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ORIGINAL ARTICLE *Clinical haemophilia*

# Patient data meta-analysis of Post-Authorization Safety Surveillance (PASS) studies of haemophilia A patients treated with rAHF-PFM

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**Summary.** A Post-Authorization Safety Study (PASS) global program was designed to assess safety and effectiveness of rAHF-PFM (ADVATE) use in haemophilia patients in routine clinical settings. The main aim of this project was to estimate the rate of inhibitors and other adverse events across ADVATE-PASS studies by meta-analysing individual patient data (IPD). *Eligible Studies*: PASS studies conducted in different countries, between 2003 and 2013, for which IPD were provided. *Eligible patients*: haemophilia A patients with baseline FVIII:C < 5%, with a known number of prior exposure days (EDs). *Primary outcome*: *de novo* inhibitors in severe, previously treated patients (PTPs) with > 150 EDs. *Secondary outcomes*: *de novo* inhibitors according to prior exposure and disease severity; other adverse events; annualized bleeding rate (ABR). *Analysis*: random-effects logistic regression. Five of seven registered ADVATE-PASS (Australia, Europe, Japan, Italy and USA) and 1188 patients were included (median follow-up 384 days). Among severe PTPs with > 150 EDs, 1/669 developed *de novo* inhibitors (1.5 per 1000; 95% confidence interval [CI] 0.2, 10.6 per 1000). Among all patients included in the PASS studies, 21 developed any type of inhibitors (2.0%, 95% CI: 0.8%, 4.7%). Less than 1% of patients presented with other serious adverse events possibly related to ADVATE. The overall median ABR was 3.83 bleeds/year (first, third quartiles: 0.60, 12.90); 1.66 (0, 4.78) in the 557 patients continuously on prophylaxis ≥ twice/week. Meta-analysing PASS data from different countries confirmed the overall favourable safety and effectiveness profile of ADVATE in routine clinical settings.

**Keywords:** bleeding rate, factor VIII, factor VIII inhibitors, hemophilia A, post-marketing, surveillance

## Introduction

The development of alloantibodies inhibiting FVIII is the main obstacle to effective and safe management of bleeding in patients with congenital haemophilia A. Consequently, the scientific community has focused on identifying the possible effects of different treatment modalities on inhibitor risk [1–4]. In particular, the occurrence of product-specific clusters of inhibitor cases and the reports on a potentially different immunogenicity of recombinant (rFVIII) and plasma-derived (pdFVIII) concentrates, and of molecules with different structures and lengths, allow someone hypothesize that the inhibitor risk may differ between products [5–8].

Recently, regulatory authorities, i.e. USA Food and Drug Administration (FDA) and European Medicine Agency (EMA), issued consensus requirements to assess and monitor the immunogenicity of new products [9–11]. This standardization addresses the limitations of comparing the safety of different concentrates using inadequate and inconsistent clinical study

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designs [11,12]. However, preauthorization studies do not typically have sufficient statistical power to comprehensively capture the drug-related adverse events, especially when rare, due to their small sample size, highly selected population and short follow-up. In addition, different outcomes can occur when the drug is used in controlled interventional settings rather than in the routine clinical practice [9,10]. Indeed, a specific FVIII concentrate has been withdrawn from the market, due to a higher than expected inhibitor incidence noted during clinical practice [5]. In this scenario, well-designed and rigorously conducted postmarketing surveillance studies are advocated to monitor the safety (in particular the immunogenicity) of any product [9,10,13].

FDA and EMA recommend assessing product-related immunogenicity in previously treated patients (PTPs) with at least 150 exposure days (EDs), as the most appropriate population [9,10]. Indeed, PTPs represent an immune tolerant population, with a rate of inhibitors of 2–3 per 1000 patients per year [7] (about 1% of the rate in previously untreated patients [PUPs] [6]), where a cluster of inhibitor cases would be easily recognized as an immunogenicity signal. Also, PTPs represent the most common typology of haemophilia patients encountered in clinical practice in Western countries [14].

With this background, Adverse Events Reporting Systems, comprehensive multinational programs of pharmacovigilance and product-specific post-authorization surveillance have been implemented to improve safety signal detection [13,15–18]. The ADVATE Post-Authorization Safety Study (ADVATE-PASS) program [19] consists of studies conducted in various countries to monitor real-world safety, immunogenicity and effectiveness of ADVATE [antihaemophilic factor (recombinant), plasma/albumin-free method, (rAHF-PFM)]. This rFVIII product was approved by both the FDA (July 2003) and EMA (March 2004) based on interventional Phase I–III studies demonstrating a good tolerance, efficacy and acceptable preliminary safety profile [20–26].

We present here a meta-analysis of the ADVATE-PASS studies based on original individual patient data (IPD), with the primary objective of synthesizing the results on the immunogenicity of ADVATE in moderate and severe PTPs treated for more than 150 EDs. As a secondary objective, data on safety in other patient groups and on effectiveness were analysed.

## Materials and methods

### *Eligible studies*

All PASS studies conducted in different countries (Australia, Europe [Austria, Belgium, Denmark, France, Germany, Greece, The Netherlands, Spain, Sweden, Switzerland and the United Kingdom] [27], Japan [28–30], Korea, PISA-Italy [31], Taiwan [32], United States [27]), between the date of ADVATE approval by FDA (25 July 2003), and July 26, 2013, were considered potentially eligible. PASS studies were multicentre (with the exception of Taiwan-PASS, which was conducted in a single centre), prospective, observational studies on patients prescribed with ADVATE in a routine clinical setting by their treating physician, and enrolled without any binding stipulation with regard to the modalities of their management. Each PASS study had an independent protocol, based on country-specific regulatory guidance. All PASS protocols were approved by the relevant Ethical Review Boards. Only those PASS studies providing sufficient data to classify patients according to the number of prior EDs were included in the analyses.

### *Eligible patients*

According to the original PASS protocols, all patients with moderate and severe haemophilia A (i.e. baseline FVIII:C < 5%), of any age, prescribed with ADVATE by their treating physicians, and with valid informed consent, were considered eligible for enrollment. In addition, patients with a known intolerance or allergic reaction to any of the constituents in the drug formulation or to mouse or hamster proteins were ineligible. Patients with mild haemophilia were formally considered ineligible in all PASS protocols with the exception of Korea- and Japan-PASS. Patients with a positive inhibitor titre at baseline were excluded only from USA-PASS.

### *Main analysis*

*Outcomes*. *Primary* outcome of the current meta-analysis was the development of inhibitors. We adopted the cut-offs specified in the original PASS protocols: 1.0 Bethesda Unit (BU) for USA-, EU- and Australia-PASS; and 0.6 BU for Japan-, Italy- and Taiwan-PASS (studies adopting the Nijmegen modification) [33]. Only inhibitors detected after the baseline were considered as a valid outcome; patients with inhibitors detected at baseline but never found positive later on were not counted as outcome, but included in the population at risk. The outcome of our primary interest was represented by *de novo* inhibitors, i.e. inhibitors developed in patients with a negative history of inhibitors and a negative titre at enrollment. Inhibitors reaching a peak titre > 5.0 BU during the study were classified as high responding (HR).

*Secondary* outcomes were a) adverse events (AEs) different from inhibitors, classified according to the seriousness and relatedness to the product, as adjudicated by the treating physicians participating in the PASS study; b) the annualized bleeding rate (ABR) in all patients and by treatment regimen, as a measure of product effectiveness.

 

*Population.* The *primary* population of interest for the current meta-analysis was represented by patients with severe disease (FVII:C < 1%), > 150 prior EDs (PTPs), a negative history of inhibitor and a negative titre at enrollment.

*Secondary* populations for inhibitor outcomes were as follows: patients with a negative history of inhibitors and a negative titre at enrollment: (i) with severe disease (FVIII:C < 1%) and > 50 previous EDs, (ii) with moderate-severe disease (FVIII:C < 2%) and > 150 previous EDs, or (iii) < 50 previous EDs. In addition, the entire PASS population was used for inhibitor outcomes, for other AEs and for effectiveness outcome.

*Treatment regimen.* Patients qualified for the studies if they were treated with ADVATE at enrollment, either newly prescribed or already on ADVATE. Information on exposure to ADVATE for the prestudy period was retrospectively collected. Patients were classified according to the type of treatment modality (on-demand or prophylaxis) in two different ways: (i) according to the regimen they were prescribed at the time they were enrolled in the study, regardless if they changed the regimen during the study; (ii) as on *continuous prophylaxis*, if prophylaxis was actually administered for at least 45 weeks per year.

### *Sensitivity analysis*

Patients were classified with respect to inhibitor history at study enrollment and we were not aware of any patients reclassified after an inhibitor was diagnosed during the PASS studies. Patients with a negative history of inhibitors and an unknown inhibitor titre at enrollment and patients with a negative titre at enrollment and an unknown history of inhibitors were included in the primary population. This approach was prespecified in the protocol to be conservative and describe the worst case scenario (with inclusion of patients who might have had an unknown positive history or baseline, thus expected to be at higher risk of inhibitor detection during the study). To demonstrate the impact of this choice, the analysis of the subset of patients without missing data was presented as a sensitivity analysis.

### *Statistical analysis*

We used a flow diagram to summarize the patients in the ADVATE-PASS program. The baseline characteristics of the patients were analysed using descriptive statistics reported as count (per cent) for categorical variables and median [first quartile (Q1), third quartile (Q3)] for continuous variables. The ABR was first calculated for each patient by annualizing the number of bleeding episodes he presented during the study according to the time the patient spent in the study. The distribution of the patient ABRs was described in terms of median (Q1, Q3). The proportion of patients developing inhibitors and the proportion of patients presenting at least one AE were modeled using random-effects logistic regression with country as random effect. The results are reported as point estimates with 95% associated confidence interval (CI). All the analyses were performed using STATA version 12 (Statacorp, College Station, TX, USA). Our report followed the STROBE checklist (online Appendix S3).

## Results

### *Studies and patients included in the meta-analysis*

Five of the seven ADVATE-PASS studies (Australia, EU, Japan, PISA, and USA) and 1188 patients with moderate or severe haemophilia A met the criteria for inclusion in the meta-analysis (Fig. 1). There were 669 severe PTPs with > 150 EDs, with a negative personal history of inhibitors and a negative titre at enrollment who met the criteria for inclusion in the primary population. The online-only Appendix S1 provides details on the reasons for exclusion of the Taiwan and Korea ADVATE-PASS studies and on the inhibitor detection reported in those studies.

Table 1 describes some relevant baseline characteristics of the patients. The prespecified study duration was 1 year for all PASS studies with the exception of Japan-PASS (2 years); the median patient follow-up was 384 days (Q1 364, Q3 504). PTPs represented the large majority of PASS patients (91.6%) and most of them had been treated for > 150 lifetime EDs at enrollment. The majority of the patients were already on ADVATE at enrollment. Most of the patients (62.6%) were prescribed prophylaxis at enrollment. A lower percentage (49.4%) was prescribed prophylaxis at enrollment and was continuously on the same regimen during the study, receiving at least two infusions per week and a median dose per infusion of 27 IU $kg^{-1}$ (Q1 20, Q3 34).

### *Safety and effectiveness outcomes*

Table 2 describes the findings for the primary and secondary outcomes.

*Development of inhibitors.* Only one patient who had severe haemophilia developed an inhibitor (low responding). This patient was previously treated with > 150 EDs and had a negative personal history of inhibitor development with a negative baseline titre. Table 3 shows the estimated frequency of inhibitor development during the study in different PTPs populations. A separate analysis of patients with HR inhibitors was not performed due to the low number of events.

 

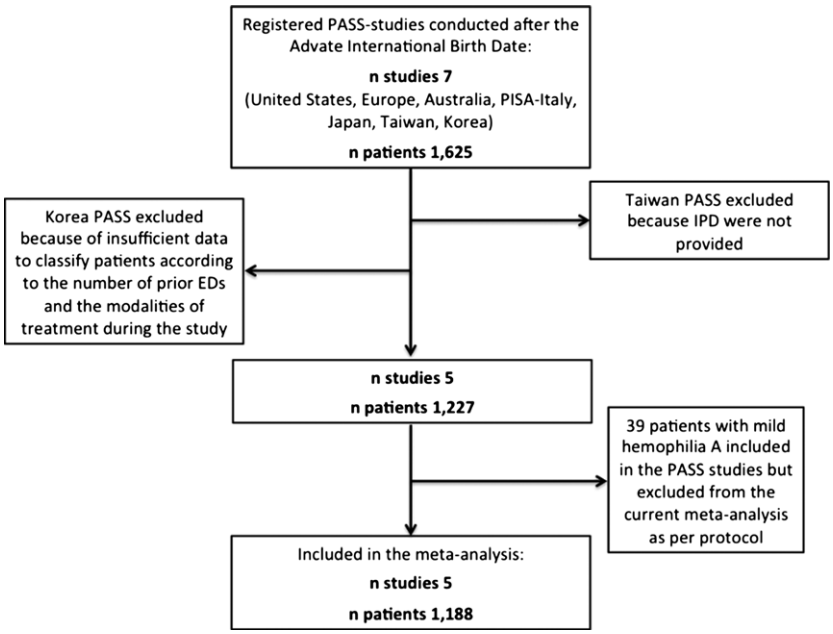


**Fig. 1.** Flow chart for study and patient selection for inclusion in the ADVATE-PASS Individual Patient Data meta-analysis. *n*, number; IPD, individual patient data; EDs, exposure days.

**Table 1.** ADVATE-PASS patient characteristics.

| Characteristics | Patients ($n$ = 1188) |
|---|---|
| PASS studies, *n* (%) | |
| Australia-PASS | 34 (2.9) |
| EU-PASS | 419 (35.3) |
| Japan-PASS | 361 (30.4) |
| IT-PASS | 281 (23.6) |
| USA-PASS | 93 (7.8) |
| Age (years), median (Q1, Q3) | 21.6 (10.0, 35.5) |
| Severe, *n* (%) | 883 (74.3) |
| Previous EDs, *n* (%) | |
| 0–50 | 96 (8.1) |
| 50–150 | 73 (6.1) |
| >150 | 1016 (85.5) |
| Unknown | 3 (0.3) |
| Regimen at enrollment, *n* (%) | |
| On demand | 434 (36.5) |
| Prophylaxis | 743 (62.6) |
| Unknown/Other* | 11 (0.9) |
| Continuous prophylaxis during the study (≥ twice/week), *n* (%)† | 587 (49.4) |
| 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) |

**Other* stays for immune tolerant induction.
†Patients switched from an on-demand regimen to prophylaxis were excluded.
EDs, Exposure Days; *n*, number of patients; Q1, first quartile; Q3, third quartile.

Among 91 patients with < 50 EDs and negative history and baseline, five developed *de novo* inhibitors (pooled percentage 5.4%, 95% confidence interval [CI] 1.4%, 21.8%), three of whom were HR. When analysing the entire study population (1188 patients), 21 patients were found positive for inhibitors, eight of whom were HR (pooled percentage 2%, 95% CI 0.8%, 4.7%). The results of the analyses did not significantly change after excluding those patients with either an unknown titre at enrollment or an unknown history of inhibitors (Table 3).

The online Appendix S2 lists and describes all the patients found to be positive for any inhibitor during the PASS studies.

### *Other adverse events*

Table 2 shows the frequency of adverse events (other than inhibitors) according to their seriousness and product relatedness. Overall, 83 adverse events judged as serious (SAEs) by the treating physicians occurred in 59 patients; most of them were bleedings at different sites, catheter-related infections and malignancy (hepatic and lung). Five SAEs in five patients were judged as product related; two of them were 'hypersensitivity' reactions (oedema and exanthema), 1 a 'cerebral haemorrhage', 1 'anaemia and abnormal hepatic function', and 1 'anxiety'. Two product-related AEs ('asthenia' and 'decreased drug effect') were judged by the treating physicians as 'significant' but 'non-serious'. Table 4 provides the results of the meta-analysis.

### *Annualized bleeding rates*

When considering all patients regardless of the treatment regimen prescribed, a median of 3.83 (Q1 0.60, Q3 12.90) bleeds per patient per year was reported. The median ABR (Q1, Q3) substantially differed among the five PASS studies: AUS 1.1 (0, 4.0), EU 3.2 (0, 10.5), Japan 9.2 (2.9, 30.1), Italy 1.0 (0, 5.0) and USA 2.7 (0, 6.8).

 

**Table 2.** Outcomes during PASS studies: description.

| Outcome and population definitions (total number of patients included in each analysis) | Description |
|---|---|
| Primary analysis | Number of patients with inhibitors (number of patients with HR inhibitors) |
| *De novo* inhibitors in severe PTPs > 150 EDs[#] (669) | 1 (0) |
| Secondary analyses | |
| *De novo* inhibitors in severe PTPs > 50 EDs[#] (717) | 1 (0) |
| *De novo* inhibitors in moderate-severe PTPs > 150 EDs[#] (799) | 1*(0) |
| *De novo* inhibitors in patients < 50 EDs[#] (91) | 5 (3) |
| All inhibitors in severe PTPs >150 EDs** (774) | 11 (4) |
| All inhibitors in all patients (1188)** | 21 (8) |
| Adverse events[†] | Number of events (number of patients with at least one event) |
| Total AEs, any seriousness (1188) | 722 (249) |
| Total SAEs (1188) | 83 (59) |
| Product-related AEs, any seriousness[‡] (1188) | 35 (21) |
| Product-related SAEs[‡] (1188) | 5 (5) |
| Annualized bleeding rate | Median (Q1, Q3) |
| All patients (1140) | 3.83 (0.60, 12.90) |
| Patients prescribed on demand at enrollment (421) | 10.38 (2.27, 27.28) |
| Patients prescribed prophylaxis at enrollment (any frequency) (710) | 2 (0, 6.73) |
| Patients on continuous prophylaxis during the study (≥twice/week) (557) | 1.66 (0, 4.78) |

*This is the same patient reported as severe PTP > 150 EDs experiencing *de novo* inhibitors.
***All inhibitors* definition includes both *de novo* and *recurrent/persistent* inhibitors.
[†]Only adverse events different from inhibitors are included.
[‡]The possible relation to the product was adjudicated by the treating physician participating to the PASS study.
[#]*De novo* inhibitors were defined as inhibitors occurring in patients with negative history of inhibitors and with negative titre at baseline.
HR, high responding; Q1, first quartile; Q3, third quartile.

**Table 3.** Development of inhibitors in previously treated patients.

| Outcome and population (number of patients in main, number in sensitivity) | Number of patients with inhibitors per 1000 (95% CI) | |
|---|---|---|
| | Main analysis* | Sensitivity analysis** |
| Primary | | |
| *De novo* inhibitors in severe PTPs > 150 EDs (669, 608) | 1.5 (0.2, 10.6) | 1.6 (0.2, 11.7) |
| Secondary | | |
| *De novo*, inhibitors in severe PTPs > 50 EDs (717, 655) | 1.4 (0.2, 9.9) | 1.5 (0.2, 10.9) |
| *De novo*, inhibitors in moderate-severe PTPs > 150 EDs (799, 730) | 1.3 (0.2, 8.9) | 1.4 (0.2, 9.8) |
| All inhibitors in severe PTPs > 150 EDs (774) | 10.0 (2.8, 35.4) | - |

*Patients with negative history of inhibitors and a negative inhibitor titre at enrollment, or with no history of inhibitors and an unknown inhibitor titre at enrollment or with a negative inhibitor titre at enrollment and an unknown history of inhibitors.
**Only patients with negative history of inhibitors and a negative inhibitor titre at enrollment; patients with incomplete data were excluded.
CI, Confidence Interval; IPD, Individual Patient Data; *n*, number of patients; PTPs, Previously Treated Patients.

**Table 4.** Other adverse events.*

| Type of adverse events | Number of patients with at least one event per 100 (95% CI) Classical IPD Meta-analysis |
|---|---|
| Total AEs | 24.0 (10.5, 37.5) |
| Total SAEs | 4.8 (1.3, 8.3) |
| Product-related AEs, any seriousness[†] | 2 (1, 4) |
| Product-related SAEs[†] | 0.3 (0, 0.7) |

*Only adverse events different from inhibitors are included.
[†]The possible relation to the product was adjudicated by the treating physician participating in the PASS study.
AE, Adverse event; CI, Confidence Interval; IPD, Individual Patient Data; SAE, Serious Adverse Event.

## Discussion

We compiled the results on the safety and effectiveness of ADVATE from PASS studies conducted in Europe, USA, Australia and Japan. Our findings confirmed, in a routine clinical setting, the favourable profile of ADVATE found in previous I–IV phase studies.

The primary analysis focused on the group of patients classically considered at low to moderate risk of inhibitors, i.e. PTPs, and on *de novo* inhibitors, i.e. developed in patients with no previous evidence of inhibitors. In this population, we found a very low rate of *de novo* inhibitors (between 1 and 2 per thousand) regardless of the number of prior EDs (> 150 EDs or > 50 EDs). When we extended the analyses to include all types of inhibitors and all patients, we found an inhibitor rate of 2%. The upper bound of the confidence interval for any inhibitor in all patients we found was 4.7%, well below the 6.8% threshold in registrational interventional studies [9]. Finally, less than 1% of patients enrolled in the ADVATE-PASS studies presented with a non-inhibitor SAE, related to the product.

Even if planned primarily for monitoring safety after the introduction of ADVATE in clinical practice, the ADVATE-PASS program collected also effectiveness data. The simple descriptive statistics for the ABRs (i.e. medians) suggested the impact of prophylaxis on bleeding frequency measured in a routine clinical setting. It is remarkable that patients on continuous prophylaxis twice or more per week experienced a median of 1.66 bleeds or less (Q1 [0], Q3 [4.78]) annually, which is consistent with the most favourable estimates seen in other studies [24].

The large number of patients represents the main strength of the current analysis and demonstrates that large haemophilia studies can investigate rare treatment-related AEs. Therefore, this manuscript presents a very innovative approach to PASS data. In fact,

 

PASS data are corporate-owned data and corporate statisticians usually perform the analysis. In this case, we asked for and obtained all IPD in their original format and language directly from Baxter Healthcare and regional offices. We designed and ran our own independent analysis plan accounting for each individual patient. We are not aware of any similar experience in the haemophilia field; this study constitutes an important step forward in the way evidence is generated in this field.

The main limitations of our meta-analysis were encountered *in the field* during the evaluation of study and patient eligibility and the creation of the pooled IPD database. These limitations were mainly derived from the lack of homogeneity among the different PASS protocols and datasets. This led to forgoing a larger sample size with the exclusion of Taiwan and Korea PASS studies for the sake of data consistency and quality. This decision reflects the complexity of running a global postmarketing surveillance program. Differences in the clinical practice and regulatory rules among countries (and, within countries, among centres) represented a barrier to a strict adherence to a centrally designed study protocol. Similarly, the retrospective assessment in a clinical practice setting limited the success rate in gathering full details about the number of EDs until inhibitor development, which has never been shown to be of relevance in PTPs and is erratically available for older patients compared to PUPs. Among the limitations of our study was the choice not to infer on the study-specific ABRs by a pooled estimate. Pooling would have required dealing with a skewed distribution and heterogeneity between countries. The safety profile of ADVATE was the main focus of this study; therefore, we preferred to provide only a description of the results with a plan to tackle the methodological issues of assessing measures of effectiveness by meta-analysis in a dedicated article where alternative approaches (i.e. frequentist and Bayesian) will be contemplated.

## Conclusions

Our meta-analysis represents the largest synthesis of evidence on ADVATE safety and effectiveness after its approval for use in clinical practice in different countries. No concern about the immunogenicity of the product among severe PTPs already treated for > 150 EDs, continuing to be treated with, or switching to ADVATE was suggested by this meta-analysis. We also explored for the first time the effectiveness of ADVATE, i.e. its efficacy in a real-world setting. Our experience has also important research implications. This study reaffirms the need for methodologically rigorous and high-level monitoring systems for future PASS programs. We proved the feasibility and relevance of independent analysis of PASS data and clearly indicated how similar regulatory data collections should be analysed and reported. If consistently replicated for other PASS programs, this approach will ultimately provide data suitable to indirectly corroborate much needed comparative effectiveness analyses and complement direct head-to-head comparisons like that provided by EUHASS [15].

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All the existing individual patient data were provided to all the authors in original language, translated and analysed at McMaster. The analysis protocol was written before data provision by MM and JC with input from AI and LT. The analysis was executed by MM and JC with input from AI and LT. VR, EM, CSD and JO provided input in the development of the protocol and took part in the discussion and interpretation of the study results. MM drafted the study report, JC prepared tables and figures. AI and LT are the warrantors of the integrity of data analysis and reporting. All the authors approved the protocol, reviewed drafts and approved the final version of the manuscript.

## Disclosures

VR, EM and CSD are employees of Baxter HealthCare. LT has worked as a consultant for, and held research contracts sponsored by many pharmaceutical companies including GlaxoSmithKline Inc, AstraZeneca, Sorono Canada Inc, F. Hoffman-La Roche Ltd, Pfizer, Theralase Inc, CanReg Inc, Merck Frosst - Schering Pharmaceuticals and Proctor and Gamble Pharmaceuticals Canada Inc. JO received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Baxter, Bayer, Biogen Idec, Biotest, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Swedish Orphan Biovitrum and Pfizer. AI has worked as a consultant for, and held research contracts sponsored by Bayer, Biogen Idec, NovoNordisk, Pfizer. MM and JC have no conflict of interest to declare. This study was supported by a research contract agreement between Baxter HealthCare and St Joseph HealthCare—Hamilton, McMaster University. MM and JC were also supported by peer-reviewed matching funds from MITACS (www.mitacs.ca, Application Ref. No. IT02516).

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Studies excluded by the current meta-analysis: reason for exclusion and reported inhibitor development.

**Appendix S2.** Individual level characteristics of patients positive for inhibitors during PASS studies.

**Appendix S3.** STROBE checklist for "Patient data meta-analysis of Post Authorization Safety Surveillance (PASS) studies: Worldwide post-marketing surveillance of hemophilia A patients treated with antihemophilic factor recombinant plasma/albumin-free method rAHF-PFM".