

Pharmacokinetics (PK), Pharmacodynamics (PD) and PK/PD Relationships of Emicizumab in Persons with Haemophilia A (PwHA) with Inhibitors from Adolescent/Adult (HAVEN 1) and Paediatric (HAVEN 2) Phase 3 Studies

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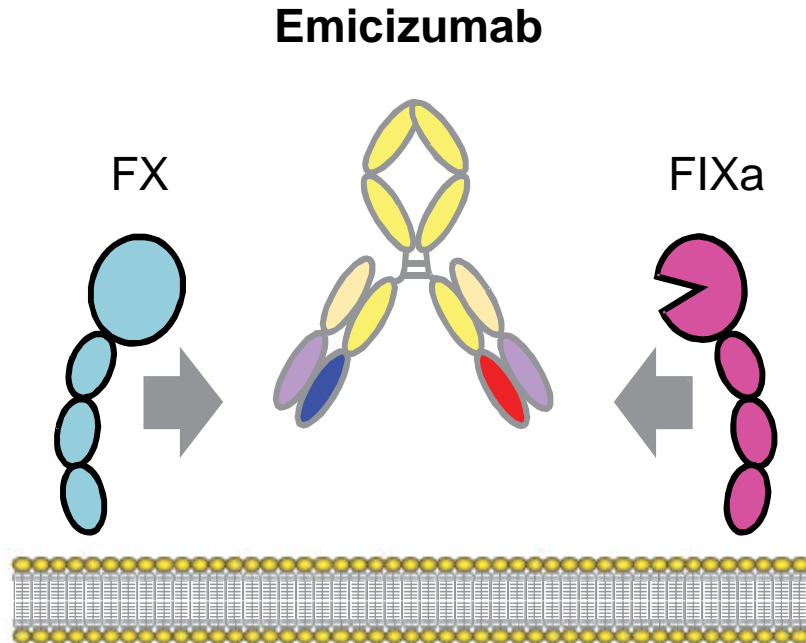
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Emicizumab

Effective Prophylaxis for PwHA with Inhibitors

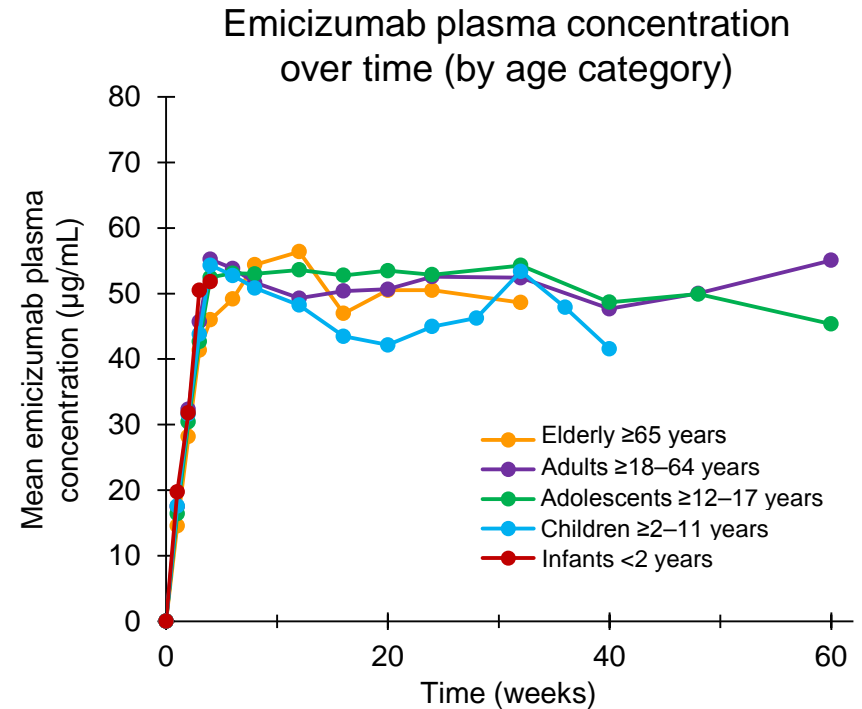
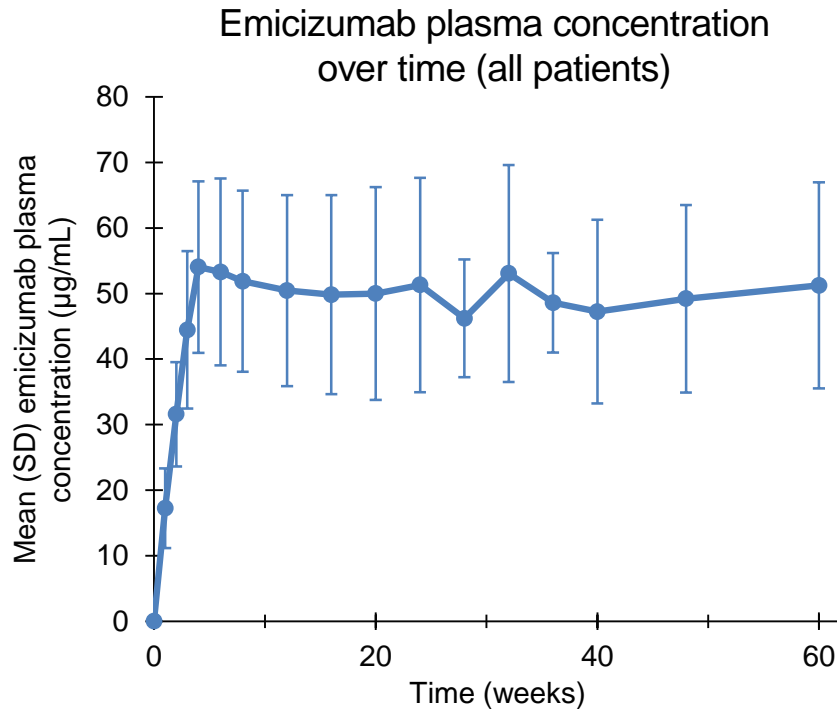


- Humanised bispecific antibody that bridges activated factor IX (FIXa) and FX to restore missing FVIIIa function
 - Approved in the United States (HEMLIBRA[®]) for prophylaxis in adult/paediatric PwHA with FVIII inhibitors
 - Committee for Medicinal Products for Human Use recommends EU approval for prophylactic treatment of PwHA with FVIII inhibitors
 - Ongoing clinical studies in PwHA with/without inhibitors

Phase 3 Clinical Trials with Emicizumab

- Emicizumab prophylaxis evaluated in PwHA with inhibitors in 2 phase 3 studies in adolescents/adults (HAVEN 1)¹ and children (HAVEN 2)²
 - Dosing: subcutaneous 3 mg/kg/week for 4 weeks and 1.5 mg/kg/week thereafter^{1,2}
 - Mean trough plasma emicizumab concentrations of ≈ 50 $\mu\text{g/mL}$ achieved^{1,2}
 - Treated annualised bleed rate reduced with emicizumab vs prior BPAs:
 - By 87% vs prior episodic BPAs (HAVEN 1)¹
 - By 79% vs prior prophylactic BPAs (HAVEN 1)¹
 - By 99% vs prior episodic or prophylactic BPAs (HAVEN 2)²
- For the current PK/PD analysis, data was pooled from all patients treated with emicizumab in both studies (HAVEN 1, n=112; HAVEN 2, n=60)
 - Median (range) emicizumab exposure at time of this analysis:
 - HAVEN 1 (21 April 2017): 42 (3–74) weeks
 - HAVEN 2 (8 May 2017): 8 (1–41) weeks

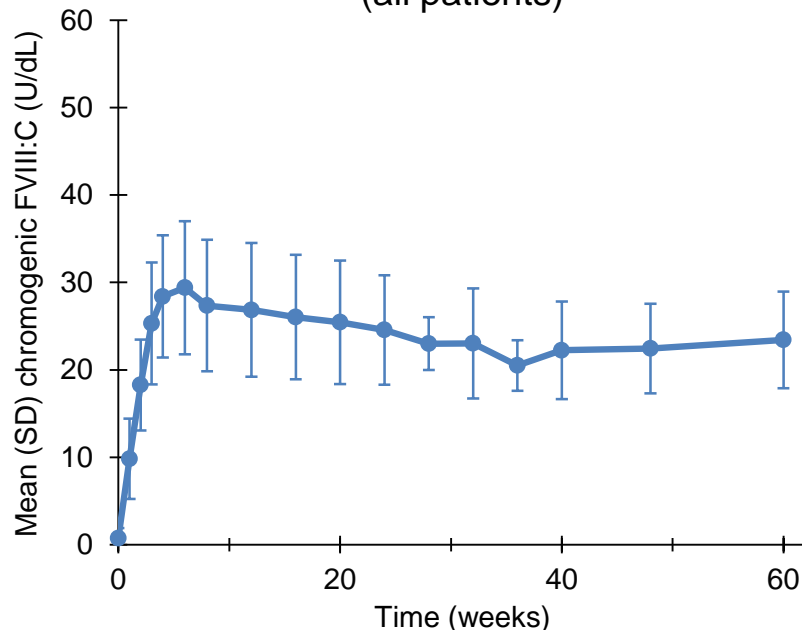
Therapeutic Efficacy Sustained Throughout Study



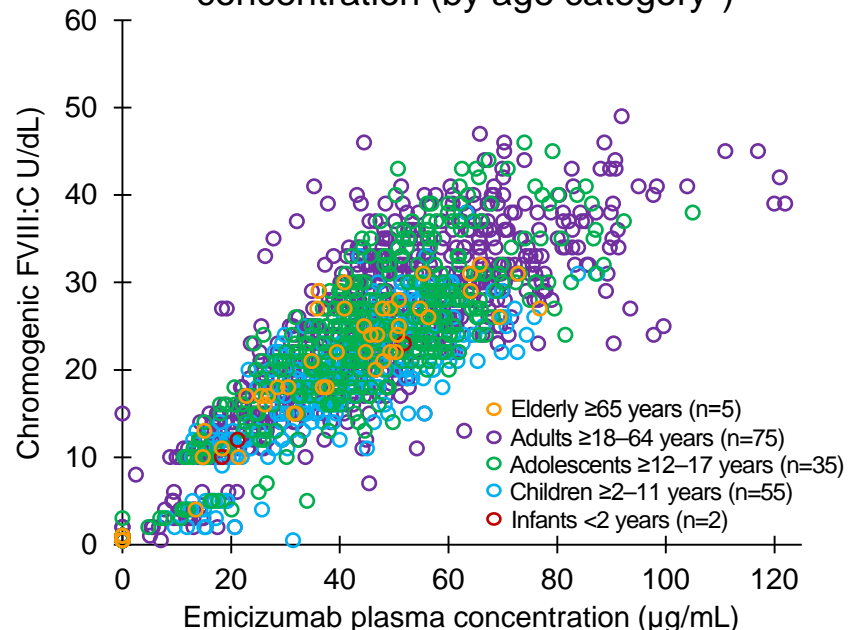
Trough plasma concentrations of ≈ 50 µg/mL were achieved by Week 4 and were comparable across age groups

FVIII Activity Increased and Sustained Throughout Study

Reported FVIII activity over time
(all patients)



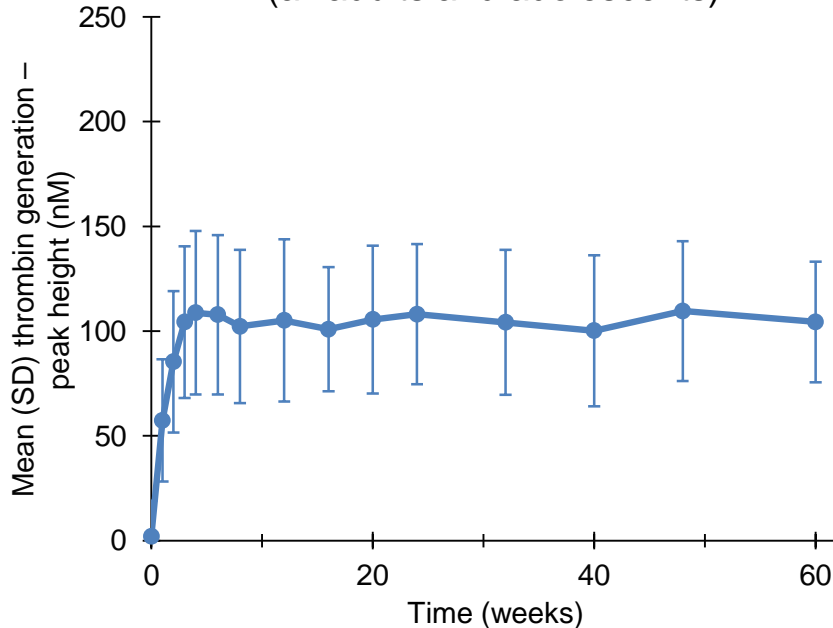
Reported FVIII activity vs emicizumab plasma concentration (by age category*)



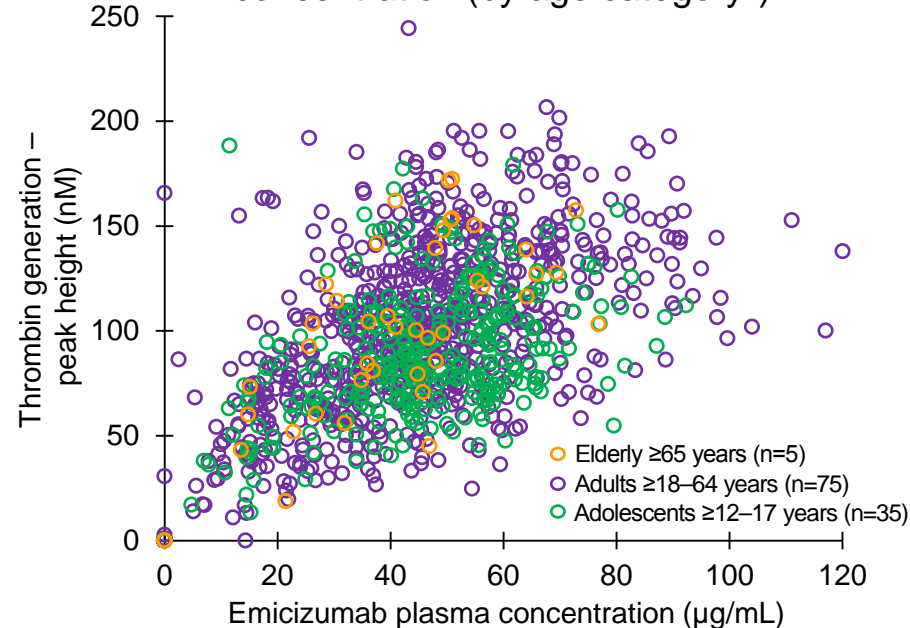
FVIII activity[†] (Hyphen chromogenic assay) increased from zero at baseline to ≈25% by Week 4 and was comparable across age groups

Thrombin Generation Increased and Sustained Throughout Study

Thrombin generation over time
(all adults and adolescents)



Thrombin generation vs emicizumab plasma concentration (by age category*)



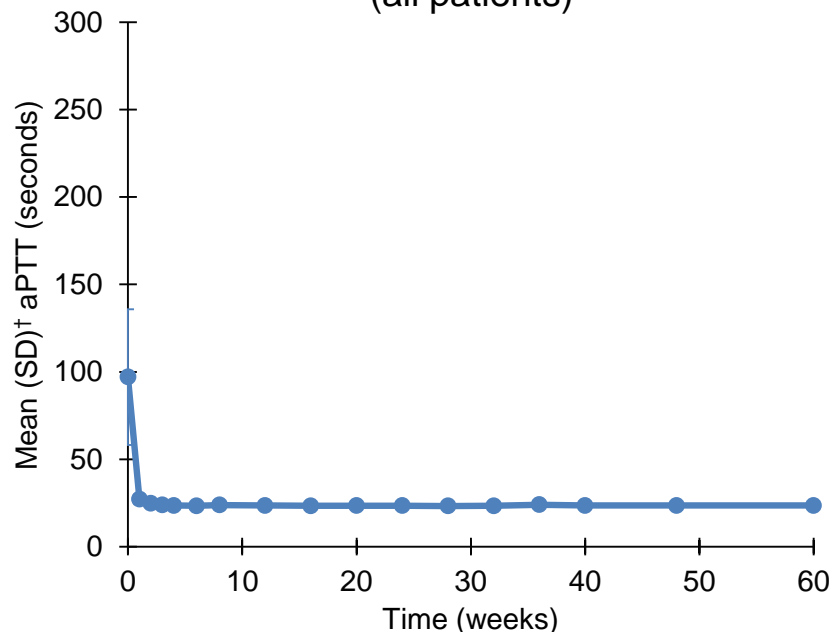
Mean thrombin generation peak height[†] increased from zero at baseline to ≈110 nM (equivalent to ≈30% of normal plasma pool) by Week 4

*Multiple measures/patient. [†]Thrombin generation test with FXIa trigger in platelet-poor citrate plasma; not tested in children. Patients with up-titration, dose modification or suspicion of heparin contamination were excluded.

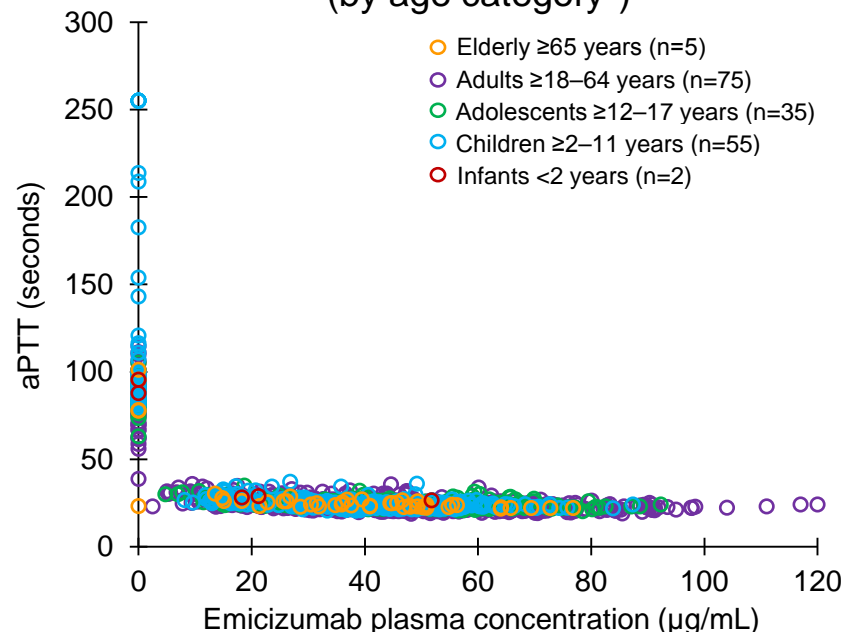
Strong Effect on aPTT

Emicizumab Does Not Require Activation Step

aPTT over time
(all patients)



aPTT vs emicizumab plasma concentration
(by age category*)



In assays of intrinsic clotting time, emicizumab behaves like FVIIIa, not FVIII;
aPTT is not an accurate measure of haemostatic potential in the presence of emicizumab

*Multiple measures/patient. [†]SD ranges smaller than width of data point after time zero. Patients with uptitration, dose modification or suspicion of heparin contamination were excluded. aPTT, activated partial thromboplastin time.

Important Biomarkers Unaffected by Emicizumab Prophylaxis

Biomarker	Description of results
FIX and FX antigens	<ul style="list-style-type: none">• Plasma levels of binding targets of emicizumab unaffected by treatment
D-dimer, prothrombin fragment 1.2 and prothrombin time (INR)	<ul style="list-style-type: none">• Largely within normal limits• Not affected by emicizumab levels• Demonstrates that emicizumab does not activate coagulation in absence of initiating signal
FVIII inhibitor titres	<ul style="list-style-type: none">• Remained stable or slightly declined during treatment (as measured by chromogenic Bethesda assay)• Lack of effect expected from lack of sequence homology between emicizumab and FVIII

Conclusions

- Consistent with clinical efficacy, PK/PD results confirm a procoagulant effect of emicizumab in paediatric, adolescent and adult PwHA with inhibitors
- Both exposure and activity were sustained and similar across age groups
 - Therapeutic emicizumab plasma levels were achieved after 4 weeks of loading doses and maintained for >1 year with weekly administration
 - FVIII activity and thrombin generation increased with loading doses and were maintained throughout treatment
 - aPTT normalised after a single emicizumab dose (before reaching therapeutic levels), so it should not be used to monitor efficacy
 - FIX and FX antigen levels and markers of activated coagulation were unaffected by emicizumab

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Thank You