ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]

Safety and effectiveness: 10 years of clinical experience

Alfonso Iorio, MD, PhD
Health Information Research Unit & Hemophilia Program
McMaster University, Canada

Disclosures for: Alfonso Iorio

In compliance with the EACCME* policy, WFH requires the following disclosures be made at each presentation

CONFLICT	DISCLOSURE — IF CONFLICT OF INTEREST EXISTS
RESEARCH SUPPORT	Baxter (Bayer, Biogen Idec, NovoNordisk, Pfizer - No conflicts)
DIRECTOR, OFFICER, EMPLOYEE	
SHAREHOLDER	
HONORARIA	Bayer, Baxter, Biogen Idec, CSL, NovoNordisk, Octapharma, Pfizer – No conflicts
ADVISORY COMMITTEE	Bayer, Baxter, Biogen Idec, CSL, NovoNordisk, Octapharma, Pfizer – No conflicts
CONSULTANT	Bayer, NovoNordisk – No conflicts

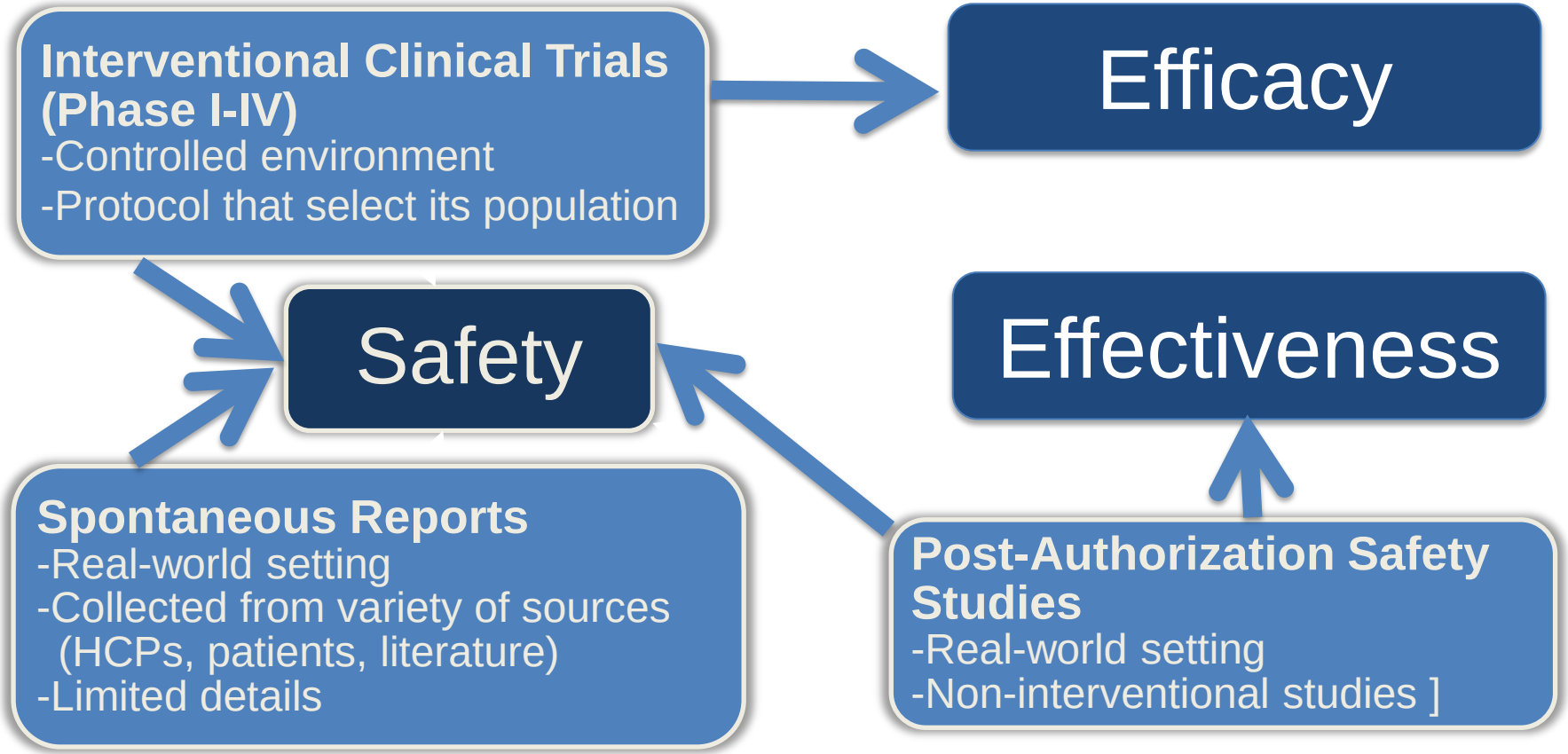
** European Accreditation Council for Continuing Medical Education*

WFH 2014 WORLD CONGRESS
Melbourne, Australia • May 11-15

DISCLAIMER

This symposium may include the opinions of the speakers, which do not necessarily reflect the views of Baxter. This symposium may also contain factual information on products and/or indications that are not approved in Australia. Baxter does not recommend the use of any of its products outside of their country specific labelling.

Safety Data From Multiple Sources



A three-components assessment

1) **The First Review of Global Spontaneous Adverse Event Reports for a Third Generation Recombinant Factor VIII Concentrate (Octocog Alfa): 10 Years of Safety Experience -** Berg R, Gringeri A, Reininger AJ

   REAL WORLD ADVERSE EVENTS REPORTS FROM ALLSOURCES (e.g. CLINICIANS, PATIENTS, PUBLISHED CASE STUDIES)

2) **Integrated Analysis of Safety Data from 12 Clinical Interventional Studies of a Plasma- and Albumin-free Recombinant Factor VIII in Persons with Hemophilia A** Shapiro A, Romanov V, Silvati-Fidell L, Matovinovic E, Wong WY, Schoenig-Diesing C

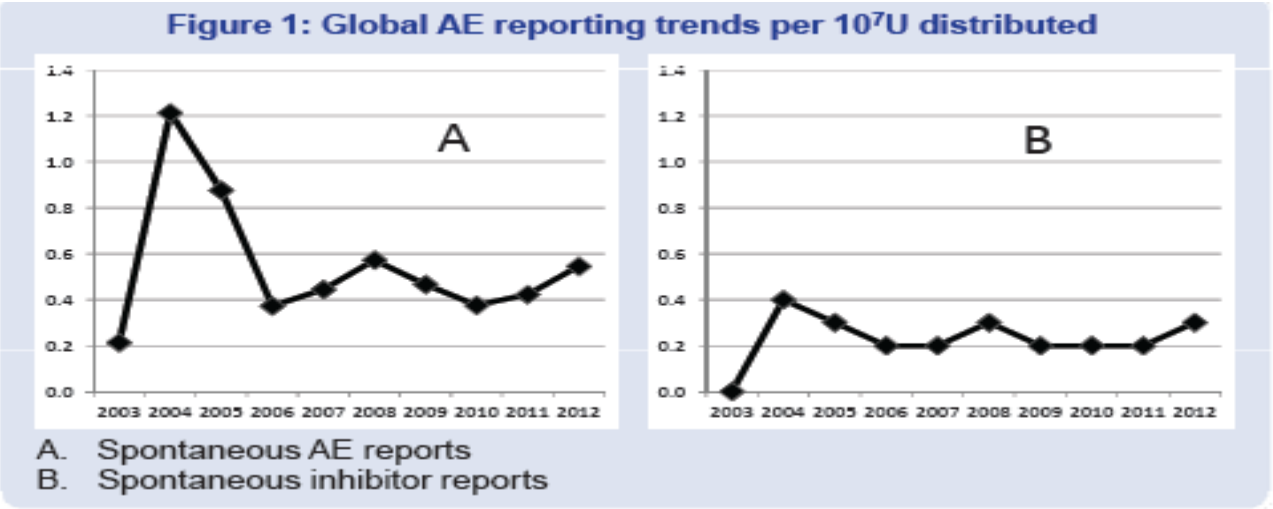
   CONTROLLED CLINICAL STUDY DATA FROM Phase I-IV

3) **Meta-analysis of Post Authorization Safety Studies (PASS): Worldwide post-marketing surveillance of hemophilia A patients treated with antihemophilic factor recombinant plasma/albumin-free method rAHF-PFM -** Marcucci M, Cheng J, Oldenburg J, Schoenig-Diesing C, Matovinovic E, Romanov V, Thabane L, Iorio A

   REAL WORLD DATA COLLECTED FROM GLOBAL NON-INTERVENTIONAL CLINICAL STUDIES

1. Spontaneous Adverse Event Reports

- Global PV safety database - July 2003-Sept 2012
- >13 BU, corresponding to an estimated 87,000 patient-years of exposure
- Reporting rate of FVIII inhibitors was stable over time



Berg, R et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands.

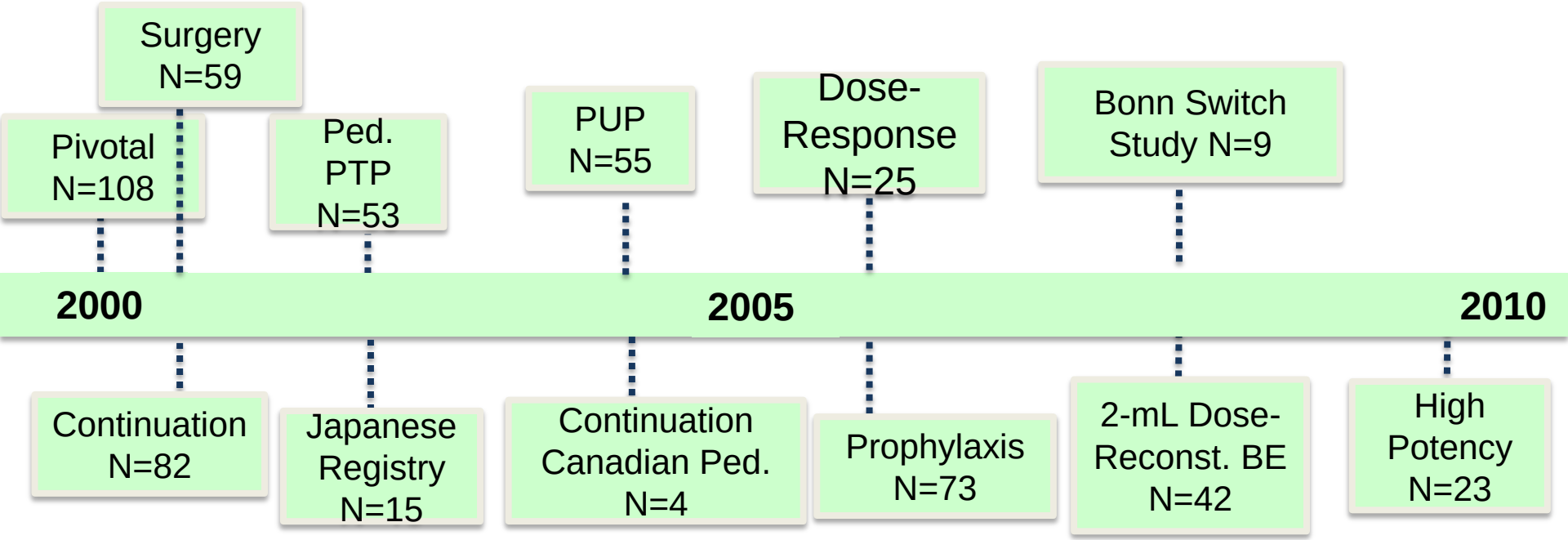
Working Summary: Spontaneous AE Reports

- **Spontaneous AE Reports**
  - No detection of previously unrecognized risks

Berg, R et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands.

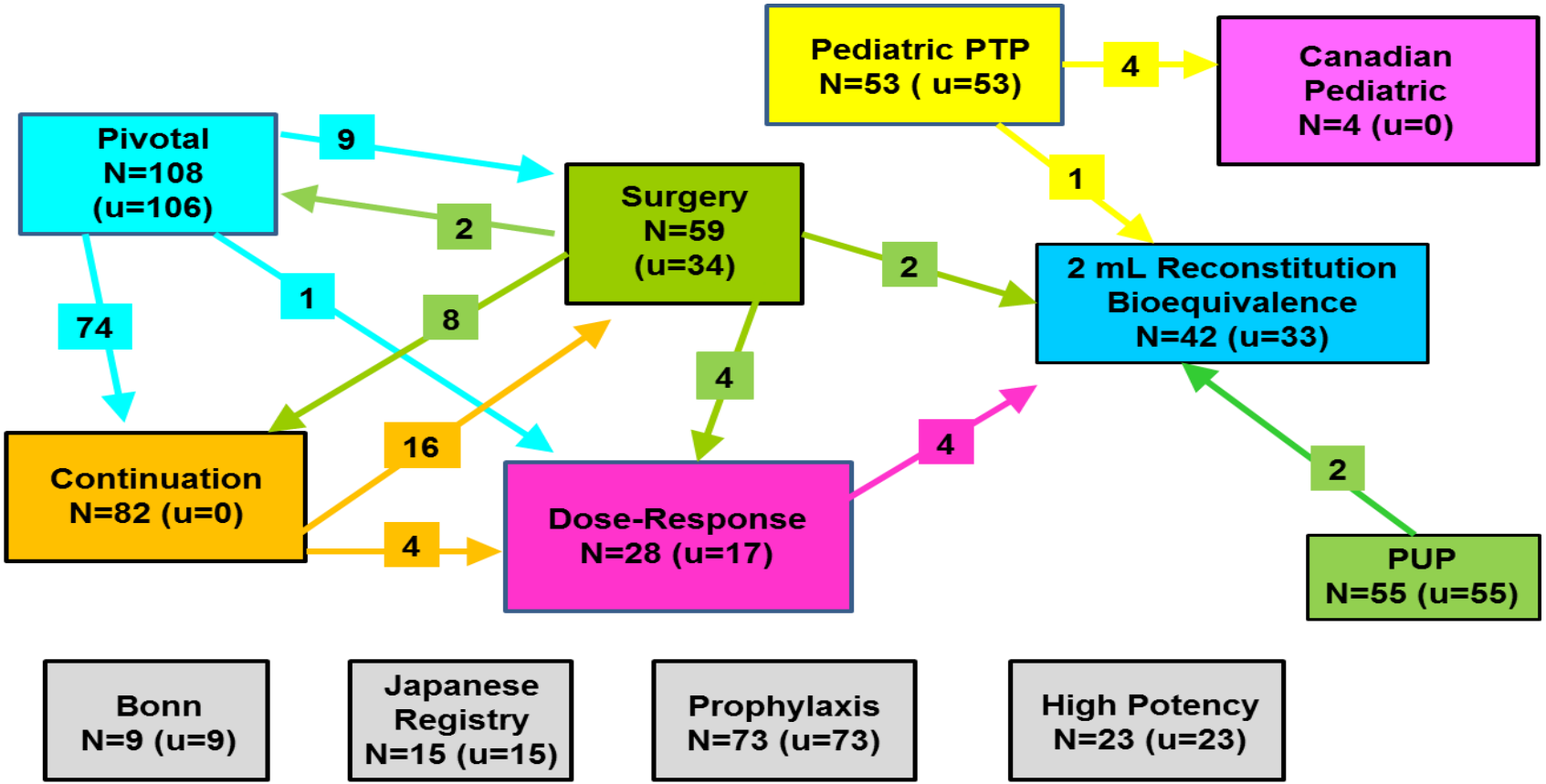
2. Interventional Studies: Overview

- Comprising of **12 studies**: Phase I through IV interventional trials, **totaling 418 unique subjects**



Shapiro A et al. Poster presented at the XXIV Congress of the ISTH, 2013, Netherlands.

2. Interventional Studies: Patient Flow and Analysis Sets



Shapiro A et al. Poster presented at the XXIV Congress of the ISTH, 2013, Netherlands.

2. Interventional Studies: Patient Flow and Analysis Sets

SAFETY ANALYSIS SET

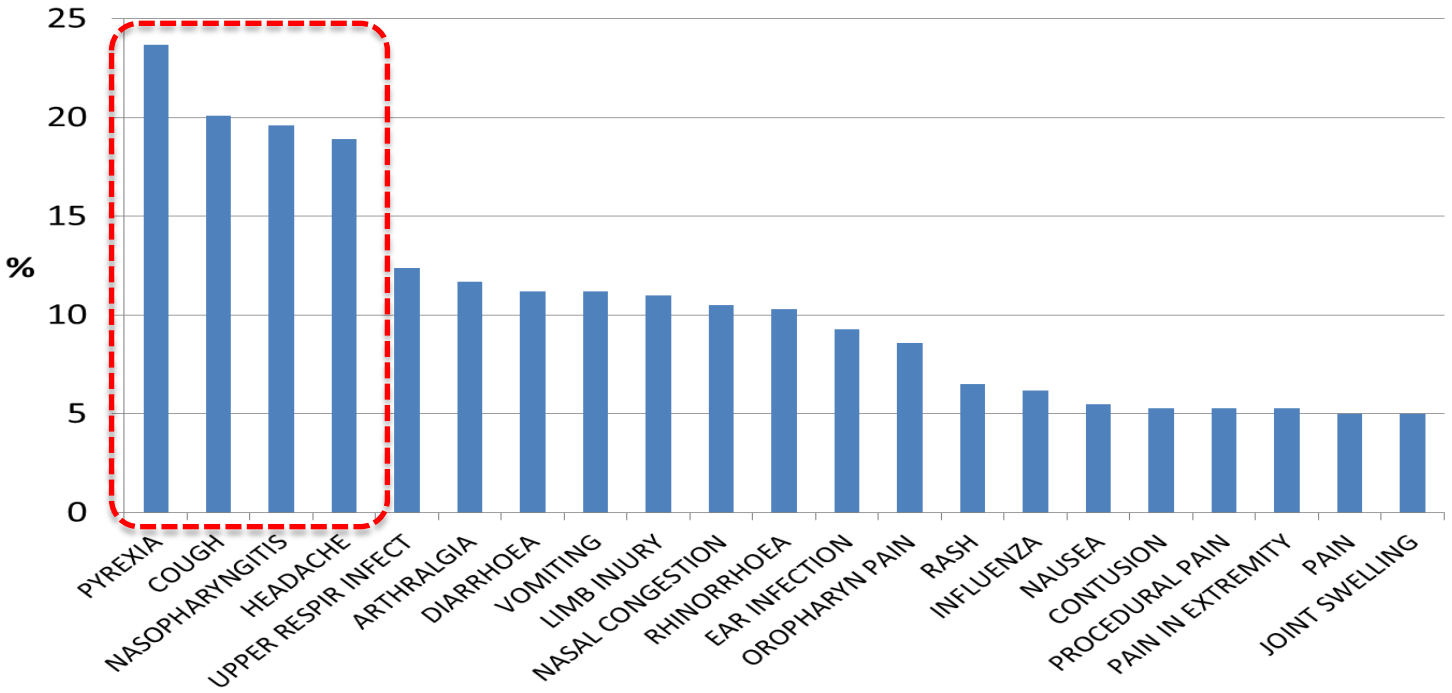
- N=418: 363 PTPs, 55 PUPs/MTPs
- Median age: 18.7 yr (0.07-72.3)
- Median EDs: 97.0 (1-709)

INHIBITOR ANALYSIS SET

- N=276: PTPs ≥ 10 EDs to rAHF-PFM during study
- N=55: PUPs/MTPs

Shapiro A et al. Poster presented at the XXIV Congress of the ISTH, 2013, Netherlands.

2. IS Results: AEs and SAEs >5% (Full Analysis N=418)



- **Common AEs:** pyrexia, cough, nasopharyngitis, headache
- **No hypersensitivity, anaphylaxis reactions, or anaphylactoid reactions** (N=418, 95% CI 0.000, 0.879)

Shapiro A et al. Poster presented at the XXIV Congress of the ISTH, 2013, Netherlands.

2. IS Results: Inhibitor Development

Parameter	PUPs/ MTPs	PTPs[a]
Inhibitor Titer Frequency All High Low	29.1 % (16/55) 12.7 % (7/55) 16.4% (9/55)	0.4% (1/276) 0% (0/276) 0.4% (1/276)
Inhibitor Risk (95 % CI)	17.1-41.1%	0.009-2.002%
Exposure Days (ED), median (range) EDs to Inhibitor, median	75 (0-87)[a], N=55 13	175 (10-709), N=276 75

a= Excluding exposure during ITI for subjects who developed inhibitors. 11 out 16 subjects who developed inhibitors went on to receive ITI

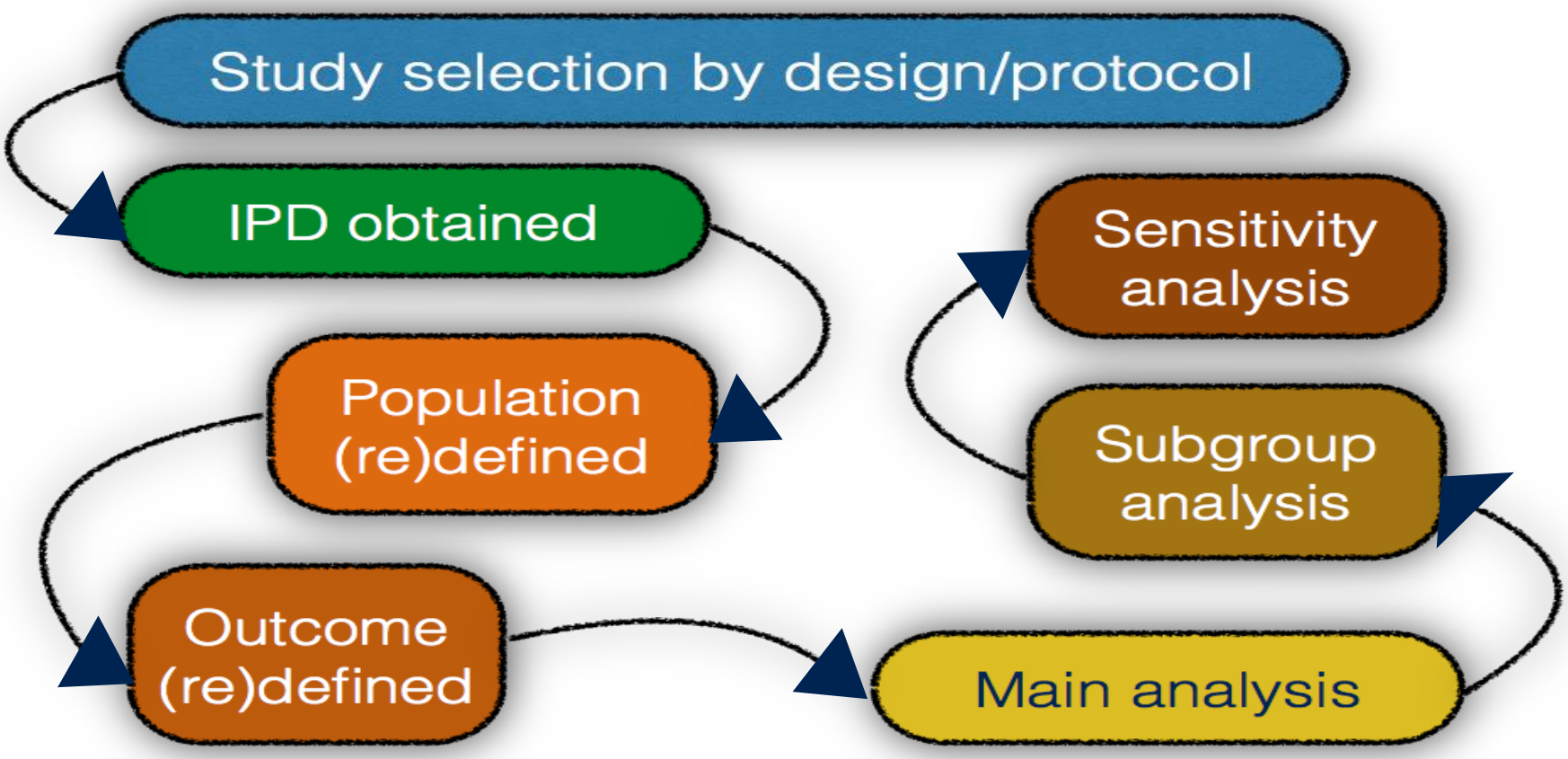
Shapiro A et al. Poster presented at the XXIV Congress of the ISTH, 2013, Netherlands.

Working Summary: Spontaneous AE Reports and IS

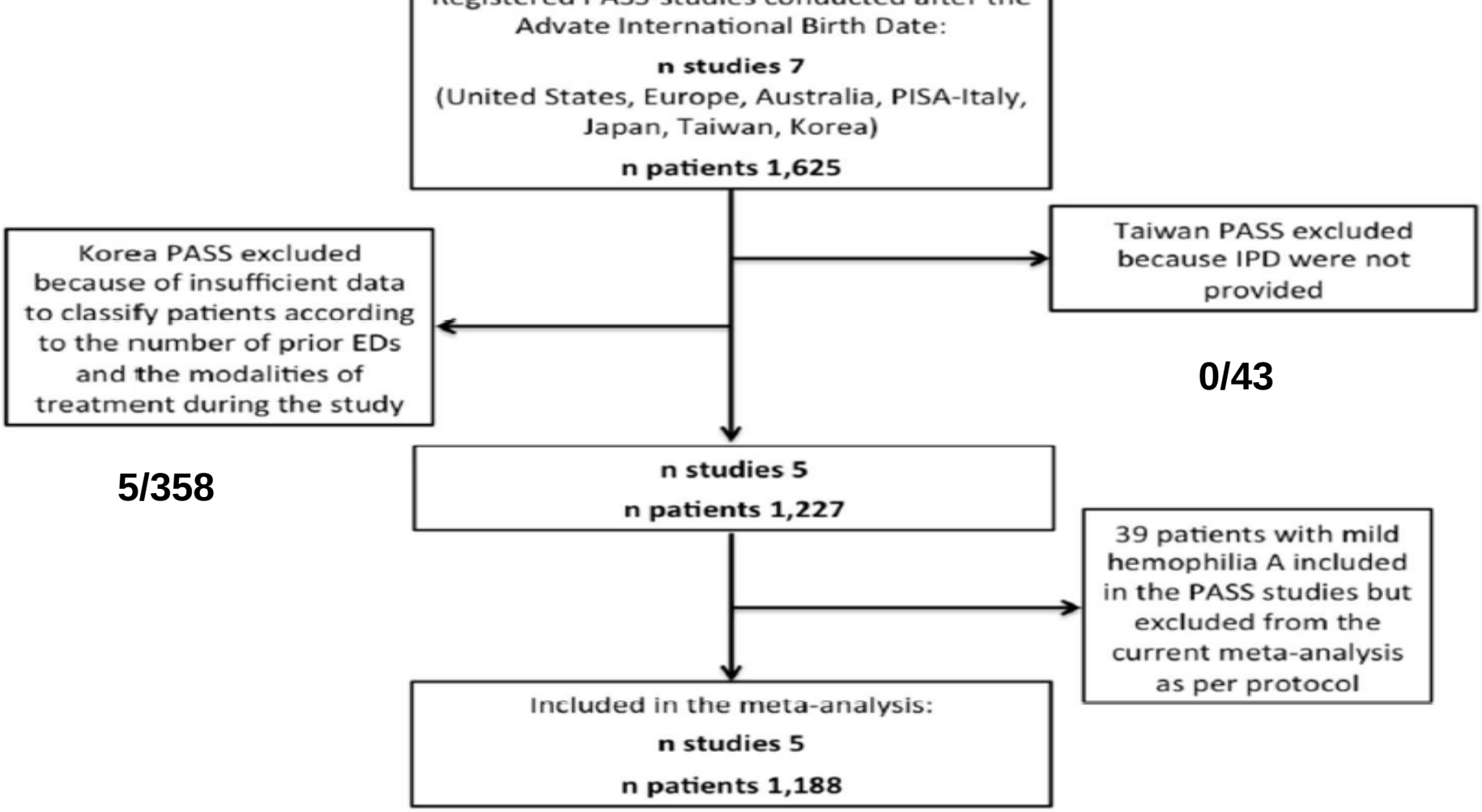
- **Spontaneous AE Reports**
  - No detection of previously unrecognized risks
- **Integrated Safety Studies**
  - 418 Subjects from 12 interventional studies were analyzed
  - 0.4% inhibitor risk in PTPs >50 EDs (1 out of 276); 95 % CI 0.009-2.002
  - No hypersensitivity, anaphylaxis, or anaphylactoid reactions
  - No withdrawal due to AEs
  - No new safety signals revealed

Berg, R et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands ; Shapiro A et al. Poster presented at the XXIV Congress of the ISTH, 2013, Netherlands.

3.Post Authorization Safety Studies



Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands



1. Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands. 2. Data on File, Vienna Austria.

3. PASS Patient Characteristics

Characteristics, n (%)		**Patients (n 1,188)**
Previous Exposure Days (EDs)		
0-50		96 (8.1)
50-150		73 (6.1)
>150		**1016 (85.5)**
Unknown		3 (0.3)
Regimen at enrolment		
On demand		434 (36.5)
Prophylaxis		743 (62.6)
Unknown/Other*		11 (0.9)

Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands

3. PASS Overall Safety Outcomes

Secondary analyses	**At risk**	**events (patients)**
Adverse Events (AEs)		
Total AEs, any severity	1,188	726 (254)
Total Serious AEs	1,188	83 (59)
Product-related AEs, any severity	1,188	37 (22)
Product-related Serious AEs	1,188	5 (5)

Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands

3. PASS Inhibitors development

Outcome and population		
	Inhibitors All/HR*/at risk	**Incident rate (%, 95% CI)**
Primary		
De novo severe PTPs >150 EDs	1/0/669	0.15 (0.02, 1.06)
Secondary		
De novo, severe PTPs >50 EDs	1/0/717	0.14 (0.02, 0.99)
De novo, moderate-severe PTPs >150 EDs	1/0/799	0.13 (0.02, 0.89)

*HR=high responding

Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands

3. PASS Effectiveness Outcomes

Secondary Analyses	**Patient Number**	**Bleeding Events (patients)**
Annualized Bleeding Rate		**median (Q1, Q3)**
All patients	1,140	3.83 (0.60, 12.90)
Patients prescribed OD at enrolment	421	10.38 (2.27, 27.29)
Prophylaxis (on study, any frequency)	707	2.00 (0, 6.73)
Prophylaxis (on study, ≥twice/week)	560	1.67 (0, 4.80)

Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands

Working Summary: Spontaneous Reports, IS, PASS

- **Spontaneous AE Reports[1]**
  - No detection of previously unrecognized risks
- **Integrated Safety Studies[2]**
  - 418 Subjects from 12 interventional studies were analyzed
  - 0.4% inhibitor risk in PTPs >50 EDs; 95 % CI 0.009-2.002
- **Post Marketing Surveillance Studies[3]**
  - 1188 patients
  - 0.14% Inhibitor risk in PTPs > 50 EDs; 95; % CI 0.002, 0.099
  - ABR 1.66 in 560 patient on => BW prophylaxis 95; % CI 0, 4.78

1. Berg, R et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands; 2. Shapiro A et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands; 3. Marcucci M et al. Poster presented at XXIV Congress of the ISTH, 2013, Netherlands.

Future developments

PASS patient characteristics, n (%)		Patients (%) (n 1,188)
History of inhibitors		
	Yes	**131 (11.0)**
	No	1047 (88.1)
	Unknown	10 (0.8)
Inhibitors detected at baseline		
	Yes	**18 (1.5)**
	No	1070 (90.1)
Unknown		100 (8.4)

Unpublished Data, McMaster University and Baxter - Poster presented at Melbourne 2014 WFH Meeting

Thank you