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Blood 142 (2023) 1238–1239

The 65th ASH Annual Meeting Abstracts

# POSTER ABSTRACTS

## 322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

### Pharmacodynamic Biomarkers in Infants with Hemophilia A Receiving Emicizumab in HAVEN 7

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**Background:** Emicizumab, a bispecific antibody that mimics the cofactor function of activated factor (F)VIII, demonstrated a favorable safety and efficacy profile in infants with severe hemophilia A (HA) without FVIII inhibitors in HAVEN 7 (NCT04431726; Pipe et al. Blood 2022, 140[S1]: 457-459). It is known that some coagulation factors including FIX and FX, the binding targets of emicizumab, have lower plasma levels during the first 6 months of life. This research investigates whether the developing coagulation system impacts the pharmacodynamics (PD) of emicizumab prophylaxis in infants with HA enrolled to HAVEN 7 from birth to ≤ 12 months of age.
**Methods:** Informed consent from the parents/legally authorized representative and ethics approval were obtained. PD was assessed by activated partial thromboplastin time (aPTT), FVIII activity using a chromogenic assay containing human FIX and FX (considered FVIII-like activity), and by FXIa-triggered thrombin generation (TG) assay. Plasma antigen levels of FIX and FX were determined using immunoassays. Plasma samples from 110 healthy infants (HIs; n=42, 0-3 months old; n=68, >3-24 months old) collected separately were also measured to generate age matched reference ranges.
**Results:** In HAVEN 7, PD biomarkers, and FIX and FX plasma levels were assessed in 55 participants during the first 52 weeks of emicizumab exposure (data cut-off May 22, 2023). At baseline, mean FVIII activity was <1 IU/dL, mean TG peak height was zero, and aPTT was prolonged as expected due to the deficiency of FVIII. By the first post-baseline visit (Week 3), aPTT was normalized to the age matched reference range in most participants and was then generally maintained in the normal range throughout the treatment period. Mean (SD) FVIII-like activity increased to 22.52 (6.05) U/dL at Week 5 after the four loading doses of emicizumab and was sustained at 21-26 U/dL thereafter. Mean (SD) TG peak height increased to 67.37 (27.21) nM at Week 5 and was sustained at 67-88 nM throughout the treatment period. Mean plasma FIX and FX concentrations were not affected by emicizumab treatment.
The PD biomarkers, and FIX and FX plasma levels were also analyzed as a function of age group. The loading period (first 4 weeks) was excluded and only "steady state" measurements were considered for the PD markers. All measurements were considered for FIX and FX plasma levels. Mean (SD) FVIII-like activity of 18.14 (5.40) U/dL in the youngest participants (1-2 months old) increased to 23.57 (7.64) U/dL at 3-4 months old and was similar (23-28 U/dL) in the older age groups. Age did not have a significant impact on mean TG peak height. There was no age effect on aPTT. Mean (SD) plasma FIX and FX antigen concentrations were 4.40 (1.09) µg/mL and 6.24 (1.29) µg/mL in the <1 month old participants, increased progressively with age until about 9 months old, and then stayed around 9-10 µg/mL for both FIX and FX. Lower plasma levels of FIX and FX, as well as FVIII activity were also observed in the HIs ≤3 months vs. >3 months of age. There was no significant difference in TG between ≤ 3 months vs. >3 months of age in HIs.
FVIII-like activity increased with increasing emicizumab concentrations in a linear fashion up to emicizumab concentrations of 100 µg/mL. Hence, the lower FVIII-like activity in the youngest participants could be partially explained by lower mean "steady state" trough emicizumab concentrations of 48.3 µg/mL at 1 month of age, which then increased to approx. 60 µg/mL at 4-5

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months of age and older. TG peak height increased with increasing emicizumab concentrations but showed large variability. Lower FIX and FX plasma levels during the first 9 months of age may also have an impact on the PD results. Even though the levels were lower in the youngest participants, increases in FVIII-like activity and TG were seen at "steady state" emicizumab in all age groups as expected based on previous studies of emicizumab. The sample sizes were small in some of the age groups analyzed.

**Conclusions:** FVIII-like activity and thrombin generation increased, and aPTT was normalized after starting emicizumab prophylaxis in HAVEN 7. Increase with age was seen on FVIII-like activity as well as FIX and FX levels. The PD profiles of emicizumab in infants with HA were consistent with those previously observed in older children and adults with HA. Hence, even with lower levels of FIX and FX observed at the youngest participants, emicizumab showed the expected PD response.

**Disclosures Kiialainen:** *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Pipe:** *Takeda:* Consultancy; *Sanofi:* Consultancy; *Regeneron/Intellia:* Consultancy; *Roche/Genentech:* Consultancy; *Pfizer:* Consultancy; *Novo Nordisk:* Consultancy; *LFB:* Consultancy; *Freeline:* Consultancy; *HEMA Biologics:* Consultancy; *GenVentiv:* Consultancy; *Equilibra Bioscience:* Consultancy; *CSL Behring:* Consultancy; *BioMarin:* Consultancy; *Bayer:* Consultancy; *ASC Therapeutics:* Consultancy; *Apcintex:* Consultancy; *Spark Therapeutics:* Consultancy; *uniQure:* Consultancy. **Fijnvandraat:** *Sanofi:* Consultancy; *F. Hoffmann-La Roche Ltd:* Consultancy; *Novo Nordisk:* Consultancy, Research Funding; *CSL Behring:* Research Funding; *Sobi:* Consultancy, Research Funding. **Kenet:** *ASC Therapeutics, Bayer, BioMarin, Novo Nordisk, Pfizer, Roche, Sanofi- Genzyme, Sobi, Takeda, Uniqure:* Consultancy; *BSF, Opko Biologics, Pfizer, Roche, Shire:* Research Funding; *Bayer, BioMarin, BPL, CSL, Pfizer, Novo Nordisk, Roche, Sanofi- Genzyme, Sobi, Spark, Takeda, Uniqure:* Honoraria; *PedNet foundation:* Membership on an entity's Board of Directors or advisory committees; *Sheba Medical Center and Sackler Faculty of Medicine, Tel Aviv University:* Current Employment. **Schmitt:** *Anti- FIXa/FX bispecific antibody:* Patents & Royalties: Co-inventor of a patent related to an anti- FIXa/FX bispecific antibody; *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Buri:** *F. Hoffmann-La Roche AG:* Current Employment, Current equity holder in publicly-traded company. **Jiménez-Yuste:** *CSL Behring:* Consultancy, Honoraria, Research Funding; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Bayer:* Consultancy, Honoraria, Research Funding; *Novo Nordisk:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria, Research Funding; *BioMarin:* Consultancy; *Sanofi:* Consultancy, Honoraria, Research Funding; *Sobi:* Consultancy, Honoraria, Research Funding; *Grifols:* Consultancy, Honoraria, Research Funding. **Oldenburg:** *University Clinic Bonn:* Current Employment; *Bayer, Biotest, Chugai, CSL-Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Swedish Orphan Biovitrum, Takeda:* Research Funding; *Bayer, Biogen Idec, Biomarin, Biotest, Chugai, CSL-Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sparks, Swedish Orphan Biovitrum, Takeda:* Honoraria; *Working Group Blood of the Ministry of Health, Bayer, Biogen Idec, Biomarin, Biotest, Chugai, CSL-Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sparks, Swedish Orphan Biovitrum, Takeda:* Consultancy; *Bayer, Biogen Idec, Biomarin, Biotest, Chugai, CSL-Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sparks, Swedish Orphan Biovitrum, Takeda:* Speakers Bureau; *Stiftung Hamotherapie-Forschung, Working Group Richtlinien zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Hamotherapie) of the Scientific Advisory Board of the German Medical Association:* Membership on an entity's Board of Directors or advisory committees; *Bayer, Biogen Idec, Biomarin, Biotest, Chugai, CSL-Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark, Swedish Orphan Biovitrum, Takeda:* Other: Reimbursement of travel expenses. **Mancuso:** *LFB:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BioMarin:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sanofi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CSL Behring:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Bayer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *IRCCS Humanitas Research Hospital:* Current Employment; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Octapharma:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novo Nordisk:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Dhalluin:** *F. 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https://doi.org/10.1182/blood-2023-173015

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