P0182

Simulation of Extended Half-Life Replacement FIX Therapy Dosing to Achieve Comparable FIX Activity to That of Fidanacogene Elaparvovec Gene Therapy in Hemophilia B Patients

Jessica Wojciechowski[1], Puneet Gaitonde[2], Lisa Wilcox[3]

[1]Pfizer Inc, Groton, CT, USA; [2]Pfizer Inc, Cambridge, MA, USA; [3]Pfizer Inc, Toronto, Canada

BACKGROUND

- Hemophilia B is an X-linked (*F9* gene) disorder of hemostasis that results in insufficient endogenous factor IX (FIX) activity.[1]
- The current standard of care for people with severe hemophilia B (FIX activity <1%) is prophylactic replacement therapy with exogenous FIX (for example, an extended half-life therapy such as eftrenonacog alfa [Alprolix®] 50 IU/kg once weekly or 100 IU/kg every 10 days).[2]
- The goal of prophylaxis is to prevent bleeding by reducing the amount of time people with hemophilia B spend with FIX activity below a target level (ie, trough).
- Fidanacogene elaparvovec (PF-06838435, formerly SPK-9001) is an adeno-associated virus (AAV)–based gene therapy designed to deliver a modified functional copy of the *F9* gene (the high-activity FIX-R338L/FIX-Padua variant), allowing for the synthesis of endogenous FIX at activity levels that can prevent many unprovoked bleeding events.
  - Fidanacogene elaparvovec is in clinical development for the treatment of hemophilia B.[3]
- Whether standard FIX replacement therapy can consistently maintain FIX activity at trough levels comparable to those observed in clinical trials after treatment with fidanacogene elaparvovec gene therapy is unknown as it will depend, in part, on the dose and dosing frequency of the replacement FIX therapy.

OBJECTIVES

- To determine the dose and frequency of FIX prophylaxis (using Alprolix as the example) required to maintain trough FIX activity at levels predicted for fidanacogene elaparvovec gene therapy up to 25 years.

METHODS

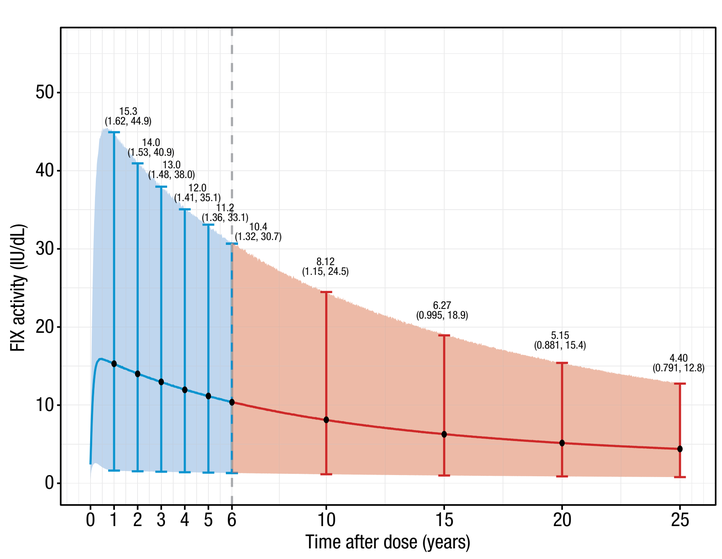
- A longitudinal pharmacometrics model using non-linear effects modeling methodologies of FIX activity data (measured using Actin FSL one-stage assay) following fidanacogene elaparvovec administration in phase 1–3 studies (NCT03861273, NCT03307980, NCT02484092) was developed. A pharmacometrics approach for characterizing FIX activity for AAV-based gene therapies was previously described using data from phase 1/2a studies.[4]
- FIX activity following the administration of 5×10^{11} vg/kg fidanacogene elaparvovec was simulated for 100,000 virtual individuals (with body weight representative of a hemophilia B population) to generate the mean gene therapy response up to 25 years (considered the reference response).[4]
- FIX activity following Alprolix dosing was simulated for 500 virtual individuals (with body weights representative of a hemophilia B population) using a published population pharmacokinetic model.[5]
- At each year for 25 years, (i) the dose (with frequency fixed as once weekly) and (ii) frequency (with dose fixed at 50 IU/kg) of Alprolix required to achieve trough FIX activity comparable to the time-matched mean fidanacogene elaparvovec response were determined for each individual using a maximum likelihood estimation algorithm.
- At each year, the Alprolix dose and frequency required to achieve the reference fidanacogene elaparvovec FIX activity were summarized using the median and 90% prediction interval (PI) of the virtual population.

RESULTS

FIX Activity Predictions Following Fidanacogene Elaparvovec Gene Therapy

- For the virtual population, mean FIX activity (based on Actin FSL) following 5×10^{11} vg/kg fidanacogene elaparvovec administration was predicted to remain above 15 IU/dL for the first year, above 8 IU/dL at 10 years, and above 4 IU/dL at 25 years (**Figure 1**).

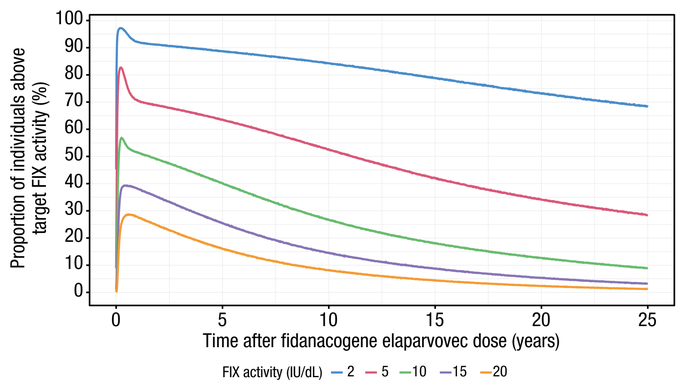
Figure 1: Predicted time-course of FIX activity (Actin FSL one-stage assay) for the simulated population following fidanacogene elaparvovec administration



Predicted FIX activity over time extrapolated up to 25 years.
Solid lines and shaded regions are the mean and 90% PI FIX activity time-course (Actin FSL) for 100,000 simulated patients with hemophilia B administered a nominal dose of 5×10^{11} vg/kg fidanacogene elaparvovec.
Black circles and error bars are mean and 90% PI of FIX activity summarized at timepoints of interest.
Dashed vertical gray line represents the end of the observed follow-up period in the analysis population.
FIX=factor IX; PI=prediction interval

- For the first 10 years after fidanacogene elaparvovec administration, >80% of individuals in the virtual population maintained FIX activity levels above 2 IU/dL; >5% of individuals maintained FIX activity levels above 20 IU/dL (**Figure 2**).

Figure 2: Proportion of individuals in the simulated population with predicted FIX activity above the selected target levels

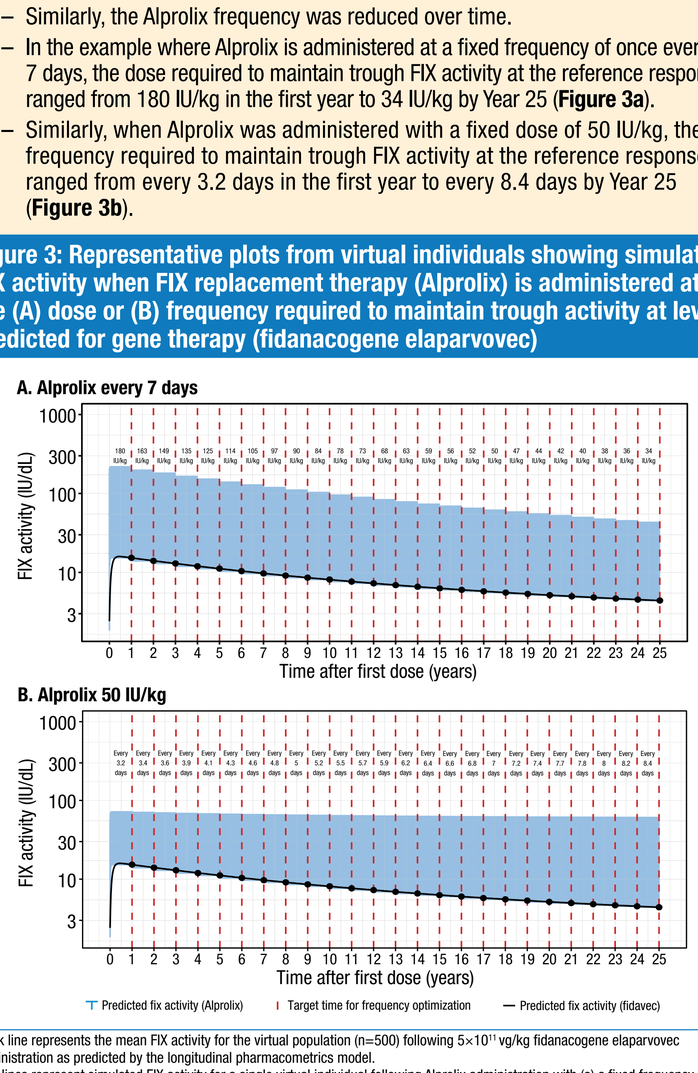


FIX=factor IX

Simulation of FIX Replacement Therapy Dosing

- Simulations of FIX activity following Alprolix administration showed high and/or frequent Alprolix dosing was required to maintain trough FIX activity at levels comparable to those predicted following 5×10^{11} vg/kg of fidanacogene elaparvovec.
- **Figure 3** depicts the Alprolix dose (**Figure 3a**) and frequency (**Figure 3b**) required to maintain trough FIX activity at the reference response of fidanacogene elaparvovec for 1 example individual in the virtual population.
  - Here, FIX activity from Alprolix (blue) was consistently above the mean fidanacogene elaparvovec (black) 5×10^{11} vg/kg response in order to maintain trough FIX activity above the reference.
  - The Alprolix dose required decreases over the 25-year period as the FIX activity from fidanacogene elaparvovec is predicted to decrease over time by the longitudinal pharmacometrics model.
  - Similarly, the Alprolix frequency was reduced over time.
  - In the example where Alprolix is administered at a fixed frequency of once every 7 days, the dose required to maintain trough FIX activity at the reference response ranged from 180 IU/kg in the first year to 34 IU/kg by Year 25 (**Figure 3a**).
  - Similarly, when Alprolix was administered with a fixed dose of 50 IU/kg, the frequency required to maintain trough FIX activity at the reference response ranged from every 3.2 days in the first year to every 8.4 days by Year 25 (**Figure 3b**).

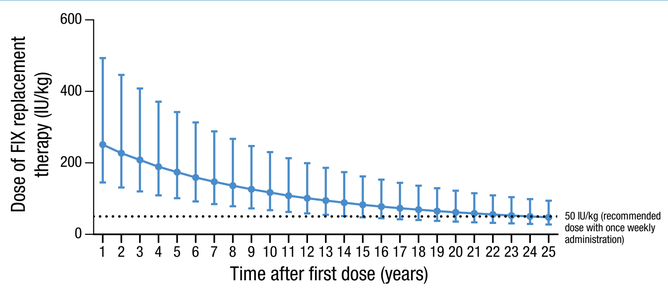
Figure 3: Representative plots from virtual individuals showing simulated FIX activity when FIX replacement therapy (Alprolix) is administered at the (A) dose or (B) frequency required to maintain trough activity at levels predicted for gene therapy (fidanacogene elaparvovec)



Black line represents the mean FIX activity for the virtual population (n=500) following 5×10^{11} vg/kg fidanacogene elaparvovec administration as predicted by the longitudinal pharmacometrics model.
Blue lines represent simulated FIX activity for a single virtual individual following Alprolix administration with (a) a fixed frequency (every 7 days) or (b) fixed dose (50 IU/kg).
Dotted vertical red lines represent the target times at which the (a) dose or (b) frequency were optimized.
Numbers above the traces indicate the (a) dose or (b) frequency required to maintain trough activity at the time-matched fidanacogene elaparvovec response.
fidavec=fidanacogene elaparvovec; FIX=factor IX

- For the entire virtual population, the median Alprolix dose required to maintain trough FIX activity at the time-matched mean fidanacogene elaparvovec response exceeded the recommended dose of 50 IU/kg every 7 days until Year 25 (**Figure 4**).

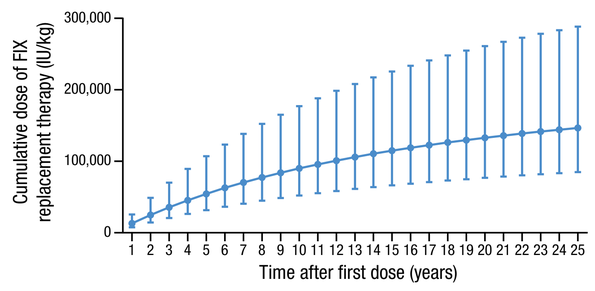
Figure 4: Median (90% PI) dose of FIX replacement therapy (Alprolix; once weekly fixed frequency) required to maintain trough FIX activity at the time-matched mean fidanacogene elaparvovec response



FIX=factor IX; PI=prediction interval

- This corresponded to a median (90% PI) cumulative required dose ranging from 13047 (7546, 25653) IU/kg over the first year to 146630 (84804, 288302) IU/kg over Years 1–25 (**Figure 5**).

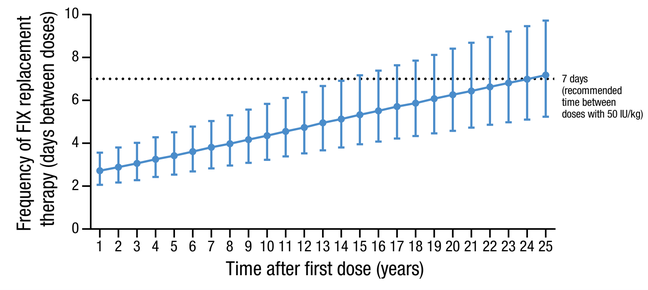
Figure 5: Median (90% PI) cumulative dose of FIX replacement therapy (Alprolix; once weekly fixed frequency) required to maintain trough FIX activity at the time-matched mean fidanacogene elaparvovec response



FIX=factor IX; PI=prediction interval

- The median frequency of Alprolix required to maintain trough FIX activity at the time-matched mean fidanacogene elaparvovec response was more frequent than the recommended every 7 days (once weekly) at 50 IU/kg until Year 25 (**Figure 6**).

Figure 6: Median (90% PI) frequency of FIX replacement therapy (Alprolix; 50 IU/kg fixed dose) required to maintain trough FIX activity at the time-matched mean fidanacogene elaparvovec response



FIX=factor IX; PI=prediction interval

- Dose and frequency results for the simulated population are summarized in the **Table**.

Table: Dose and frequency of FIX replacement therapy (Alprolix) required to maintain trough FIX activity at levels predicted for fidanacogene elaparvovec

	Time after first dose (years)			
Parameter	**1**	**5**	**10**	**25**
Target FIX activity, mean, IU/dL	15.30	11.17	8.12	4.40
Amount, median (90% PI)[a], IU	19704 (11156, 42440)	13661 (7735, 29426)	9204 (5211, 19825)	3755 (2126, 8087)
Dose, median (90% PI)[a], IU/kg	251 (145, 493)	174 (101, 342)	117 (67.8, 230)	47.8 (27.7, 94.0)
Cumulative dose, median (90% PI)[a], IU/kg	13047 (7546, 25653)	54494 (31516, 107147)	90088 (52104, 177134)	146630 (84804, 288302)
Frequency, median (90% PI)[b], days	2.72 (2.06, 3.56)	3.42 (2.54, 4.51)	4.35 (3.23, 5.84)	7.18 (5.24, 9.72)

[a] Frequency fixed at once weekly (every 7 days).
[b] Dose fixed at 50 IU/kg.
FIX=factor IX; PI=prediction interval

CONCLUSIONS

- Even with an extended half-life FIX replacement therapy (Alprolix), the simulated doses and frequencies required to maintain reference FIX activity trough levels comparable to fidanacogene elaparvovec exceeded recommended dosing regimens listed in the Alprolix package insert (50 IU/kg once weekly or 100 IU/kg once every 10 days).[2]
  - Assuming a fixed frequency of once weekly, required doses exceeded 100 IU/kg in the first 10 years.
  - Assuming a fixed dose of 50 IU/kg, required frequencies were less than ~4.5 days between doses in the first 10 years.
- These are conservative estimates as additional doses might be needed for on-demand treatment of bleeds.
- The findings suggest fidanacogene elaparvovec gene therapy results in FIX activity that is not achievable within the labeled posology for Alprolix.

REFERENCES

1. Srivastava A, et al. Haemophilia 2020;26:1-158.
2. Alprolix US prescribing information. Bioverativ Therapeutics; 2020.
3. George LA, et al. N Engl J Med 2017;377:2215-27.
4. Wojciechowski J, et al. 2023 American Conference on Pharmacometrics; poster T-018.
5. Diao L, et al. Clin Pharmacokinet 2014;53:467-77.

DISCLOSURES

JW, PG, and **LW** are employees of and shareholders in Pfizer.

ACKNOWLEDGMENTS

This study was funded by Pfizer. Medical writing support was provided by Courtney M. Cameron, PhD, of Engage Scientific Solutions and funded by Pfizer.

Electronic Poster
Please scan this QR code with your smartphone app to view or obtain a copy of this poster. If you don't have a smartphone, access the poster via the internet at:
https://scientificpubs.congressposter.com/p/vhnkuafvd9n7jcv9

Presented at the 17th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), February 6–9, 2024, Messe Frankfurt, Germany