 | 0, 1.61 |
| GePaRD, Germany | Estimate | 0 (0 / 14,785) | 0 (0 / 98) | 0.73 (6 / 82,106) | 0 (0 / 1,459) | 0 (0 / 8,070) |
| | 95% CI | 0, 2.60 | 0, 377 | 0.33, 1.59 | 0, 26.3 | 0, 4.76 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 23,519) | 0 (0 / 275) | 0.73 (6 / 82,106) | 0 (0 / 4,895) | 0 (0 / 32,322) |
| | 95% CI | 0, 1.63 | 0, 138 | 0.33, 1.59 | 0, 7.84 | 0, 1.19 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 1.02 | 0 | 0 |
| | 95% CI | 0, NE | 0, NE | 0.26, 4.06 | 0, NE | 0, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.3b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NE | NE | Inf | NE |
| | 95% CI | NE, NE | NE, NE | 0.15, Inf | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | NE | NE | Inf | NE |
| | 95% CI | NE, NE | NE, NE | 0.61, Inf | NE, NE |
| Beta-Binomial Meta-Analysis | Estimate | 0.56 | 3.82 | >9995 | 6.05 |
| | 95% CI | 0.56, 0.56 | 3.82, 3.82 | >9995, >9995 | 6.05, 6.05 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 10.3c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Third or Subsequent Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0.73 | 0 |
| | 95% CI | NE, NE | NE, NE | 0.15, 1.32 | NE, NE |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 | 0 | 0.73 | 0 |
| | 95% CI | NE, NE | NE, NE | -0.46, 1.59 | NE, NE |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 1.02 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.4a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 2,261) | 0 (0 / 564) | NE | 0 (0 / 5,791) | 0 (0 / 1,973) |
| | 95% CI | 0, 17.0 | 0, 67.7 | NE, NE | 0, 6.63 | 0, 19.4 |
| Swedish National Registries | Estimate | 0.57 (2 / 35,224) | 7.00 (1 / 1,428) | NE | 0 (0 / 3,322) | 0.18 (1 / 54,746) |
| | 95% CI | 0.16, 2.07 | 1.24, 39.6 | NE, NE | 0, 11.6 | 0.03, 1.03 |
| GePaRD, Germany | Estimate | 0.78 (5 / 64,389) | 0 (0 / 972) | 0.53 (10 / 189,614) | 2.40 (1 / 4,160) | 0.41 (1 / 24,678) |
| | 95% CI | 0.33, 1.82 | 0, 39.4 | 0.29, 0.97 | 0.42, 13.6 | 0.07, 2.30 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.69 (7 / 101,874) | 3.37 (1 / 2,964) | 0.53 (10 / 189,614) | 0.75 (1 / 13,273) | 0.25 (2 / 81,397) |
| | 95% CI | 0.33, 1.42 | 0.60, 19.1 | 0.29, 0.97 | 0.13, 4.27 | 0.07, 0.90 |
| Beta-Binomial Meta-Analysis | Estimate | 0.77 | 3.42 | 0.65 | 0.80 | 0.36 |
| | 95% CI | 0.29, 2.09 | 0.47, 24.3 | 0.20, 2.27 | 0.12, 5.71 | 0.09, 1.46 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 10.4b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 3.11 | 38.3 | NE | 0 |
| | 95% CI | 0.41, 23.7 | 4.00, 367 | NE, NE | 0, 63.3 |
| GePaRD, Germany | Estimate | 1.92 | 0 | 1.30 | 5.93 |
| | 95% CI | 0.30, 12.4 | 0, 97.5 | 0.21, 7.89 | 0.62, 56.8 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 2.80 | 13.7 | 2.15 | 3.07 |
| | 95% CI | 0.66, 11.8 | 1.80, 105 | 0.53, 8.71 | 0.40, 23.4 |
| Beta-Binomial Meta-Analysis | Estimate | 2.12 | 9.41 | 1.79 | 2.19 |
| | 95% CI | 0.40, 11.6 | 0.83, 103 | 0.30, 11.3 | 0.20, 23.3 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 10.4c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Dialysis - Any Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 | 0 | NE | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.39 | 6.82 | NE | -0.18 |
| | 95% CI | -0.48, 1.25 | -6.90, 20.5 | NE, NE | -0.54, 0.18 |
| GePaRD, Germany | Estimate | 0.37 | -0.41 | 0.12 | 2.00 |
| | 95% CI | -0.67, 1.42 | -1.20, 0.39 | -0.74, 0.98 | -2.78, 6.78 |
| KfH-QiN, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.44 | 3.13 | 0.28 | 0.51 |
| | 95% CI | -0.27, 1.21 | 0.31, 18.8 | -0.40, 0.77 | -0.36, 4.03 |
| Beta-Binomial Meta-Analysis | Estimate | 0.41 | 3.06 | 0.29 | 0.43 |
| | 95% CI | -0.75, 1.70 | -0.12, 23.8 | -0.88, 1.85 | -0.86, 5.27 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.1: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - First Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 1.71 (20 / 116,980) | 1.71 (1 / 5,870) | 0 (0 / 20) | 1.71 (1 / 5,840) | 0 | -1.71 |
| | 95% CI | 1.11, 2.64 | 0.30, 9.65 | 0, 1430 | 0.30, 9.69 | 0, 943 | -5.07, 1.64 |
| Danish Central Region EMR Database (Max) | Estimate | 1.71 (20 / 116,980) | 6.82 (4 / 5,870) | 0 (0 / 20) | 6.85 (4 / 5,840) | 0 | -6.85 |
| | 95% CI | 1.11, 2.64 | 2.65, 17.5 | 0, 1430 | 2.66, 17.6 | 0, 225 | -13.6, -0.14 |
| SNDS Database, France | Estimate | 0.17 (1 / 57,200) | NA | NA | NA | NA | NA |
| | 95% CI | 0.03, 0.99 | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | 0.77 (3 / 39,002) | NA | NA | NA | NA | NA |
| | 95% CI | 0.26, 2.26 | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | 0.71 (3 / 42,468) | 0 (0 / 1,599) | 0.73 (3 / 40,869) | 0 | -0.73 |
| | 95% CI | NA | 0.24, 2.08 | 0, 24.0 | 0.25, 2.16 | 0, 32.7 | -1.56, 0.10 |
| GePaRD, Germany | Estimate | 3.31 (6 / 18,112) | 0.64 (9 / 140,916) | 0 (0 / 2,346) | 0.65 (9 / 138,570) | 0 | -0.65 |
| | 95% CI | 1.52, 7.23 | 0.34, 1.21 | 0, 16.3 | 0.34, 1.23 | 0, 25.2 | -1.07, -0.23 |
| KfH-QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis (Min) | Estimate | 1.17 (30 / 231,294) | 0.69 (13 / 189,254) | 0 (0 / 3,965) | 0.70 (13 / 185,279) | 0 | -0.70 |
| | 95% CI | 0.80, 1.70 | 0.40, 1.18 | 0, 9.67 | 0.41, 1.20 | 0, 13.8 | -1.20, 8.97 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 1.16 | 0.69 | 0 | 0.85 | 0 | -0.85 |
| | 95% CI | 0.78, 1.73 | 0.40, 1.19 | 0, >9995 | 0.40, 1.89 | 0, >9995 | -1.63, >9995 |
| Pooled (Crude) Analysis (Max) | Estimate | 1.17 (30 / 231,294) | 0.85 (16 / 189,254) | 0 (0 / 3,965) | 0.86 (16 / 185,279) | 0 | -0.86 |
| | 95% CI | 0.80, 1.70 | 0.52, 1.37 | 0, 9.67 | 0.53, 1.40 | 0, 11.2 | -1.40, 8.81 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 1.16 | 1.92 | 0 | 1.03 | 0 | -1.03 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.78, 1.73 | 0.79, 4.77 | 0, >9995 | 0.57, 1.91 | 0, >9995 | -1.70, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.2: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - Second Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| SNDS Database, France | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | 0.48 (1 / 20,822) | 0 (0 / 760) | 0.50 (1 / 20,062) | 0 | -0.50 |
| | 95% CI | NA | 0.08, 2.72 | 0, 50.3 | 0.09, 2.82 | 0, 101 | -1.48, 0.48 |
| GePaRD, Germany | Estimate | NA | 0.29 (2 / 67,895) | 8.18 (1 / 1,223) | 0.15 (1 / 66,672) | 54.5 | 8.03 |
| | 95% CI | NA | 0.08, 1.07 | 1.44, 46.2 | 0.03, 0.85 | 5.69, 522 | -8.00, 24.0 |
| KfH-QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis | Estimate | NA | 0.34 (3 / 88,717) | 5.04 (1 / 1,983) | 0.23 (2 / 86,734) | 21.9 | 4.81 |
| | 95% CI | NA | 0.12, 0.99 | 0.89, 28.5 | 0.06, 0.84 | 2.87, 167 | 0.64, 28.3 |
| Beta-Binomial Meta-Analysis | Estimate | NA | 0.34 | 5.04 | 0.23 | 21.9 | 4.81 |
| | 95% CI | NA | 0.11, 1.07 | 0.73, 35.2 | 0.06, 0.96 | 2.09, 243 | 0.41, 35.1 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.3: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| SNDS Database, France | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| GePaRD, Germany | Estimate | NA | 0.29 (10 / 348,945) | 0 (0 / 5,015) | 0.29 (10 / 343,930) | 0 | -0.29 |
| | 95% CI | NA | 0.16, 0.53 | 0, 7.65 | 0.16, 0.54 | 0, 26.3 | -0.47, -0.11 |
| KfH-QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis | Estimate | NA | 0.29 (10 / 348,945) | 0 (0 / 5,015) | 0.29 (10 / 343,930) | 0 | -0.29 |
| | 95% CI | NA | 0.16, 0.53 | 0, 7.65 | 0.16, 0.54 | 0, 26.3 | -0.54, 7.36 |
| Beta-Binomial Meta-Analysis | Estimate | NA | NE | NE | NE | NE | NE |
| | 95% CI | NA | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 11.4: Combined Analysis Across Research Partner Databases By Dextran Category - Excluding Zero-Event Studies - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| Danish Central Region EMR Database (Min) | Estimate | 0.41 (30 / 736,070) | 0.23 (1 / 42,780) | 0 (0 / 50) | 0.23 (1 / 42,730) | 0 | -0.23 |
| | 95% CI | 0.29, 0.58 | 0.04, 1.32 | 0, 787 | 0.04, 1.33 | 0, 3580 | -0.69, 0.22 |
| Danish Central Region EMR Database (Max) | Estimate | 0.41 (30 / 736,070) | 0.94 (4 / 42,780) | 0 (0 / 50) | 0.94 (4 / 42,730) | 0 | -0.94 |
| | 95% CI | 0.29, 0.58 | 0.36, 2.40 | 0, 787 | 0.36, 2.41 | 0, 874 | -1.85, -0.02 |
| SNDS Database, France | Estimate | 0.26 (2 / 78,292) | NA | NA | NA | NA | NA |
| | 95% CI | 0.07, 0.93 | NA | NA | NA | NA | NA |
| PHARMO, Netherlands | Estimate | 0.35 (4 / 114,639) | NA | NA | NA | NA | NA |
| | 95% CI | 0.14, 0.90 | NA | NA | NA | NA | NA |
| Swedish National Registries | Estimate | NA | 0.40 (4 / 100,761) | 0 (0 / 3,507) | 0.41 (4 / 97,254) | 0 | -0.41 |
| | 95% CI | NA | 0.15, 1.02 | 0, 10.9 | 0.16, 1.06 | 0, 26.6 | -0.81, -0.01 |
| GePaRD, Germany | Estimate | 1.45 (8 / 54,999) | 0.38 (21 / 557,756) | 1.16 (1 / 8,584) | 0.36 (20 / 549,172) | 3.20 | 0.80 |
| | 95% CI | 0.74, 2.87 | 0.25, 0.58 | 0.21, 6.60 | 0.24, 0.56 | 0.55, 18.7 | -1.49, 3.09 |
| KfH-QiN, Germany | Estimate | NA | NA | NA | NA | NA | NA |
| | 95% CI | NA | NA | NA | NA | NA | NA |
| Pooled (Crude) Analysis (Min) | Estimate | 0.44 (44 / 984,000) | 0.37 (26 / 701,297) | 0.82 (1 / 12,141) | 0.36 (25 / 689,156) | 2.27 | 0.46 |
| | 95% CI | 0.32, 0.59 | 0.25, 0.54 | 0.15, 4.67 | 0.25, 0.54 | 0.39, 13.2 | -0.24, 4.30 |
| Beta-Binomial Meta-Analysis (Min) | Estimate | 0.45 | 0.37 | 0.84 | 0.39 | 2.17 | 0.45 |
| | 95% CI | 0.32, 0.63 | 0.24, 0.60 | 0.12, 5.90 | 0.20, 0.77 | 0.28, 17.0 | -0.38, 5.54 |
| Pooled (Crude) Analysis (Max) | Estimate | 0.44 (44 / 984,000) | 0.41 (29 / 701,297) | 0.82 (1 / 12,141) | 0.41 (28 / 689,156) | 2.03 | 0.42 |
| | 95% CI | 0.32, 0.59 | 0.29, 0.59 | 0.15, 4.67 | 0.28, 0.59 | 0.35, 11.8 | -0.29, 4.26 |
| Beta-Binomial Meta-Analysis (Max) | Estimate | 0.45 | 0.41 | 0.84 | 0.47 | 1.77 | 0.37 |

| Database | Statistic | IP per 10,000 IV Penicillin | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|---|
| | 95% CI | 0.32, 0.63 | 0.29, 0.60 | 0.12, 5.86 | 0.28, 0.83 | 0.24, 13.5 | -0.45, 5.42 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.1a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - First Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.51 (1 / 19,485) | 9.36 (1 / 1,068) | NE | 0 (0 / 1,599) | 0.49 (1 / 20,316) |
| | 95% CI | 0.09, 2.91 | 1.65, 52.8 | NE, NE | 0, 24.0 | 0.09, 2.79 |
| GePaRD, Germany | Estimate | 1.31 (5 / 38,101) | 0 (0 / 784) | 0.47 (4 / 85,282) | 0 (0 / 2,346) | 0 (0 / 14,403) |
| | 95% CI | 0.56, 3.07 | 0, 48.8 | 0.18, 1.21 | 0, 16.3 | 0, 2.67 |
| Pooled (Crude) Analysis | Estimate | 1.04 (6 / 57,586) | 5.40 (1 / 1,852) | 0.47 (4 / 85,282) | 0 (0 / 3,945) | 0.29 (1 / 34,719) |
| | 95% CI | 0.48, 2.27 | 0.95, 30.5 | 0.18, 1.21 | 0, 9.73 | 0.05, 1.63 |
| Beta-Binomial Meta-Analysis | Estimate | 1.07 | 5.45 | 0.56 | 0 | 0.34 |
| | 95% CI | 0.41, 2.87 | 0.75, 38.6 | 0.15, 2.20 | 0, >9995 | 0.05, 2.41 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 12.1b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - First Dispensing or Administration - Relative Risk

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 1.04 | 19.0 | NE | 0 |
| | 95% CI | 0.11, 9.99 | 1.99, 182 | NE, NE | 0, 48.8 |
| GePaRD, Germany | Estimate | Inf | NE | Inf | NE |
| | 95% CI | 0.49, Inf | NE, NE | 0.18, Inf | NE, NE |
| Pooled (Crude) Analysis | Estimate | 3.62 | 18.7 | 1.63 | 0 |
| | 95% CI | 0.57, 22.9 | 1.96, 179 | 0.24, 10.8 | 0, 33.8 |
| Beta-Binomial Meta-Analysis | Estimate | 3.18 | 16.2 | 1.68 | 0 |
| | 95% CI | 0.36, 28.2 | 0.97, 248 | 0.16, 18.0 | 0, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 12.1c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - First Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.02 | 8.87 | NE | -0.49 |
| | 95% CI | -1.37, 1.41 | -9.50, 27.2 | NE, NE | -1.46, 0.47 |
| GePaRD, Germany | Estimate | 1.31 | 0 | 0.47 | 0 |
| | 95% CI | 0.16, 2.46 | NE, NE | 0.01, 0.93 | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.75 | 5.11 | 0.18 | -0.29 |
| | 95% CI | -0.65, 2.03 | 0.59, 30.2 | -1.18, 0.97 | -1.63, 9.44 |
| Beta-Binomial Meta-Analysis | Estimate | 0.73 | 5.11 | 0.23 | -0.34 |
| | 95% CI | -1.35, 2.47 | -0.04, 37.9 | -1.78, 1.78 | -1.74, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.2a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Second Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Swedish National Registries | Estimate | 1.28 (1 / 7,842) | 0 (0 / 248) | NE | 0 (0 / 760) | 0 (0 / 11,972) |
| | 95% CI | 0.23, 7.22 | 0, 153 | NE, NE | 0, 50.3 | 0, 3.21 |
| GePaRD, Germany | Estimate | 0 (0 / 13,236) | 0 (0 / 194) | 0 (0 / 46,021) | 8.18 (1 / 1,223) | 1.38 (1 / 7,221) |
| | 95% CI | 0, 2.90 | 0, 194 | 0, 0.83 | 1.44, 46.2 | 0.24, 7.84 |
| Pooled (Crude) Analysis | Estimate | 0.47 (1 / 21,078) | 0 (0 / 442) | 0 (0 / 46,021) | 5.04 (1 / 1,983) | 0.52 (1 / 19,193) |
| | 95% CI | 0.08, 2.69 | 0, 86.2 | 0, 0.83 | 0.89, 28.5 | 0.09, 2.95 |
| Beta-Binomial Meta-Analysis | Estimate | 0.60 | 0 | 0 | 5.17 | 0.64 |
| | 95% CI | 0.09, 4.30 | 0, >9995 | 0, >9995 | 0.75, 36.9 | 0.09, 4.63 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.2b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Second Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Swedish National Registries | Estimate | Inf | NE | NE | NE |
| | 95% CI | 0.40, Inf | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 | 0 | 0 | 5.90 |
| | 95% CI | 0, 2.10 | 0, 142 | 0, 0.60 | 0.62, 56.5 |
| Pooled (Crude) Analysis | Estimate | 0.91 | 0 | 0 | 9.68 |
| | 95% CI | 0.10, 8.72 | 0, 167 | 0, 1.60 | 1.01, 92.7 |
| Beta-Binomial Meta-Analysis | Estimate | 0.93 | 0 | 0 | 8.02 |
| | 95% CI | 0.06, 14.7 | 0, >9995 | 0, >9995 | 0.50, 124 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.2c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Second Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Swedish National Registries | Estimate | 1.28 | 0 | NE | 0 |
| | 95% CI | -1.22, 3.77 | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | -1.38 | -1.38 | -1.38 | 6.79 |
| | 95% CI | -4.10, 1.33 | -4.10, 1.33 | -4.10, 1.33 | -9.46, 23.0 |
| Pooled (Crude) Analysis | Estimate | -0.05 | -0.52 | -0.52 | 4.52 |
| | 95% CI | -2.51, 2.21 | -2.95, 85.6 | -2.95, 0.31 | 0.01, 28.0 |
| Beta-Binomial Meta-Analysis | Estimate | -0.05 | -0.64 | -0.64 | 4.53 |
| | 95% CI | -3.83, 3.52 | -3.41, >9995 | -3.27, >9995 | -1.35, 36.0 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.3a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| GePaRD, Germany | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.27 (8 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.14, 0.53 | 0, 7.65 | 0.06, 2.08 |
| Pooled (Crude) Analysis | Estimate | 0.59 (1 / 16,895) | 0 (0 / 248) | 0.27 (8 / 299,533) | 0 (0 / 5,015) | 0.37 (1 / 27,254) |
| | 95% CI | 0.10, 3.35 | 0, 153 | 0.14, 0.53 | 0, 7.65 | 0.06, 2.08 |
| Beta-Binomial Meta-Analysis | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.3b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| GePaRD, Germany | Estimate | 1.61 | 0 | 0.73 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.12, 4.48 | 0, 20.9 |
| Pooled (Crude) Analysis | Estimate | 1.61 | 0 | 0.73 | 0 |
| | 95% CI | 0.17, 15.5 | 0, 421 | 0.12, 4.48 | 0, 20.9 |
| Beta-Binomial Meta-Analysis | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.3c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Third or Subsequent Dispensing or Administration - Risk Difference**

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| GePaRD, Germany | Estimate | 0.22 | -0.37 | -0.10 | -0.37 |
| | 95% CI | -1.14, 1.59 | -1.09, 0.35 | -0.84, 0.64 | -1.09, 0.35 |
| Pooled (Crude) Analysis | Estimate | 0.22 | -0.37 | -0.10 | -0.37 |
| | 95% CI | -1.54, 3.00 | -2.08, 152 | -1.81, 0.31 | -2.08, 7.29 |
| Beta-Binomial Meta-Analysis | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.4a: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Any Dispensing or Administration - Incidence Proportion**

| | | IP per 10,000 | | | | |
|---|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex** | **Iron(III) Isomaltoside Complex** | **Sodium Ferric Gluconate Complex** | **Iron(III)-Hydroxide Dextran Complex** | **Iron Sucrose Complex / Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.56 (2 / 35,889) | 6.83 (1 / 1,465) | NE | 0 (0 / 3,507) | 0.17 (1 / 59,900) |
| | 95% CI | 0.15, 2.03 | 1.21, 38.6 | NE, NE | 0, 10.9 | 0.03, 0.95 |
| GePaRD, Germany | Estimate | 0.88 (6 / 68,232) | 0 (0 / 1,226) | 0.28 (12 / 430,836) | 1.16 (1 / 8,584) | 0.41 (2 / 48,878) |
| | 95% CI | 0.40, 1.92 | 0, 31.2 | 0.16, 0.49 | 0.21, 6.60 | 0.11, 1.49 |
| Pooled (Crude) Analysis | Estimate | 0.77 (8 / 104,121) | 3.72 (1 / 2,691) | 0.28 (12 / 430,836) | 0.83 (1 / 12,091) | 0.28 (3 / 108,778) |
| | 95% CI | 0.39, 1.52 | 0.66, 21.0 | 0.16, 0.49 | 0.15, 4.68 | 0.09, 0.81 |
| Beta-Binomial Meta-Analysis | Estimate | 0.78 | 3.73 | 0.31 | 0.84 | 0.30 |
| | 95% CI | 0.37, 1.71 | 0.52, 26.5 | 0.12, 0.80 | 0.12, 6.03 | 0.09, 0.99 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 12.4b: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Any Dispensing or Administration - Relative Risk**

| | | RR | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 3.34 | 40.9 | NE | 0 |
| | 95% CI | 0.44, 25.5 | 4.27, 391 | NE, NE | 0, 65.6 |
| GePaRD, Germany | Estimate | 2.15 | 0 | 0.68 | 2.85 |
| | 95% CI | 0.50, 9.31 | 0, 76.5 | 0.17, 2.72 | 0.37, 21.7 |
| Pooled (Crude) Analysis | Estimate | 2.79 | 13.5 | 1.01 | 3.00 |
| | 95% CI | 0.80, 9.67 | 1.93, 94.0 | 0.31, 3.33 | 0.43, 20.9 |
| Beta-Binomial Meta-Analysis | Estimate | 2.61 | 12.5 | 1.02 | 2.82 |
| | 95% CI | 0.64, 10.8 | 1.25, 123 | 0.23, 4.66 | 0.28, 27.5 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 12.4c: Combined Analysis Across Research Partner Databases By Individual Category - Excluding Zero-Event Studies - Any Dispensing or Administration - Risk Difference

| | | RD per 10,000 | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **Ferric Carboxymaltose Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III) Isomaltoside Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Sodium Ferric Gluconate Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** | **Iron(III)-Hydroxide Dextran Complex vs Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.39 | 6.66 | NE | -0.17 |
| | 95% CI | -0.45, 1.23 | -6.72, 20.0 | NE, NE | -0.49, 0.16 |
| GePaRD, Germany | Estimate | 0.47 | -0.41 | -0.13 | 0.76 |
| | 95% CI | -0.43, 1.37 | -0.98, 0.16 | -0.72, 0.46 | -1.60, 3.11 |
| Pooled (Crude) Analysis | Estimate | 0.49 | 3.44 | 0.00 | 0.55 |
| | 95% CI | -0.14, 1.27 | 0.35, 20.7 | -0.54, 0.28 | -0.30, 4.41 |
| Beta-Binomial Meta-Analysis | Estimate | 0.48 | 3.43 | 0.01 | 0.54 |
| | 95% CI | -0.29, 1.41 | 0.12, 26.1 | -0.69, 0.52 | -0.48, 5.69 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 13.1: Combined Analysis Across Research Partner Databases By Dextran Category - Before 2013 - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 80,883) | NE | 0 (0 / 80,883) | NE | NE |
| | 95% CI | 0, 0.47 | NE, NE | 0, 0.47 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 7,282) | 0 (0 / 4,771) | 0 (0 / 2,511) | NE | 0 |
| | 95% CI | 0, 5.27 | 0, 8.05 | 0, 15.3 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.32 (2 / 63,471) | 0 (0 / 2,604) | 0.33 (2 / 60,867) | 0 | -0.33 |
| | 95% CI | 0.09, 1.15 | 0, 14.7 | 0.09, 1.20 | 0, 44.9 | -0.78, 0.13 |
| GePaRD, Germany | Estimate | 0.27 (10 / 374,620) | 0 (0 / 6,939) | 0.27 (10 / 367,681) | 0 | -0.27 |
| | 95% CI | 0.15, 0.49 | 0, 5.53 | 0.15, 0.50 | 0, 20.3 | -0.44, -0.10 |
| KfH-QiN, Germany | Estimate | 0 (0 / 1,249,123) | 0 (0 / 594) | 0 (0 / 1,248,529) | NE | 0 |
| | 95% CI | 0, 0.03 | 0, 64.3 | 0, 0.03 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.07 (12 / 1,775,379) | 0 (0 / 14,908) | 0.07 (12 / 1,760,471) | 0 | -0.07 |
| | 95% CI | 0.04, 0.12 | 0, 2.58 | 0.04, 0.12 | 0, 37.8 | -0.12, 2.51 |
| Beta-Binomial Meta-Analysis | Estimate | 0.06 | 0 | 0.07 | 0 | -0.07 |
| | 95% CI | 0.03, 0.17 | 0, >9995 | 0.02, 0.24 | 0, >9995 | -0.19, >9995 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 13.2: Combined Analysis Across Research Partner Databases By Dextran Category - After 2013 - Any Dispensing or Administration**

| Database | Statistic | IP per 10,000 Any IV Iron | IP per 10,000 IV Iron Dextrans | IP per 10,000 IV Iron Non-Dextrans | RR | RD per 10,000 |
|---|---|---|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | 0 (0 / 4,835) | NE | 0 (0 / 4,835) | NE | NE |
| | 95% CI | 0, 7.94 | NE, NE | 0, 7.94 | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 3,034) | 0 (0 / 842) | 0 (0 / 2,192) | NE | 0 |
| | 95% CI | 0, 12.6 | 0, 45.4 | 0, 17.5 | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0.75 (2 / 26,601) | 0 (0 / 591) | 0.77 (2 / 26,010) | 0 | -0.77 |
| | 95% CI | 0.21, 2.74 | 0, 64.6 | 0.21, 2.80 | 0, 84.3 | -1.83, 0.30 |
| GePaRD, Germany | Estimate | 0.67 (8 / 119,650) | 10.1 (1 / 992) | 0.59 (7 / 118,658) | 17.1 | 9.49 |
| | 95% CI | 0.34, 1.32 | 1.78, 56.9 | 0.29, 1.22 | 2.74, 106 | -10.3, 29.2 |
| KfH-QiN, Germany | Estimate | 0 (0 / 1,177,868) | 0 (0 / 328) | 0 (0 / 1,177,540) | NE | 0 |
| | 95% CI | 0, 0.03 | 0, 116 | 0, 0.03 | NE, NE | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0.08 (10 / 1,331,988) | 3.63 (1 / 2,753) | 0.07 (9 / 1,329,235) | 53.6 | 3.56 |
| | 95% CI | 0.04, 0.14 | 0.64, 20.5 | 0.04, 0.13 | 8.79, 327 | 0.57, 20.5 |
| Beta-Binomial Meta-Analysis | Estimate | 0.09 | 3.64 | 0.11 | 33.2 | 3.53 |
| | 95% CI | 0.04, 0.24 | 0.53, 25.4 | 0.04, 0.34 | 3.76, 317 | 0.39, 25.4 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 14.1: Combined Analysis Across Research Partner Databases By Dextran Category - After First Switch

| Database | Statistic | IP per 10,000 From: Dextrans To: Non-Dextrans | IP per 10,000 From: Non-Dextrans To: Dextrans |
|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 318) | 36.1 (2 / 554) |
| | 95% CI | 0, 119 | 9.91, 131 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 2) |
| | 95% CI | 0, 7930 | 0, 6580 |
| KfH-QiN, Germany | Estimate | 0 (0 / 13) | 0 (0 / 52) |
| | 95% CI | 0, 2280 | 0, 688 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 332) | 32.9 (2 / 608) |
| | 95% CI | 0, 114 | 9.03, 119 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 32.9 |
| | 95% CI | 0, 0 | 8.26, 136 |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 14.2: Combined Analysis Across Research Partner Databases By Dextran Category - After Any Switch

| Database | Statistic | IP per 10,000 From: Dextrans To: Non-Dextrans | IP per 10,000 From: Non-Dextrans To: Dextrans |
|---|---|---|---|
| Danish Central Region EMR Database | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE |
| | 95% CI | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 3) | NE |
| | 95% CI | 0, 5610 | NE, NE |
| Swedish National Registries | Estimate | 0 (0 / 554) | 31.9 (2 / 627) |
| | 95% CI | 0, 68.9 | 8.75, 116 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 2) |
| | 95% CI | 0, 7930 | 0, 6580 |
| KfH-QiN, Germany | Estimate | 0 (0 / 61) | 0 (0 / 73) |
| | 95% CI | 0, 592 | 0, 500 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 619) | 28.5 (2 / 702) |
| | 95% CI | 0, 61.7 | 7.82, 103 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 29.0 |
| | 95% CI | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.1a: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Ferric Carboxymaltose Complex

| | | IP per 10,000 From: Ferric Carboxymaltose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 240) | NE | NE | 0 (0 / 100) |
| | 95% CI | 0, 161 | NE, NE | NE, NE | 0, 381 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 4) | NE | 0 (0 / 5) | 0 (0 / 6) |
| | 95% CI | 0, 4900 | NE, NE | 0, 4340 | 0, 3900 |
| Swedish National Registries | Estimate | 60.6 (1 / 165) | NE | 0 (0 / 41) | 0 (0 / 364) |
| | 95% CI | 10.7, 335 | NE, NE | 0, 857 | 0, 104 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 7) | NE | 0 (0 / 1) |
| | 95% CI | 0, 7930 | 0, 3540 | NE, NE | 0, 7930 |
| KfH-QiN, Germany | Estimate | 0 (0 / 8) | 0 (0 / 911) | 0 (0 / 4) | 0 (0 / 59) |
| | 95% CI | 0, 3240 | 0, 42.0 | 0, 4900 | 0, 611 |
| Pooled (Crude) Analysis | Estimate | 24.2 (1 / 418) | 0 (0 / 918) | 0 (0 / 50) | 0 (0 / 530) |
| | 95% CI | 4.28, 136 | 0, 41.7 | 0, 713 | 0, 72.4 |
| Beta-Binomial Meta-Analysis | Estimate | 24.2 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.1b: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Iron(III) Isomaltoside Complex

| | | IP per 10,000 From: Iron(III) Isomaltoside Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 50) | NE | NE | 0 (0 / 70) |
| | 95% CI | 0, 787 | NE, NE | NE, NE | 0, 527 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | 0 (0 / 1) |
| | 95% CI | NE, NE | NE, NE | NE, NE | 0, 7930 |
| Swedish National Registries | Estimate | 0 (0 / 29) | NE | 0 (0 / 2) | 0 (0 / 18) |
| | 95% CI | 0, 1170 | NE, NE | 0, 6580 | 0, 1760 |
| GePaRD, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| KfH-QiN, Germany | Estimate | 0 (0 / 4) | NE | NE | 0 (0 / 3) |
| | 95% CI | 0, 4900 | NE, NE | NE, NE | 0, 5610 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 83) | NE | 0 (0 / 2) | 0 (0 / 92) |
| | 95% CI | 0, 469 | NE, NE | 0, 6580 | 0, 405 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | NE | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.1c: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Sodium Ferric Gluconate Complex

| | | IP per 10,000<br>From: Sodium Ferric Gluconate Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | 0 (0 / 12) | NE | 0 (0 / 2) | 0 (0 / 6) |
| | 95% CI | 0, 2420 | NE, NE | 0, 6580 | 0, 3900 |
| KfH-QiN, Germany | Estimate | 0 (0 / 5,220) | 0 (0 / 3) | 0 (0 / 48) | 0 (0 / 192) |
| | 95% CI | 0, 7.35 | 0, 5610 | 0, 741 | 0, 196 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 5,232) | 0 (0 / 3) | 0 (0 / 50) | 0 (0 / 198) |
| | 95% CI | 0, 7.34 | 0, 5610 | 0, 713 | 0, 190 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.1d: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch From Iron(III)-Hydroxide Dextran Complex

| | | IP per 10,000 From: Iron(III)-Hydroxide Dextran Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 26) | 0 (0 / 1) | NE | 0 (0 / 12) |
| | 95% CI | 0, 1290 | 0, 7930 | NE, NE | 0, 2420 |
| Swedish National Registries | Estimate | 0 (0 / 173) | 0 (0 / 11) | NE | 0 (0 / 134) |
| | 95% CI | 0, 217 | 0, 2590 | NE, NE | 0, 279 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | NE | NE | NE |
| | 95% CI | 0, 7930 | NE, NE | NE, NE | NE, NE |
| KfH-QiN, Germany | Estimate | 0 (0 / 6) | NE | 0 (0 / 7) | NE |
| | 95% CI | 0, 3900 | NE, NE | 0, 3540 | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 206) | 0 (0 / 12) | 0 (0 / 7) | 0 (0 / 146) |
| | 95% CI | 0, 183 | 0, 2420 | 0, 3540 | 0, 256 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.1e: Combined Analysis Across Research Partner Databases By Individual Category - After First Switch

| | | IP per 10,000<br>From: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 120) | 0 (0 / 80) | NE | NE |
| | 95% CI | 0, 300 | 0, 442 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 35) | 0 (0 / 6) | NE | 0 (0 / 18) |
| | 95% CI | 0, 989 | 0, 3900 | NE, NE | 0, 1760 |
| Swedish National Registries | Estimate | 0 (0 / 3,107) | 0 (0 / 200) | NE | 39.1 (2 / 511) |
| | 95% CI | 0, 12.3 | 0, 188 | NE, NE | 10.7, 142 |
| GePaRD, Germany | Estimate | NE | NE | 0 (0 / 3) | NE |
| | 95% CI | NE, NE | NE, NE | 0, 5610 | NE, NE |
| KfH-QiN, Germany | Estimate | 0 (0 / 39) | NE | 0 (0 / 52) | NE |
| | 95% CI | 0, 897 | NE, NE | 0, 688 | NE, NE |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 3,301) | 0 (0 / 286) | 0 (0 / 55) | 37.8 (2 / 529) |
| | 95% CI | 0, 11.6 | 0, 131 | 0, 653 | 10.4, 137 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 0 | 37.9 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.2a: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Ferric Carboxymaltose Complex

| | | IP per 10,000<br>From: Ferric Carboxymaltose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 300) | NE | NE | 0 (0 / 120) |
| | 95% CI | 0, 129 | NE, NE | NE, NE | 0, 318 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 4) | NE | 0 (0 / 7) | 0 (0 / 9) |
| | 95% CI | 0, 4900 | NE, NE | 0, 3540 | 0, 2990 |
| Swedish National Registries | Estimate | 43.7 (1 / 229) | NE | 0 (0 / 76) | 0 (0 / 634) |
| | 95% CI | 7.71, 243 | NE, NE | 0, 481 | 0, 60.2 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 2) | 0 (0 / 1) | 0 (0 / 2) |
| | 95% CI | 0, 7930 | 0, 6580 | 0, 7930 | 0, 6580 |
| KfH-QiN, Germany | Estimate | 0 (0 / 15) | 0 (0 / 2,395) | 0 (0 / 10) | 0 (0 / 112) |
| | 95% CI | 0, 2040 | 0, 16.0 | 0, 2780 | 0, 332 |
| Pooled (Crude) Analysis | Estimate | 18.4 (1 / 549) | 0 (0 / 2,397) | 0 (0 / 94) | 0 (0 / 877) |
| | 95% CI | 3.25, 103 | 0, 16.0 | 0, 393 | 0, 43.8 |
| Beta-Binomial Meta-Analysis | Estimate | 20.3 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.2b: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Iron(III) Isomaltoside Complex

| | | IP per 10,000 From: Iron(III) Isomaltoside Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 80) | NE | NE | 0 (0 / 110) |
| | 95% CI | 0, 437 | NE, NE | NE, NE | 0, 337 |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | 0 (0 / 1) |
| | 95% CI | NE, NE | NE, NE | NE, NE | 0, 7930 |
| Swedish National Registries | Estimate | 0 (0 / 63) | NE | 0 (0 / 4) | 0 (0 / 36) |
| | 95% CI | 0, 575 | NE, NE | 0, 4900 | 0, 964 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | 0 (0 / 7) | NE | 0 (0 / 1) |
| | 95% CI | 0, 7930 | 0, 3540 | NE, NE | 0, 7930 |
| KfH-QiN, Germany | Estimate | 0 (0 / 13) | 0 (0 / 3) | NE | 0 (0 / 4) |
| | 95% CI | 0, 2280 | 0, 5610 | NE, NE | 0, 4900 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 157) | 0 (0 / 10) | 0 (0 / 4) | 0 (0 / 152) |
| | 95% CI | 0, 233 | 0, 2780 | 0, 4900 | 0, 246 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | NE | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.2c: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Sodium Ferric Gluconate Complex

| | | IP per 10,000 From: Sodium Ferric Gluconate Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Iron(III)-Hydroxide Dextran Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| Swedish National Registries | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| GePaRD, Germany | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| KfH-QiN, Germany | Estimate | 0 (0 / 6,895) | 0 (0 / 4) | 0 (0 / 61) | 0 (0 / 292) |
| | 95% CI | 0, 5.57 | 0, 4900 | 0, 592 | 0, 130 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 6,895) | 0 (0 / 4) | 0 (0 / 61) | 0 (0 / 292) |
| | 95% CI | 0, 5.57 | 0, 4900 | 0, 592 | 0, 130 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

## Table 15.2d: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Iron(III)-Hydroxide Dextran Complex

| | | IP per 10,000<br>From: Iron(III)-Hydroxide Dextran Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex** |
| Danish Central Region EMR Database | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 29) | 0 (0 / 1) | NE | 0 (0 / 12) |
| | 95% CI | 0, 1170 | 0, 7930 | NE, NE | 0, 2420 |
| Swedish National Registries | Estimate | 0 (0 / 292) | 0 (0 / 19) | NE | 0 (0 / 243) |
| | 95% CI | 0, 130 | 0, 1680 | NE, NE | 0, 156 |
| GePaRD, Germany | Estimate | 0 (0 / 12) | NE | 0 (0 / 2) | 0 (0 / 6) |
| | 95% CI | 0, 2420 | NE, NE | 0, 6580 | 0, 3900 |
| KfH-QiN, Germany | Estimate | 0 (0 / 22) | NE | 0 (0 / 36) | 0 (0 / 3) |
| | 95% CI | 0, 1490 | NE, NE | 0, 964 | 0, 5610 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 355) | 0 (0 / 20) | 0 (0 / 38) | 0 (0 / 264) |
| | 95% CI | 0, 107 | 0, 1610 | 0, 918 | 0, 143 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 0 | 0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

**Table 15.2e: Combined Analysis Across Research Partner Databases By Individual Category - After Any Switch From Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex**

| | | IP per 10,000<br>From: Iron Sucrose Complex/ Iron(III)-Hydroxide Sucrose Complex | | | |
|---|---|---|---|---|---|
| **Database** | **Statistic** | **To: Ferric Carboxymaltose Complex** | **To: Iron(III) Isomaltoside Complex** | **To: Sodium Ferric Gluconate Complex** | **To: Iron(III)-Hydroxide Dextran Complex** |
| Danish Central Region EMR Database | Estimate | 0 (0 / 140) | 0 (0 / 100) | NE | NE |
| | 95% CI | 0, 277 | 0, 366 | NE, NE | NE, NE |
| SNDS Database, France | Estimate | NE | NE | NE | NE |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |
| PHARMO, Netherlands | Estimate | 0 (0 / 38) | 0 (0 / 7) | NE | 0 (0 / 21) |
| | 95% CI | 0, 918 | 0, 3540 | NE, NE | 0, 1550 |
| Swedish National Registries | Estimate | 0 (0 / 3,298) | 0 (0 / 215) | NE | 36.6 (2 / 547) |
| | 95% CI | 0, 11.6 | 0, 176 | NE, NE | 10.0, 132 |
| GePaRD, Germany | Estimate | 0 (0 / 1) | NE | NE | NE |
| | 95% CI | 0, 7930 | NE, NE | NE, NE | NE, NE |
| KfH-QiN, Germany | Estimate | 0 (0 / 125) | 0 (0 / 3) | 0 (0 / 204) | 0 (0 / 2) |
| | 95% CI | 0, 298 | 0, 5610 | 0, 185 | 0, 6580 |
| Pooled (Crude) Analysis | Estimate | 0 (0 / 3,602) | 0 (0 / 325) | 0 (0 / 204) | 35.1 (2 / 570) |
| | 95% CI | 0, 10.7 | 0, 116 | 0, 185 | 9.63, 127 |
| Beta-Binomial Meta-Analysis | Estimate | 0 | 0 | 0 | 39.0 |
| | 95% CI | NE, NE | NE, NE | NE, NE | NE, NE |

CI = confidence interval; IP = incidence proportion; IV = intravenous; NA = not applicable; NE = not estimable; RD = risk difference; RR = relative risk

- Values less than 999 were reported to three digits on the indicated scale; values greater than 999 were reported to three informative digits.

- Due to rounding, crude RR estimates may not always be obtained to the reported level of precision by dividing the reported IPs directly, if applicable.

- IP estimates from beta-binomial regression models for minimum and maximum scenarios, when applicable, may differ slightly for a given compound even in situations where numerators and denominators are the same in both scenarios. This occurrence is due to model estimation procedures that account for the differing number of events of the other compounds in minimum and maximum scenarios. Footnotes highlighting these small discrepancies have been added to in-text tables when applicable.

# Annex 5.
# 2014 and 2016 Feasibility Assessment Report

Annex 5_RTI-HS_IV Iron_FeasibAssessm