Albutrepenonacog alfa (Idelvion®) for the treatment of Italian patients with hemophilia B: a budget impact model

Lorenzo Pradelli 1, Sara Villa 2, Giancarlo Castaman 3
1 AdRes HE&OR, Turin, Italy
2 CSL Behring, Milan, Italy
3 Centre for Hemorrhagic Diseases, University Hospital “Careggi”, Florence, Italy

INTRODUCTION

Hemophilia B is an X-linked recessive congenital bleeding disorder caused by the deficiency of coagulation factor IX (FIX). This deficiency is invariably caused by mutations of F9 gene, localized on the long arm of the chromosome X [1].

According to the data collected from 94% of the 54 Italian Hemophilia Treatment Centers and reported in the National Registry of Congenital Coagulopathies (NRCC) [2], in 2014 in Italy the prevalence of hemophilia B was 1.4/100,000 inhabitants. Since hemophilia B is an X-linked disorder, it mainly affects male people (2.7/100,000 inhabitants) who represent 98.5% of cases (n. = 809/821).

In hemophilia B, bleeding events can occur spontaneously, or following minor/major trauma or surgery, into joints (hemarthrosis), muscle (hematomas), or mucous membranes. Intracranial, neck/throat, and gastrointestinal bleeds are life threatening and require immediate treatment. The clinical manifestation of bleeding episodes relates to the severity of disease and depends on the circulating plasma levels of FIX [1] (Table 1). According to NRCC data, in Italy severe, moderate and mild hemophilia B represent 35.7%, 21.7%, and 42.6% of all cases, respectively [2].
Recurrent joint bleeding may lead to chronic arthropathy and progressive damages to the joint tissues that result in chronic pain, disabilities and poor quality of life. As reported by Kodra et al. [3] more than 75% of adult patients with hemophilia (A or B) have physical problems mainly related to mobility (75%) and pain/discomfort (76.7%), while both children and adults report a perceived reduction of quality of life of more than 25%. Hemophilia B is also associated with an high economic burden, since the mean annual total cost per patient estimated by Kodra et al. is equal to € 117,731.72, mainly represented by direct health care costs (€ 109,768.70) of which 98% are imputable to drug costs [3].

Therapeutic strategies in the management of hemophilia B include replacement therapy with exogenous FIX concentrate for acute treatment of bleeding episodes (on-demand therapy) and prevention of bleeding episodes to preserve normal musculoskeletal functions (prophylaxis therapy) [1]. Prophylaxis therapy is usually recommended for patients with severe hemophilia B who have the greatest risk of bleeding episodes, while in patients with mild and moderate disease on-demand treatment in case of acute bleed is indicated. As recommended by The Italian Association of Hemophilia Centres [4], in order to avoid spontaneous bleeding events, the aim of prophylaxis replacement therapy is to keep trough FIX level > 1-2 IU/dl, which usually requires intravenous infusion of FIX every 3 days. The need to administer FIX 2 or 3 times per weeks and the difficulty to manage the injection, especially in children, may lead to an inconsistent treatment adherence, with a consequent increase of bleeding rate. FIX concentrates with longer half-life, which require fewer injections, may reduce the burden for the patient and improve adherence.

In Italy plasma-derived (pdFIX) and recombinant (rFIX) concentrates are available, with a prevalent consumption of rFIX, regardless of disease severity (82% in severe, 73% in moderate, and 94% in mild hemophilia B) [2]. Currently in Italy, three rFIX are available for treatment of hemophilia B: nonacog alfa (BeneFIX®, Pfizer S.r.l.), efetrenonacog alfa (Alprolix®, Swedish Orphan Biovitrum S.r.l.) and albutrepenonacog alfa (Idelvion®, CSL Behring S.p.A.).

BeneFIX® (nonacog alfa) was the first rFIX to get marketing authorization in 1997. Efficacy and safety of two prophylaxis regimens (50 IU/kg twice weekly and 100 IU/kg once weekly) vs on-demand therapy were evaluated in a multicenter, randomized, open-label trial conducted on patients with moderately severe to severe hemophilia B (FIX:C ≤ 2%) [5]. Fifteen male subjects (age 6-65 years) with ≥ 12 bleeding episodes within 12 months of study participation were enrolled; the study included four periods: 1) a 16-week on-demand treatment; 2) randomization and 16-week prophylactic treatment with BeneFIX® 50 IU/kg twice weekly or 100 IU/kg once weekly, 3) a 8-week on-demand treatment, 4) cross-over and 16 weeks receiving the alternate study prophylactic regimen. The primary efficacy endpoint was the Annualized Bleeding Rate (ABR) of two prophylactic regimens vs on-demand therapy. Mean ABR values were 35.1, 2.6, and 4.6 for the first on-demand period, the 50 IU/kg twice weekly prophylaxis, and the 100 IU/kg once weekly prophylaxis, respectively. Both prophylaxis regimens had significantly reduced ABR compared to on-demand therapy (p < 0.0001), while no significant differences were observed between prophylaxis regimens (p = 0.22) [5]. In order to better assess the efficacy and safety of once-weekly prophylaxis with BeneFIX® compared with on-demand, 25 male patients (age 12-65 years) with moderately severe to severe hemophilia B (FIX:C ≤ 2%), ≥ 12 bleeding episodes in the previous 12-months and ≥ 100 exposure days to FIX, were enrolled in a pivotal, multicenter, open-label trial [6]. Patients received on-demand therapy for 26 weeks followed by a 52-week prophylaxis period with 100 IU/kg of BeneFIX®. Mean ABR (primary endpoint) was significantly lower during prophylaxis period compared with on-demand (3.6 vs 32.9; p < 0.0001). The majority of bleeding events occurred (82.1%) responded to the first infusion.

Alprolix® is a recombinant rFIX fusion protein with a prolonged half-life that was developed to reduce the frequency between injections. Efficacy and safety of Alprolix® were evaluated in a phase 3, non-randomized, open-label study which enrolled 123 male patients (≥ 12 years) with severe hemophilia B (FIX:C ≤ 2%) [7]. Participants were assigned to one of four treatment groups which received: 1) weekly dose-adjusted prophylaxis (50 IU/kg to start), 2) interval-adjusted prophylaxis (100 IU/kg every 10 days to start), 3) on-demand treatment, 4) interval-adjusted prophylaxis (100 IU/kg once weekly starting at 50 IU/kg).

## Table I. FIX level and severity of disease

<table>
<thead>
<tr>
<th>Severity</th>
<th>FIX level</th>
<th>Bleeding episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt; 1 IU/dl (&lt; 0.01 IU/ml) or &lt; 1% of normal level</td>
<td>Spontaneous bleeding into joints or muscles</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5 IU/dl (0.01-0.05 IU/ml) or 1-5% of normal level</td>
<td>Occasional spontaneous bleeding. Prolonged bleeding with minor trauma or surgery</td>
</tr>
<tr>
<td>Mild</td>
<td>6-40 IU/dl (0.06-0.40 IU/ml) or 5-40% of normal level</td>
<td>Spontaneous bleeding is rare. Severe bleeding with major trauma or surgery</td>
</tr>
</tbody>
</table>

Modified from [1]
treatment in the perioperative period. Prophylactic treatments significantly reduced the ABR compared with on-demand, indeed ABR value were 3.0, 1.4, and 17.7 in groups 1, 2, and 3, respectively. The median weekly dose in group 1 was 45 IU/kg and the median dosing interval in the group 2 was 12.5 days. 90.4% of bleeding episodes occurred was resolved with one injection, the median dose per injection to resolve bleeding episodes was 46 IU/kg. Alprolix® was assessed in pediatric population in the kids B-LONG study, a phase 3, multicenter, open-label trial conducted on 30 previously treated boys (age < 12 years) with hemophilia B (FIX:C ≤ 2%) [8].

All participants received the first prophylactic dose (50-60 IU/kg weekly) which could be increased to a maximum of 100 IU/kg (adjustment to dose) and frequency of administration to a maximum of twice weekly (adjustment to dosing frequency). The median ABR was 2.0 and 33% of patients reported no bleeding. The median average prophylactic dose was 58.6 IU/kg per week [8].

In the clinical development program (PROLONG-9FP), which included previously treated adult and pediatric patients with severe hemophilia B (FIX ≤ 2%), Idelvion® demonstrated a favorable pharmacokinetics profile, which allows for a prolonged period between two doses in the prophylactic setting, maintaining an adequate FIX level, and fewer infusions at lower dose to stop bleeding per hemorrhagic episode [9-12]. This improvement could mean a reduction of costs associated with fewer infusions.

Purpose of this analysis is to estimate the impact of Idelvion®, a rFIX with prolonged FIX half-life, on the budget of the National Health System for the Italian population of patients with severe hemophilia B.

IDELVION®

Idelvion® is a purified protein produced by recombinant DNA technology, generated by the genetic fusion of recombinant albumin to rFIX (rIX-FP). The cleavable linker that derives from the endogenous activation peptide in native FIX, remains intact until FIX is activated, after which it is released and made available for the coagulation process [13]. Idelvion® is indicated for the treatment and prophylaxis of bleeding in all age groups of patients with hemophilia B [14]. In February 2010, Idelvion® has received orphan designation by the European Commission [15], which has been maintained [16] after the marketing authorization released on May 2016 [17], basing on the results of two pivotal studies conducted in adult/adolescent [11] and pediatric population [12].

PROLONG study on adult/adolescent patients

The study of Santagostino et al. [11] is a prospective, non-randomized, multinational, open-label phase 3 study, designed to evaluate pharmacokinetics (PK), efficacy and safety of Idelvion® for prophylactic and on-demand treatment of previously treated patients (adult/adolescent, age: 12-65 years) with severe or moderate hemophilia B (FIX ≤ 2 IU/dl).

All patients were included in a 14-day PK assessment period and received a single dose of Idelvion® (50 IU/kg). Patients were assigned to either prophylaxis treatment group (group 1) or on-demand treatment group (group 2). Patients in group 1 received Idelvion® (35-50 IU/kg, at investigator’s discretion) every 7 days for 26 weeks; thereafter, if they had no spontaneous bleeds for at least 4 weeks and were receiving ≤ 40 IU/kg or ≤ 50 IU/kg, they were allowed to switch to a dosing interval of 10 or 14 days, respectively, with 75 IU/kg and continued prophylaxis for the remaining treatment period.

Patients in group 2 received on-demand treatment (35-50 IU/kg) for 26 weeks followed by weekly prophylaxis (35-50 IU/kg) for additional 26 weeks or longer. The primary endpoints were the difference of the Annualized spontaneous Bleeding Rate (AsBR) between 7-day prophylaxis and on-demand treatment period in group 2, and the safety of Idelvion® in terms of occurrence of inhibitors against FIX. The secondary endpoints included the ABR in all prophylaxis regimens and the number of injections required to achieve hemostasis when treating bleeding episodes.

The study enrolled 63 patients (40 in group 1 and 23 in group 2). Nineteen patients in the group 2 switched from on-demand treatment to weekly prophylaxis with a significant reduction of the median AsBR (15.43 vs 0.0; p < 0.0001). In group 1, after the first 26 weeks on weekly prophylaxis 28 patients (70%) switched to the 14-day (21 patients) or 10-day (7 patients) prophylaxis regimen at the dose of 75 IU/kg. No significant differences were observed in terms of ABRs between the 7- and 10/14-day regimens with a median of 0.0 spontaneous bleeds/year for all regimens. Results were similar for total and joint ABRs. A comparison be-
Albutrepenonacog alfa (Idelvion®) for the treatment of Italian patients with hemophilia B: a budget impact model

The PK assessment showed mean FIX trough levels equal to 20 IU/dl (range 2.5-36.2 IU/dl) and 12.4 IU/dl (range 3.1-25.4 IU/dl) at day 7 during once week prophylaxis with 40 IU/kg and at day 14 during 14-day prophylaxis with 75 IU/kg, respectively. Finally, Idelvion® demonstrated a favorable safety profile with no serious adverse events observed and no patient who developed inhibitors to FIX or antidrug antibodies.

The results from this study demonstrate the safety and the efficacy of Idelvion® in adult/adolescent patients and support the dosing interval up to 14 days during prophylaxis treatment since its ability to maintain FIX trough level above the commonly recommended target. These results are confirmed by the study of Zhang et al. [18] in which a population PK model was developed in order to simulate different dosing scenarios of Idelvion®. After a single intravenous infusion of Idelvion® (25-75 IU/kg) the predicted median trough FIX level remained > 5 IU/dl for up to 9.5, 12, and 16 days in adult/adolescent, children between 6-12 years, and children aged < 6 years, respectively. The median trough FIX levels were maintained > 5 IU/dl for the duration of the dosing interval both for weekly regimens with 25, 35 and 40 IU/kg and with 75 IU/kg every 14 days in adolescent/adult patients, and for the weekly regimens with 35 and 49 IU/kg in children [18].

PROLONG study on pediatric patients

The study of Kenet et al. [12] is a prospective, non-randomized, international, open-label, phase 3 study designed to evaluate efficacy, PK profile, and safety of Idelvion® in previously treated pediatric patients (< 12 years) with severe or moderate severe hemophilia B (FIX ≤ 2%).

All patients were included in a 14-day PK assessment period and received a single dose of Idelvion® (50 IU/dl). The patients then received weekly prophylaxis with Idelvion® at dose 35-50 IU/kg (at investigator’s discretion) for up to 18 months. The primary objectives of the study were to evaluate the safety (in terms of occurrence of inhibitors against FIX) and the PK profile. The secondary endpoints included AsBRs in the 7-day prophylactic regimen and the number of injections required to achieve hemostasis during a bleeding episode.

The study enrolled 27 pediatric patients. The comparison of the PK profile of Idelvion® 50 IU/kg with previous FIX treatment showed a higher incremental recovery (< 6 years = 0.95 vs 0.676 IU/dl per IU/kg; 6-11 years = 1.06 vs 0.793 IU/dl per IU/kg), a more than five-fold longer half-life (< 6 years = 89.6 vs 19.9 h; 6-11 years = 92.8 vs 17.7 h), slower clearance (< 6 years = 1.187 vs 7.158 ml/h/kg; 6-11 years = 1.059 vs 5.812 ml/h/kg) and greater area under the time-concentration curve (< 6 years = 4.583 vs 886 IU*h/dl; 6-11 years = 5.123 vs 890 IU*h/dl). Patients maintained a median trough FIX level = 13.4 IU/dl during 7-day prophylaxis regimen.

The median total AsBR and ABR during the 7-day prophylaxis regimen were 0.0 and 3.12, respectively, with no differences between the two age groups (AsBR = 0.0 in patients < 6 years and 0.78 in patients 6-11 years; ABR = 2.64 in patients < 6 years and 3.39 in patients 6-11 years). A total of 106 bleeding episodes occurred during the study (45 in patients < 6 and 61 in patients 6-11 years) and 68.9% of them were traumatic. 94 (88.7%) and 9 (8.5%) of these episodes were successfully treated with 1 or 2 injections, with a probability of success (defined as the probability of achieving hemostasis with 1 or 2 injections) of 97.2% (CI95% = 92.0-99.0). Finally, Idelvion® demonstrated a favorable safety profile with no serious adverse events observed and no patient who developed inhibitors to FIX or antidrug antibodies.

The results from this study demonstrate the safety and efficacy of Idelvion® in the pediatric population and support the dosing interval up to 7 days during prophylaxis treatment since it maintains FIX trough level above the commonly recommended target.
PROLONG extension study

This phase 3, open-label, multicenter, extension study was designed to investigate the long-term efficacy and safety of Idelvion® in patients who had completed the previously described Santagostino and Kenet studies [19]. Treatment intervals could be extended to 10 or 14 days with 50-75 IU/kg of Idelvion®, adult patients who were controlled on a 14-day regimen could switch to a 21-day regimen with 100 IU/kg of Idelvion®. The primary objective of the study is to evaluate the safety (in terms of occurrence of inhibitors against FIX); secondary endpoints include clinical efficacy and overall adverse events.

A total of 83 patients were enrolled (52 from [11], 24 from [12] and 7 who started prophylaxis following major surgery). In adult/adolescent population 45 (87%) patients ≥ 12 years switched from 7-day to 10- or 14-day regimen and 10 patients ≥ 18 years switched from 14- to 21-day interval. In the pediatric population (< 12 years) 11 (46%) patients switched to 10- or 14-day interval.

The interim results suggest the possibility to extend treatment intervals both in adult/adolescent (AsBR during 21-day regimen = 0.0) and in children (AsBR during 10- and 14-day regimen = 0.0 and 1.16, respectively).

METHODS

A budget impact model was adapted to simulate the economic impact of partially substituting Idelvion® for other rFIX for prophylactic treatment of patients with severe hemophilia B in Italy. The analysis is conducted from the perspective of the Italian National Health System over a 3-year period.

The economic impact is estimated by the analysis of total costs in a cohort of patients with severe hemophilia B eligible for prophylaxis with Idelvion® and comparing a scenario in which Idelvion® is not available (Scenario w/o Idelvion®) with a scenario following the introduction of Idelvion® (Scenario with Idelvion®) (Figure 1).

Population

Target population is defined based on 2014 data of NRCC [2], which collects epidemiological and therapeutic data from 54 Hemophilia Treatment Centers and reports a total of 821 patients with hemophilia B. Since hemophilia B mainly affects male people, for second and third year of analysis, the growth rate for the Italian male population is applied [20].

According to a conservative approach, only patients with severe disease are taken into account, therefore the estimated eligible population is calculated applying the percentage of patients with severe illness and identifying the subgroup of patients who receive rFIX, as reported in NRCC [2]. Patients flow resulted in 240, 242 and 243 patients for year 1, 2 and 3, respectively. Based on the Italian Hemophilia Registry data total target population is divided into pediatric (< 12 years) and adolescents/adults population [21]. The calculation of the target population is reported in Table II.

Comparators and scenarios

Target patients are assigned to treatment with the rFIX products currently reimbursed in Italy: albutrepenonacog alfa (Idelvion®), efrenonacog alfa (Alprolix®) and nonacog alfa (BeneFIX®). The comparison between current (Scenario w/o Idelvion®) and alternative (Scenario with Idelvion®) scenario derives from a simulation of prescribing scenarios. Table III shows the patient disposition according to the usage rate prediction of the different rFIX over the 3 years of analysis for the two scenarios considered.

Clinical inputs

All patients are assumed to be on a prophylaxis regimen for the entire period of the simulation, therefore clinical inputs include the drug dosages used in prophylaxis and to
treat bleeding episodes. The choice of considering only prophylactic regimens is related to a series of considerations: prophylaxis represents the most followed regimen in severe hemophilia (about 70% according to the latest ISTISAN report [2]); it represents an event much greater share of total FIX expenditures, and it is anticipated that new Idelvion® patients will be predominantly treated with a prophylactic regimen, in order to benefit from its clinical feature of longer interdose intervals. The model considers the prophylaxis dosages to maintain FIX level ≥ 2% while the dose to treat a single episode is calculated based on the ABR, as reported in registration studies and/or in the scientific evaluation documents by the regulatory agencies EMA and FDA, and the Incremental Recovery (IR), defined as the increase of FIX per IU/kg administered. The dose estimation calculated based on IR has been preferred to the trial based usages as this is the practical approach used to determine the dose in the clinical setting. Table IV reports the clinical inputs used in the analysis.

Cost inputs

According to the study of Kodra et al. [3], in which drug costs account for 98% of all direct health costs for hemophilia, the model considers only drug acquisition costs related to the
prophylaxis treatment and the management of bleeding events. The consumption of each FIX is calculated taking into account an average weight of 25 kg for the pediatric population (< 12 years), and of 70 kg for patients adolescents/adults (≥ 12 years).

According to NHS perspective, ex-factory prices per IU [22] are used for each product (Table IV).

**Sensitivity analysis**

Sensitivity analysis is provided by feeding the model with alternative input sources to test the robustness of the results obtained and the parameters used in the base-case and to better understand the main drivers of the economic analysis.

- Maximum dose of the drugs: the maximum dosages recommended in SPCs are tested for Idelvion® (< 12 years = 50 IU/kg once a week; ≥ 12 years = 75 IU/kg every 10 days) [14] and Alprolix® (< 12 years = 60 IU/kg once a week; ≥ 12 years = 100 IU/kg every 10 days) [23]. Due to the lack of data in SPC the dose to maintain the trough level > 5% (50 IU/kg three times a week [19]) are used for both adult and pediatric population treated with BeneFIX®.
- Idelvion® market share: ±20% of Idelvion® market share are tested.

**RESULTS**

**Cost per patient**

Figure 2 shows the mean annual pharmaceutical costs per patient affected by severe hemophilia B treated in prophylaxis with the three rFIXs currently available in Italy. Results are reported for prophylaxis and bleeding treatment in the two age groups.

**Budget impact**

Table V shows the number of patients allocated to the different treatment strategies in the two scenarios analyzed.

The results of the budget impact analysis show that for an estimated target population eligible for treatment with rFIX of 240 patients for the first, 242 for the second, and 243 for the third year, the economic impact of partially substituting Idelvion® for other rFIX for prophylactic treatment would result in a potential saving for the Italian NHS of € 1,302,995, € 2,132,448, and € 2,725,789 in the course of the first, second and third year of treatment, respectively (Table VI). The cumulative budget impact for 3 years results in a total saving for the Italian NHS of € -6,161,232.

**Sensitivity analysis**

Figure 3 shows the results of the scenario analysis.
DISCUSSION

Hemophilia B is a rare bleeding disorder associated with high economic and societal burden. On-demand therapy with pdFIX or rFIX concentrate is indicated for the acute treatment of bleeding episodes in the patients with mild and moderate disease. In patients with severe hemophilia B with high bleeding risk, a prophylaxis regimen is recommended in order to preserve normal musculoskeletal functions [1].

The enhanced PK profile shown by Idelvion®, a recombinant human coagulation FIX generated by the fusion with albumin, compared to existing FIX therapies, allows prolonged period between two doses in the prophylactic setting, maintaining an adequate FIX level, and fewer infusions at lower dose to stop bleeding per hemorrhagic episode [9-12,18,19]. The results from the pivotal studies [11,12] support the dosing interval up to 14 and 7 days in adult/adolescent and pediatric population since both dosages demonstrated to keep trough FIX level > 1-2 IU/dl which is the commonly recommended target [4].

An important aspect related to the prophylaxis with FIX is the suboptimal adherence to the treatment due to the high number of infusion required. A poor adherence to FIX regimen, which may include dose-skipping and under-dosing, may lead to an increased bleeding rates and chronic pain. The prolonged period between injections could improve the adherence to the treatment and the clinical outcomes, while reducing total costs. In our economic analysis the mean cost per patient results lower for Idelvion® with respect to Alprolix® in the adult population, while among children Idelvion® is associated to slightly higher acquisition costs; the prophylaxis cost strongly drives pharmaceutical costs, representing about 91-95% of them. Under the hypothesis that Idelvion® gains 32%, 52% and 66% of the uptake, respectively at the end of the 1st, 2nd and 3rd year from the access, the model estimates for the Scenario with Idelvion® a total saving of 6.2 million Euros. From a resources reallocation point of view, this value means that 30 more patient-years could be covered without any expenditure increase. The result of sensitivity analysis shows a budget impact not significantly influenced by Idelvion® prevalence; instead, dose adjustment appears strongly associated to financial variations: in the hypothesis that Idelvion® at mean dose would be used in patients otherwise treated with BeneFIX® or Alprolix® at their maximum recommended doses, savings are maximized.

The main limitation of this analysis concerns the assumption that only, and all, severe patients receive prophylaxis; the model construction also ignores the positive effect of the better clinical outcomes on hemarthrosis onset with consequent minor need of physiotherapy/prosthetic substitution, and related clinical and economic advantages.

CONCLUSIONS

The introduction of Idelvion® among the available therapeutic options against hemophilia B is expected to decrease pharmaceutical costs and to improve patient’s quality of life (less frequent infusions, higher trough levels, better protection against spontaneous bleeding), as compared with the other concentrates.

Acknowledgments

We would like to thank Orietta Zaniolo (AdRes HE&OR) for help with data management and analysis.

Funding

The study was sponsored by CSL Behring Italy.

Conflict of interest

LP is co-owner and employee of Adres, which has received project funding by CSL Behring Italy for the conduct of the study. LP is editorial member of Farmeconomia. Health Economics and Therapeutic Pathways.

SV is employee of CSL Behring Italy.

GC has received speaker honoraria from CSL Behring Italy.

REFERENCES


   *Blood Transfus* 2014; 12 Suppl 3: s567-75; https://doi.org/10.2450/2014.0042-14s


   *Haemophilia* 2014; 20: 398-406; https://doi.org/10.1111/hae.12344


   *Lancet Haematol* 2017; 4: e75-e82; https://doi.org/10.1016/S2352-3026(16)30193-4

   *Blood* 2012; 120: 2405-11; https://doi.org/10.1182/blood-2012-05-429688

    *Haemophilia* 2015; 21 784-90; https://doi.org/10.1111/hae.12721


15. EMA. Committee for Orphan Medicinal Products. Public summary of opinion on orphan designation. Recombinant fusion protein linking human coagulation factor IX with human albumin for the treatment of hemophilia B. 


20. ISTAT. Growth rate for Italian male population. Available at www.demo.istat.it (last accessed June 2017)