An Indirect Comparison of the Efficacy of Prophylactic Use of rFIXFc and rFIX Products and Simulation of the Effect of Compliance on Effectiveness

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Presenter Disclosures

Disclosures for Alfonso Iorio

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CONFLICT	DISCLOSURE – IF CONFLICT OF INTEREST EXISTS
RESEARCH SUPPORT	Baxter, Biogen Idec, and Novo Nordisk
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Introduction and Objective

- Prophylaxis for hemophilia B requires 2-3 infusions/week.
- rFIXFc may require fewer infusions.
- Compliance may be affected by number of infusions.
- No head-to-head clinical studies of rFIXFc and rFIX have been conducted.

Objectives:

➢ To indirectly compare the efficacy of rFIXFc and rFIX products, using published data.

➢ To model the potential impact of improved compliance.

rFIX, recombinant factor IX, rFIXFc, recombinant factor IX Fc fusion protein.

Clinical Studies Analysed

- Inclusion criteria:
  - Clinical studies on prophylactic use of rFIX in PTPs reporting annualised bleeding rate (ABR) or number of bleeding events

Study	Product	Baseline FIX, % of normal	Duration, Weeks	Subjects with On-study Prophylaxis, N	Mean ABR ± SD[a]
Powell et al 2013[1,a]	rFIXFc	≤2%	52	63	3.07 ± 2.87
Roth et al 2001[2]	rFIX (BeneFIX)	≤5%	104	19	5.49 ± 5.00
Lambert et al 2007[3]	rFIX (BeneFIX)	≤2%	32	17	3.11 ± 3.76
Valentino et al 2013[4]	rFIX (BeneFIX)	≤2%	56	44	4.60 ± n/r
Windyga et al 2014[5]	rFIX (Rixubis)	≤2%	26	56	2.60 ± n/r

[a]Includes data from the once-weekly prophylaxis arm of the study, and data on file (Biogen Idec).

Meta-Analysis and Indirect Comparison

- **Unadjusted indirect comparison of efficacy**

    - rFIXFc: mean ABR = 3.07[1]

    - rFIX: pooled mean ABR based on random effects meta-analysis = 3.84
      (I^2 = 57.5%)

    - Unreported standard deviations were estimated assuming a Poisson distribution and corrected for overdispersion.

1. Powell JS, et al. *New Engl J Med*. 2013;369(24):2313-2323. 2. Roth DA, et al. *Blood*. 2001;98(13):3600-3606. 3. Lambert T, et al. *Haemophilia*. 2007;13(3):233-243. 4. Valentino LA, et al. *Haemophilia*. 2014. [epub ahead of print.] doi: 10.1111/hae.12344. 5. Windyga J, et al. *Haemophilia*. 2014;20(1):15-24. 6. DerSimonian R, Laird N. *Controlled Clin Trials*. 1986;7(3):177-188

Meta-Analysis and Indirect Comparison

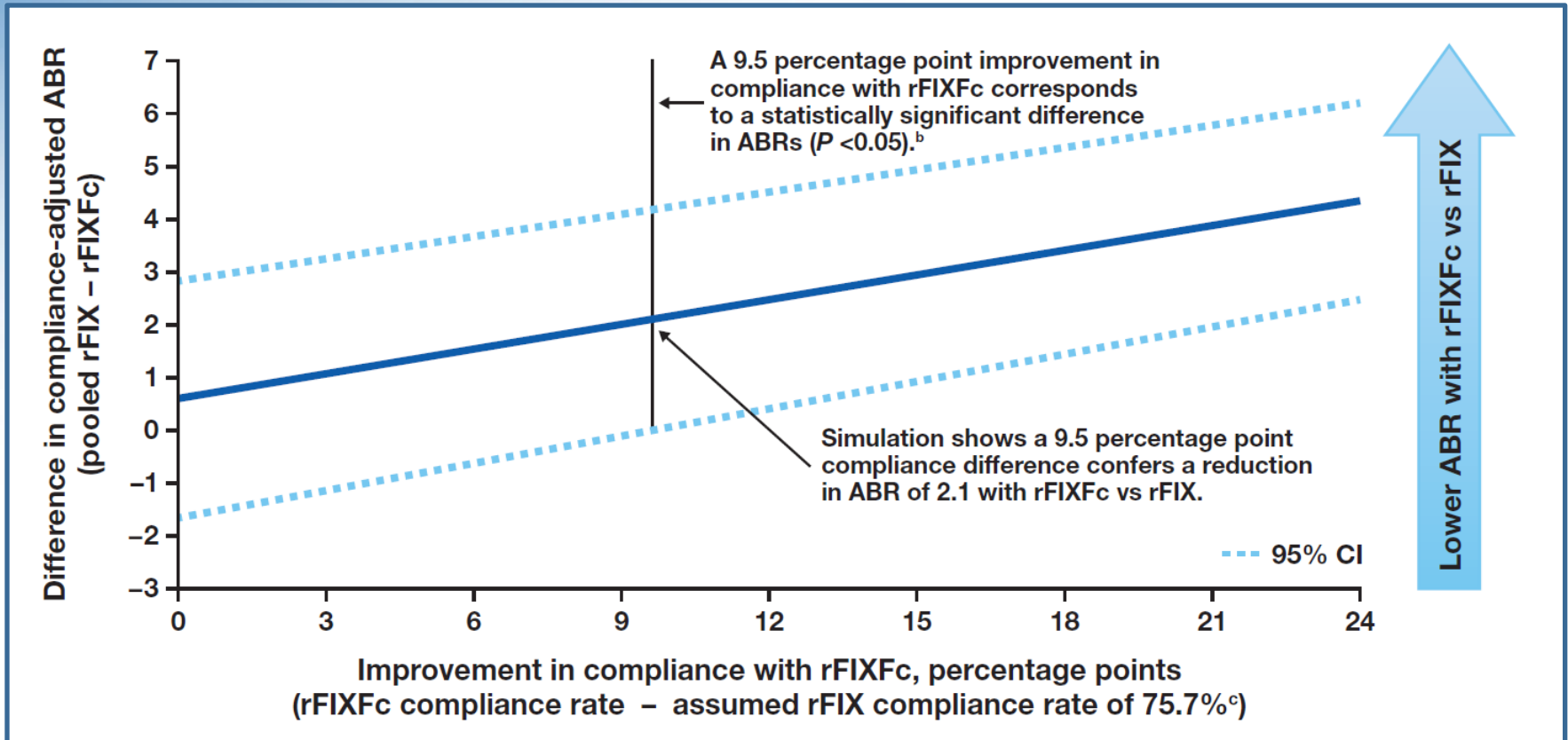| rFIX comparator	Once weekly rFIXFc prophylaxis	
	Δ in ABR[a]	*P* value[b]
Individual rFIX studies		
Roth et al[2]	−2.42	0.11
Lambert et al[3]	−0.04	0.79
Valentino et al (100 IU/kg)[4]	−1.53	0.12
Valentino et al (50 IU/kg)[4]	0.47	0.60
Windyga et al[5]	−1.13	0.33
All rFIX studies pooled (I^2 = 57.5%)[c]	−0.77	0.23

[a]Negative value indicates fewer bleeds with rFIXFc compared with rFIX.
[b]Student's *t* test used for comparisons of individual studies; *Z* test used for comparison of pooled estimate.
[c]Pooled estimates are based on meta-analysis with random effects using the DerSimonian and Laird method.[6]
ABR, annualised bleeding rate; rFIX, recombinant factor IX; rFIXFc, recombinant factor IX fusion protein.

1. Powell JS, et al. *New Engl J Med*. 2013;369(24):2313-2323. 2. Roth DA, et al. *Blood*. 2001;98(13):3600-3606. 3. Lambert T, et al. *Haemophilia*. 2007;13(3):233-243. 4. Valentino LA, et al. *Haemophilia*. 2014. [epub ahead of print.] doi: 10.1111/hae.12344. 5. Windyga J, et al. *Haemophilia*. 2014;20(1):15-24. 6. DerSimonian R, Laird N. *Controlled Clin Trials*. 1986;7(3):177-188

Simulation Based on Compliance Level of 75.7%

[a]Pooled estimates of ABRs on prophylaxis based on random effects meta-analysis of all rFIX comparator studies. Standard deviations for the *Roth et al*[1], *Lambert et al*[2], and *Valentino et al*[3] studies were estimated assuming Poisson distributions and adjusted for over-dispersion; other studies are as reported.
[b]When assumed rFIX compliance rate is 75.7%. Note that lower 95% confidence limit is >0.
[c]Based on estimates of current levels of prophylaxis compliance reported in *Ho et al* (*Haemophilia*. 2014;20(1):39-43).

ABR, annualised bleeding rate; rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc fusion protein.
1. Roth DA, et al. *Blood*. 2001;98(13):3600-3606. 2. Lambert T, et al. *Haemophilia*. 2007;13(3):233-243. 3. Valentino LA, et al. *Haemophilia*. 2014. [epub ahead of print.] doi: 10.1111/hae.12344.

Study Limitations

- This comparison is indirect.

- A random-effects meta-analysis approach was used to account for between-study variance.

- The effect of changes in compliance are based on the assumption that ABR is correlated to compliance over the range of values reported in clinical trials for patients treated with on-demand or prophylaxis regimens.

Conclusions

- Based on unadjusted indirect comparison of 6 clinical studies for rFIXFc and rFIX products
  - The efficacy of prophylaxis treatment with once-weekly rFIXFc is comparable to more frequently infused rFIX.
  - Less frequent infusions with rFIXFc may enhance compliance and consequently effectiveness, as suggested by compliance modeling.
  - Simulations suggest improvements in compliance of ≥ 9 to 14% with rFIXFc would yield a statistically significant reduction in mean ABR.

- Additional studies are necessary to validate these findings and assess the true impact of rFIXFc on real-world effectiveness.

ABR, annualised bleeding rate; rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc fusion protein.