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# POSTER ABSTRACTS

## 801.GENE THERAPIES

### Characterizing a Cohort of Patients with Hemophilia B Treated with Fidanacogene Elaparvovec from the Phase 3 Benegene-2 Study Who Returned to Factor IX Prophylaxis

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**Background:** Fidanacogene elaparvovec (PF-06838435, formerly SPK-9001) is an adeno-associated virus (AAV)-based gene therapy designed to deliver a high-activity human factor IX (FIX) variant transgene, FIX-R338L, resulting in endogenous FIX production in people with hemophilia B. To date, 45 participants with moderately severe to severe (FIX:C ≤2%) hemophilia B have received fidanacogene elaparvovec as part of the ongoing phase 3 study, BENEGENE-2 (NCT03861273). Of these 45 participants, 6 returned to prophylaxis (RTP) of FIX after initially responding to treatment. We describe the characteristics of the RTP participants.

**Methods:** Participants with baseline FIX activity ≤2% received a single dose of 5e11 vg/kg fidanacogene elaparvovec (AAVrh74 variant) as part of the phase 3 study (N=45). Participants suspended prophylaxis following vector infusion (1 participant continued for 2 weeks post infusion), which could be resumed per the investigator's discretion and the protocol provided guidance for when to consider resuming prophylaxis: ≥2 consecutive central laboratory FIX activity levels ≤2% at least 2 weeks apart and/or ≥2 spontaneous joints bleeds within 4 weeks and/or ≥3 spontaneous bleeds overall (joint and non-joint).

**Results:** Prior to fidanacogene elaparvovec infusion, all 45 participants had completed at least 6 months of prophylaxis as part of the lead-in study (BENEGENE-1, NCT03587116). The mean age (range) of all 45 study participants was 33.2 y (18-62) and the 6 RTP participants had a mean age (range) of 28.3 y (18-47), of whom 4 were <30 y old. The region, race, and weight of the 6 RTP participants were representative of the entire study population (Table 1). All RTP participants initially responded to gene therapy and achieved peak FIX activity levels >5%, determined by one-stage actin-FSL (7-22.1%) and one-stage Synthasil (18.3-45.5%) across Days 36-97. Time to RTP from fidanacogene elaparvovec dose ranged from Days 155 to 623. The reasons reported for RTP were low FIX activity in 5 participants, of whom 1 had a prior history of intracerebral hemorrhage, and increased bleeds in 1 participant. Five participants recorded ≥1 bleeding event prior to resumption of prophylaxis. All RTP participants were treated with ≥1 course of corticosteroids for presumed cellular immune response. In all cases, maximum alanine aminotransferase was 1-2x upper limit of normal. Two RTP participants had an ELISPOT drawn within ±1 day of starting corticosteroids; both were negative for capsid peptides (Table 2). In comparison, 4 participants who took corticosteroids but did not resume prophylaxis were positive for capsid. All 6 RTP participants had a decline in FIX activity from peak levels in the absence of inhibitors, but displayed variable decline prior to and during corticosteroid treatment, or after completion of corticosteroid wean, with and without some elevation of liver enzyme at the time of the decline.

**Conclusion:** The 6 RTP participants who received fidanacogene elaparvovec in the phase 3 study (BENEGENE-2) initially responded to therapy before a heterogenous decline in FIX activity. The limited number of participants and lack of consistent patterns and demographic features make identifying predictors of potential RTP challenging. Although all RTP participants were treated with corticosteroids during this study, not all participants treated with corticosteroids RTP of FIX. Predictors of

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loss of response have not been identified and further work is ongoing to potentially identify factors associated with increased risk of RTP.

**Disclosures Frenzel:** *Pfizer:* Consultancy, Other: Grant, Research Funding; *Roche:* Consultancy; *CSL Berhing:* Consultancy, Research Funding; *Biomarin:* Consultancy. **Kavakli:** *BioMarin:* Membership on an entity's Board of Directors or advisory committees; *CSL Behring:* Membership on an entity's Board of Directors or advisory committees; *Novo Nordisk:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Roche:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees. **Klamroth:** *Sanofi:* Honoraria, Other: Advisory board; *Roche/Chugai:* Honoraria, Other: Advisory board; *Pfizer:* Honoraria, Other: Advisory board; *Octapharma:* Honoraria, Other: Advisory board; *Novo Nordisk:* Honoraria, Other: Advisory board; *Grifols:* Honoraria, Other: Advisory board; *CSL Behring:* Honoraria, Other: Advisory board; *Biotest:* Honoraria, Other: Advisory board; *BioMarin:* Honoraria, Other: Advisory board; *Bayer:* Honoraria, Other: Advisory board; *Sobi:* Honoraria, Other: Advisory board; *Takeda:* Honoraria, Other: Advisory board. **Shapiro:** *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Novo Nordisk Haemophilia Foundation:* Membership on an entity's Board of Directors or advisory committees; *Sanofi-Genzyme/Bioverativ:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novo Nordisk:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Clinical trial investigator ; *Indiana Hemophilia and Thrombosis Center:* Current Employment; *CSL-Behring:* Membership on an entity's Board of Directors or advisory committees; *Freeline:* Other: Clinical trial investigator ; *Sanofi:* Other: Clinical trial investigator . **Sun:** *Pfizer:* Current Employment, Current equity holder in publicly-traded company. **Fuiman:** *Pfizer:* Current Employment, Current equity holder in publicly-traded company. **McKay:** *Pfizer:* Current Employment, Current equity holder in publicly-traded company. **Fang:** *Pfizer Inc:* Current Employment, Current equity holder in publicly-traded company. **Biondo:** *Pfizer Inc:* Current Employment, Current equity holder in publicly-traded company. **Plonski:** *Pfizer:* Consultancy, Current equity holder in publicly-traded company. **Rupon:** *Pfizer:* Current Employment, Current equity holder in publicly-traded company.

**OffLabel Disclosure:** Fidanacogene elaparvovec incorporates a hepatotropic AAV capsid and a high-activity FIX transgene encoding FIX-R338L and is currently in development for patients with severe and moderately severe hemophilia B.

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**Table 1:** Baseline characteristics of participants who returned to prophylaxis treatment and all participants from the phase 3 study

| Characteristic | RTP participants n=6 | Phase 3 participants N=45 |
|---|---|---|
| Age, y | | |
| Mean | 28.3 | 33.2 |
| Range | 18-47 | 18-62 |
| Weight, kg | | |
| Mean | 91.2 | 86.7 |
| Range | 74.5-119.8 | 53.4-141.6 |
| BMI, kg/m$^2$ | | |
| Mean | 27.9 | 27.9 |
| Range | 22.5-35.0 | 17.6-48.4 |
| Race, n (%) | | |
| Asian | 1 (16.7) | 7 (15.6) |
| Black or African American | 0 | 1 (2.2) |
| White | 3 (50.0) | 33 (73.3) |
| Not reported | 2 (33.3) | 4 (8.9) |
| Region, n (%) | | |
| Asia-Pacific | 1 (16.7) | 6 (13.3) |
| Europe | 3 (50.0) | 13 (28.9) |
| Middle East | 1 (16.7) | 9 (20.0) |
| North America | 1 (16.7) | 12 (26.7) |
| South America | 0 | 3 (6.7) |
| Australia | 0 | 2 (4.4) |
| Target joints, n (%) | 2 (33.3) | 13 (28.9) |

**Table 2:** RTP participant characteristics, day of RTP, summary of laboratory results and bleeding events

| Participant # | Age at screening, years | Race | RTP day | Peak FIX (Actin FSL, Synthasil) | FIX prior to RTP (Actin FSL, Synthasil) | Cortico-steroid tx, days post infusion | Cortico-steroid starting dose | BL ELISPOT | ELISPOT w/in 24 h of steroids | ELISPOT w/in 2 wk of steroids | BL liver status (ALT, AST) | BL ABR | Bleeding events prior to RTP (total / treated) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 18 | White | 365 | 9.8, 18.3 (d61, d61) | 0.5, <2.0 (d365) | 79–119 | 60 mg QD | UTD | N/A | UTD | 12, 13 | 1.58 | 2 / 2 |
| 7 | 22 | White | 198 | 9.3, 19.5 (d36, d36) | 1.3, 3.9 (d196) | 53–169 | 80 mg QD | Pos | N/A | Neg | 19,19 | 0.98 | 0 |
| 11 | 47 | Asian | 623 | 11.3, 26.6 (d69, d97) | 2.1, 4.2 (d610) | 21–216 | 25 mg TID | Neg | Neg | Neg | 17,12 | 0.62 | 1 / 1 |
| 22 | 27 | Un-known | 155 | 7, 19.1 (d51, d58) | 1.2, 5.3 (d128) | 65–145 | 100 mg QD | Pos | N/A | N/A | 61, 31 | 22.41 | 2 / 0 |
| 23 | 21 | Un-known | 275 | 11.7, 23.7 (d84, d63) | 2.3, 6.2 (d211) | 123–178 | 100 mg QD | N/A | Neg | N/A | 16, 17 | 3.42 | 3 / 2 |
| 36 | 35 | White | 410 | 22.1, 45.5 (d86, d86) | 5.8, 10.5 (d352) | 20–359 | 80 mg QD | N/A | N/A | Pos | 44, 26 | 0.95 | 5 / 2 |

ABR=annualized bleeding rate; ALT=alanine transaminase; AST=aspartate aminotransferase; BL=baseline; ELISPOT=enzyme-linked immunosorbent spot; FIX=factor IX; N/A=not applicable; Neg=negative; Pos=positive; QD=once daily; RTP=return to prophylaxis; TID=3 times a day; tx=treatment; UTD=unable to determine

**Figure 1**

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