Clotting Disorders
2025 ASH Classical Hematology Highlights

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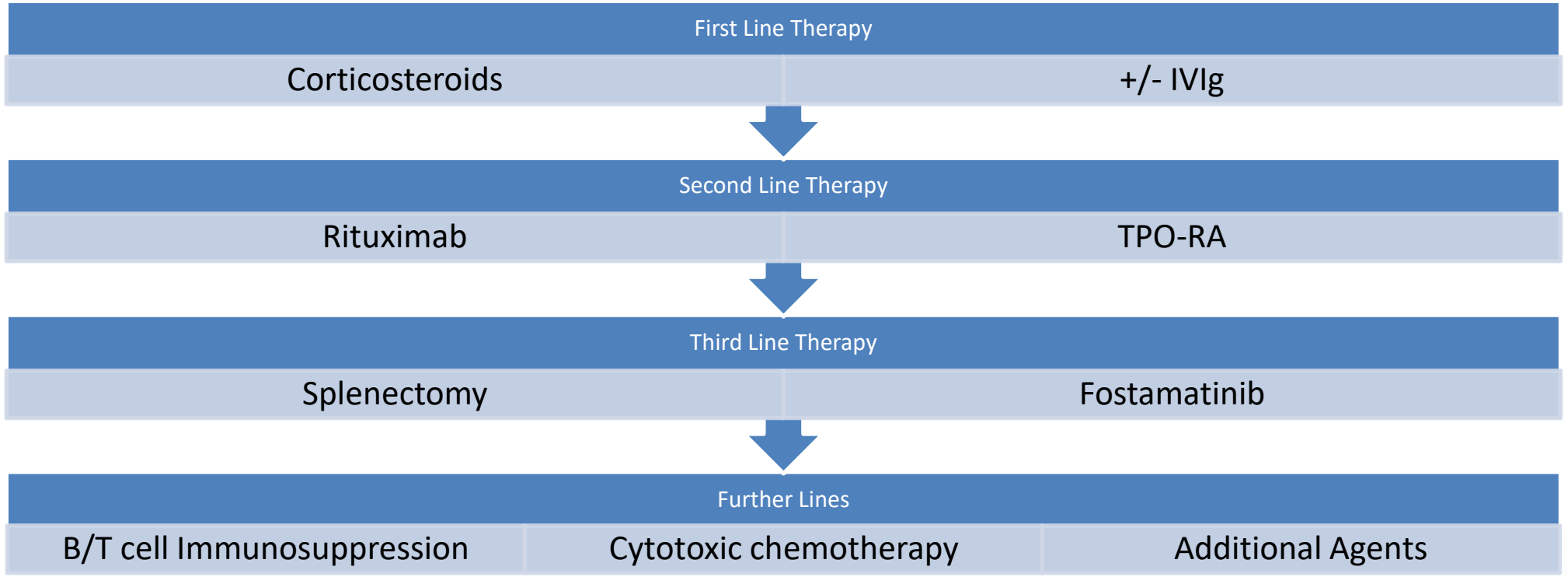
Disclosures

AA-MDSIF – Speaker
Bayer – Advisory Board

Objectives

1. Review current and upcoming treatments for ITP
2. Discuss cost / factor effectiveness of current hemophilia treatments

Immune Thrombocytopenia Purpura



Considering Combination

Insights on treatment of adult ITP: algorithm for management and role of multimodal therapy (Ghanima W, et al)

Educational Program Review of major combination studies and possible early integration

Combination arm	Monotherapy arm	Study design	Efficacy	Remarks
Rituximab (375 mg/m^2 weekly for 4 weeks) + dexamethasone (1-6, 4-day cycle)[5]	Dexamethasone (1-6, 4-day cycle)	Open-label RCT with 1:1 randomization, (n = 133)	Response rates at 6 months were 58% in the combination vs 37% in the dexamethasone groups, p = 0.02, with significantly longer time to relapse (p = 0.03)	Increased incidence of grade 3-4 adverse events in the combination group
Rituximab (375 mg/m^2 weekly for 4 weeks) + dexamethasone (4-day cycle)[6]	Dexamethasone (4-day cycle)	Open-label RCT with 1:1 randomization (n = 101)	Response rate at 6 months 63% vs 36%, p = 0.004	Increased incidence of grade 3-4 adverse events in the combination group
Mycophenolate mofetil (MMF) (1-2 g daily) + prednisolone or dexamethasone.[7]	Prednisolone or dexamethasone	Open-label RCT with 1:1 randomization (n = 120)	Rate of treatment failure was 22% in the MMF group vs 44% in the control group; HR = 0.41 (95% CI: 0.21-0.80; p = 0.008	Patients in the MMF group reported worse HRQoL
Tacrolimus (initial dose 0.03 mg/kg/day for 12 weeks) + dexamethasone[8]	Dexamethasone (1-2, 4-day cycles)	Phase 2, open-label RCT with 1:1 randomization (n = 140)	Sustained response in the combination group was 65% vs 43% in the monotherapy (p = 0.007), rates of treatment failure (19.4% vs 38.2%, p = 0.0014)	Published only in abstract form
rhTPO (300 ug/kg sc for up to 14 days) + dexamethasone (1-2, 4-day cycle)[10]	Dexamethasone (1-2, 4-day cycle)	Open-label RCT with 1:1 randomization (n = 206)	The combination resulted in higher initial (89% vs 67%; p<0.001) and durable response rates at 6 months (51% vs 36%; p = 0.02) compared with dexamethasone	Well-tolerated study drugs; only one thromboembolic event occurred in the combination; rhTPO is only available in certain countries in Asia
Oseltamivir (75 mg × 2/day for 10 days) + dexamethasone (1-2 4-day cycle)[11]	Dexamethasone (1-2, 4-day cycle)	Phase 2 open-label, RCT with 1:1 randomization (n = 96)	Response at day 14 (86% vs 66%; p = 0.030) and at 6 month (53% vs 30%; p = 0.032) in the combination vs monotherapy groups	19% suffered from gastrointestinal side effects in the combination group
ATRA (10 mg × 2/day for 12 weeks) + dexamethasone (14-day cycle)[12]	Dexamethasone (1-2, 4-day cycle)	Phase 2 open-label, RCT with 1:1 randomization (n = 132)	Sustained* response rate at 6 months in the combination arm was 68% vs 41% in the monotherapy arm (= R = 3, p = 0.0017)	Dry skin was reported in 48% of the patients treated with ATRA

Combination – Second Line

Combination arm	Monotherapy arm	Study design	Efficacy	Remarks
rhTPO (300 ug/kg sc for up to 14 days) + rituximab (100 mg weekly x4)[30]	Rituximab (100 mg weekly × 4)	Open-label RCT with 2:1 randomization (n = 123)	Complete response was achieved 45% vs 24% (p = 0.02) and overall response was achieved in 79% vs 71% (p = 0.36) of patients in the combination monotherapy groups, with the combination having significantly shorter median response time (7 vs 28 days; $p<0.01$)	There was no difference in the duration of response between the two groups; side effects were generally mild
ATRA (20 mg/m^2 for 12 weeks) + low dose rituximab (100 mg weekly for 6 weeks)[31]	Rituximab (100 mg weekly for 6 weeks)	Open-label RCT with 2:1 randomization (N = 168)	Overall response was achieved in 80% vs 59% (between-group difference, 0.22; 95% CI, 0.07-0.36), and sustained response was achieved in 61% vs 41% (between-group difference, 0.20; 95% CI, 0.04-0.35) in combination vs monotherapy groups	Most common adverse events for the combination group were dry skin and headache/dizziness
ATRA (10 mg × 2/day) + danazol (200 mg × 2/day) for 16 weeks[32]	Danazol (200 mg × 2/day) for 16 weeks	Phase 2 open-label RCT; 1:1 randomization (N = 96)	Sustained response at 12 months was achieved in 62% of patients receiving ATRA plus danazol vs 25% in patients receiving danazol monotherapy (OR 4.94, p = 0.00037)	Skin desquamation was reported in 62% of patients in the combination arm
rhTPO (100 ug/kg sc for up to 14 days) + danazol (200 mg × 3 daily)[33]	Danazol (200 mg × 3 daily)	2 phase (14 days each), open-label RCT with 1:1 randomization (N = 140)	Total response rate in the combination group was 60% vs 36%, p = 0.01	Well-tolerated treatments with mild side effects

Caveats

		TPO-RA Rituximab Fostamatinib Splenectomy	MMF Cyclosporine Danazol Cyclosporine Others Splenectomy
Corticosteroids IVIG			
1st line		2nd line	3rd line
Cortico-Steroids +	Rituximab TPO-RA Tacrolimus Oseltamivir ATRA MMF	Rituximab + TPO-RA Rituximab + ATRA Danazol + ATRA Danazol + TPO-RA	TPO-RA + Immunomodulatory

Combination therapy as salvage therapy for first line corticosteroid failure?
Higher response + Higher Cure rates vs Increased Toxicity and Increased Cost

On the horizon: upcoming new agents for the management of ITP (Lambert M)

Educational review

Efficacy and Safety Assessment of a Treatment Combining Rituximab and Belimumab in Adults with Persistent Immune Thrombocytopenia (RITUX PLUS) (Mahevas M, et al)

Belimumab -- monoclonal antibody target B-lymphocyte stimulator (BLyS)
Currently approved for SLE

N=15
80% CR+R with 66.7% with CR

Safety and efficacy of classical complement pathway inhibition with sutimlimab in chronic immune thrombocytopenia (Broome C, et al)

Sutimlimab – monoclonal antibody target anti-C1s
Currently approved for C.A.D

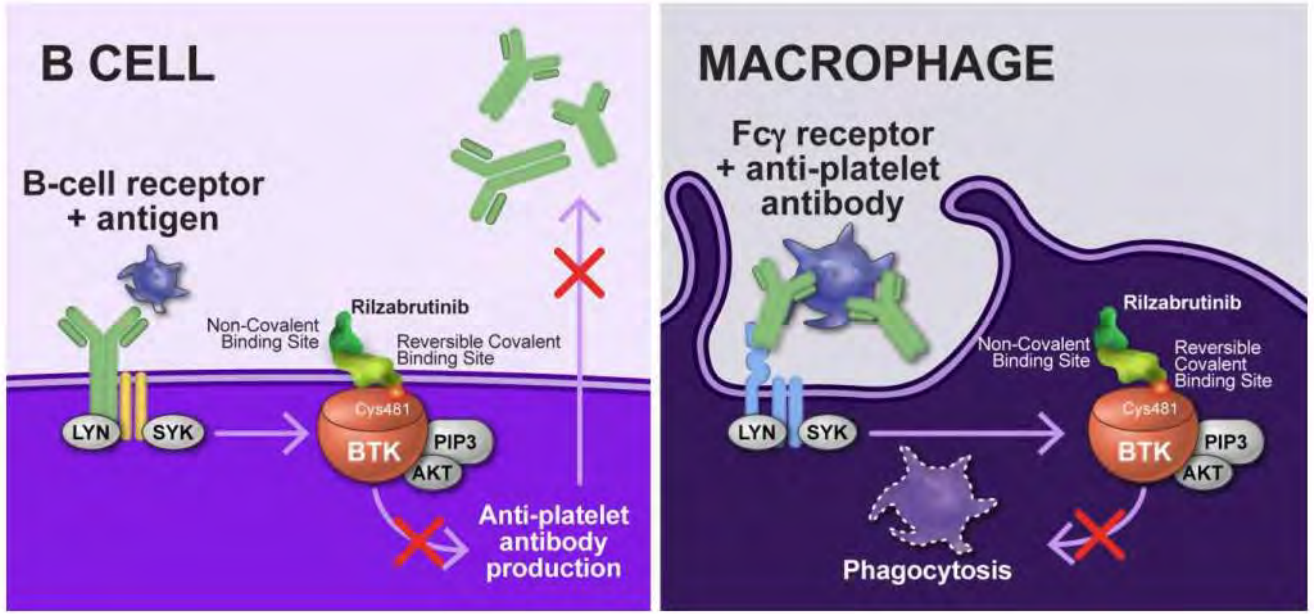
N=12
CR+R 42% and CR in 33%

Efficacy and Safety of Oral Bruton Tyrosine Kinase Inhibitor (BTKi) Rilzabrutinib in Adults with Previously Treated Immune Thrombocytopenia (ITP): A Phase 3, Placebo-Controlled, Parallel-Group, Multicenter Study (LUNA 3) (Kuter D, et al)

Bruton Tyrosine Kinase Inhibitor Rilzabrutinib Is Specifically Designed for Immune-Mediated Diseases

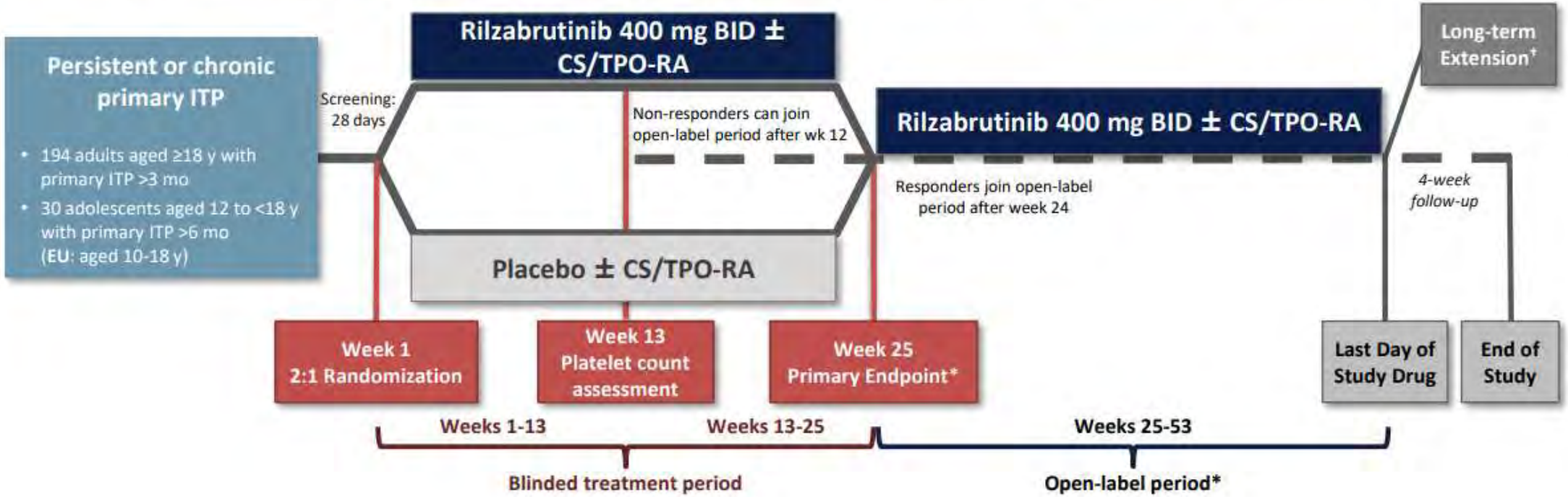
Rilzabrutinib can mediate its therapeutic effect in ITP patients through a dual mechanism of action

- Inhibition of B cell activation
- Interruption of platelet phagocytosis by FcγR in spleen and liver



LUNA 3 Study Design

- LUNA 3 is a multicenter, double-blind, placebo-controlled phase 3 study assessing efficacy and safety of oral rilzabrutinib in adults and adolescents with persistent or chronic ITP



	Rilzabrutinib	Placebo
Response (> 50k/ul or doubled)	65%	33%
Durable Response	29%	0%
Reported Fatigue	7.95 (2.13 SD)	-0.13 (2.86 SD)
Bleeding Episodes	-0.04 (0.02)	0.05 (0.02)
Diarrhea	23%	4%
Nausea	17%	6%

Coagulopathy

Emizicumab and age

Comparing the Risk of Thrombotic Events in Older Persons with Hemophilia a on Emicizumab Prophylaxis to Non-Emicizumab Products: A Single Center Observational Cohort Study (Vemuru S, et al)

Observational cohort study compared the risk of thrombotic events during the time that people ≥ 50 years with severe and moderately severe hemophilia A were on emicizumab prophylaxis

n = 32

- 46.9% had hyperlipidemia
- 68.8% had hypertension
- 12.5% had diabetes
- 50% currently or formerly smoked

Four thrombotic events occurred during the study period, all of which were either TIA or CVA; three events occurred while patients were on emicizumab prophylaxis.

The cumulative probabilities of a thrombotic event

- 0.156 while on emicizumab
- 0.043 while not on emicizumab.

The risk of thrombotic events was non-significantly increased (HR=2.65 [95% CI: 0.5, 15.7]) while on emicizumab compared to time not on emicizumab.

Other cardiovascular risk factors:

- hyperlipidemia (aHR=2.97 [95% CI: 0.58, 15.08]
- hypertension (aHR=3.14 [95% CI: 0.6, 17.67]
- BMI (aHR= 5.61 [95% CI: 0.46, 67.75]
- smoking (aHR= 2.64 [95% CI: 0.4, 17.22]
- diabetes (aHR= 2.41 [95% CI: 0.38, 15.17]

Emizicumab dosing

DosEmi study: a phase IV, multicenter, open-label, crossover study to evaluate non-inferiority of pharmacokinetic-guided reduced dosing compared with conventional dosing of emicizumab in people with hemophilia A (Donners, A, et al)

Netherland based phase IV, multicentre, open-label, crossover study

Evaluate noninferiority of bleed control of ≥6 months on conventional dosing in comparison to ≥6 months on dose intervention.

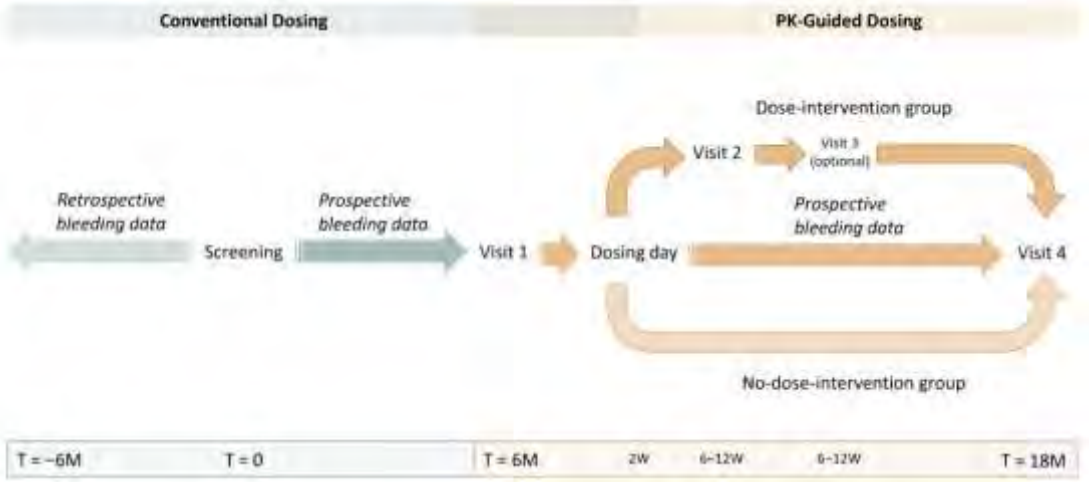
Reducing the dose of emicizumab at a trough concentrations of 30 µg/mL using (PK) parameters.

N = (95)

Primary Endpoint: Relevant decrease (risk difference) of 15% w/o treated bleeds

Secondary Endpoint: Spontaneous joint or muscle bleeds and ABR.

Cost-effectivity between conventional dosing and individualized PK-guided dosing of emicizumab will be compared.



PK-guided dose advice based on a maximum a posteriori (MAP) Bayesian analysis of the individual observed concentration using an online platform https://opticlot.nl

Population PK parameters per "Population Pharmacokinetic Analysis and Exploratory Exposure–Bleeding Rate Relationship of Emicizumab in Adult and Pediatric Persons with Hemophilia A" (Retout S, 2020)

Pharmacokinetic-Guided Reduction of Emicizumab in Patients with Congenital Hemophilia a in the Netherlands: Interim Analysis from the Dosemi Study (Van Der Zewt, et al.)

72 pnts enrolled --
Severe hemophilia A, no FVIII inhibitors (n=25, 93%).
30 patients with emicizumab dose reduction in 27 out of 30 patients.

Dose was decreased from a median of 6 (IQR 5.2 – 6.4) mg/kg/4wks to 3.4 (IQR 2.8 – 3.9) mg/kg/4wks. (Generally q2w dosing)
The median follow up during PK-guided dosing was 4.6 (IQR: 3.2 – 10.5) months

13 patients completed the entire six months on PK-guided dosing.
Bleeding control remained stable over the follow-up period

Without	Conventional	PK-directed	
Treated bleeds	76%	71%	(p=0.222)
(Hemarthrosis)	82%	87%	(p=0.609)

All bleeds were traumatic except in one patient who developed a spontaneous ultrasound confirmed muscle bleed on PK-guided dosing.

No emicizumab related adverse events nor thrombotic events were observed after dose reduction

ATLAS-DR

Reduced Doses of Factor Concentrates and Bypassing Agents to Treat Breakthrough Bleeds in Patients with Hemophilia A and B on Fitusiran Antithrombin-Based Dosing Regimen: ATLAS-OLE (Pipe S, et al)

Fitusiran, a subcutaneous investigational siRNA therapeutic, lowers antithrombin (AT) to increase thrombin generation and rebalance hemostasis in people with hemophilia A/B (PwHA/B), irrespective of inhibitor status.

In three phase 3 trials of fitusiran (ATLAS)

- A >89% reduction in annualized bleeding rate was demonstrated with fitusiran
- Initial 80mg/mo dosing in ATLAS – OLE with ~3% with thrombotic event
  - AT3 levels < 10% with elevated Thrombin Potential

This current analysis compared a subset of participants receiving the fitusiran antithrombin-based dosing regimen (AT-DR) in ATLAS-OLE

- Goal AT3 (15-35%) adjusted to 50mg vs 20mg q1-2mo

Thrombotic event ODR 2.28/100pntyr (OLE) vs ODR 0.82/100pntyr

Fitusiran AT-DR

modeled factor equivalency of 20-40% in both PwHA and PwHB on fitusiran prophylaxis

The majority of breakthrough bleeds were successfully managed with only one infusion of reduced dose CFC or BPA.

Mean (SD)	W/ Fitusiran	W/o Fitusiran
FVIII	12.0 [6.0] IU/kg	45.3 [41.8] IU/kg
FIX	22.3 [10.8] IU/kg	73.6 [54.7] IU/kg
aPCC	50.1 [32.2] U/kg	207.8 [373.5] U/kg
rVIIa	86.5 [85.8] ug/kg	637.3 [1090.8] ug/kg

Cost Comparison of Efanesoctocog Alfa with Existing Factor VIII Replacement Therapies for Major Surgeries in People with Severe Hemophilia A (Staber J, et al)

SHL / EHL in Major Surgery

octocog alfa, rurioctocog alfa pegol, and efmoroctocog alfa every 8–24 hours to prevent bleeding, up to 7 days or until the wound had healed sufficiently

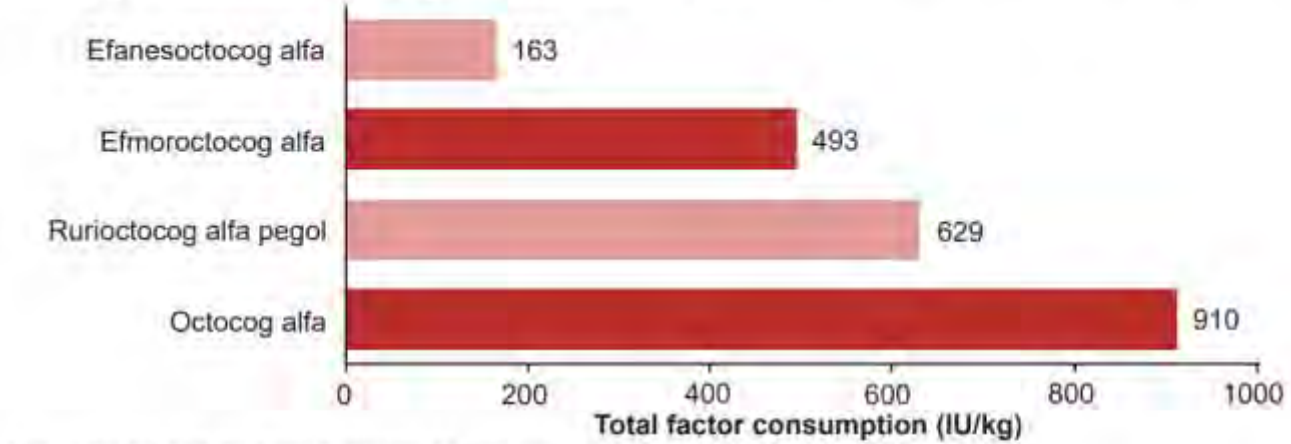
Doses frequently ranging from 30-50UI/kg BID

efanesoctocog alfa dosing include preoperative loading dose of 50 IU/kg, followed by 30 IU/kg or 50 IU/kg every 2 to 3 days, as needed

Cost analysis by clinical study FDA label recommendation with Wholesale Acquisition Costs for 91kg male underoing major surgery

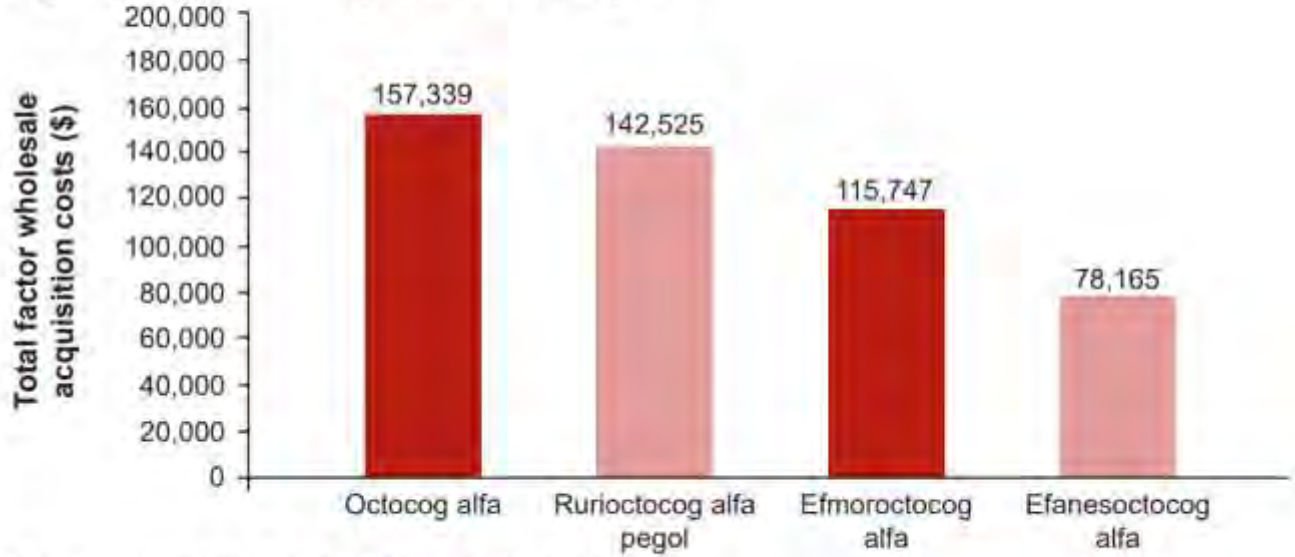
FVIII therapy	Clinical data source	Clinical data description	Reported perioperative period	Median FVIII consumption (IU/kg)	Cost ($/IU)
Octocog alfa	Registrational clinical study in FDA label[6]	58 patients (aged ≥5 years) with severe HA who underwent 65 surgical procedures including 22 major surgeries[a]	During hospitalization	228–1,825	1.90
Rurioctocog alfa pegol	Phase 3 clinical study in FDA label[7] (NCT01913405)	21 previously treated male patients (aged ≥12–75 years) with severe HA who underwent 21 major surgeries[b]	7 days	464–1,457	2.49
Efmoroctocog alfa	Phase 3 extension studies in FDA label[8] (NCT01181128, NCT01458106, and NCT01454739)	21 patients (aged ≥12 years) with severe HA who underwent 23 major surgeries[c]	14 days	121–733	2.58
Efanesoctcog alfa	Phase 3 clinical study in FDA label[9,10] (NCT04161495)	12 patients (aged ≥12 years) with severe HA who underwent 13 major surgeries[d]	14 days	45–361	5.26

Figure 1. Median total factor consumption (IU/kg) per major surgery for SHL, EHL, and high-sustained FVIII replacement therapies



EHL, extended half-life; FVIII, factor VIII; IU, international units; kg, kilogram; SHL, standard half-life.
The reported perioperative period was during hospitalization for octocog alfa, 7 days for rurioctocog alfa pegol, and 14 days for both efmoroctocog alfa and efanesoctocog alfa.

Figure 2. Total factor costs ($) per major surgery for SHL, EHL, and high-sustained FVIII replacement therapies



EHL, extended half-life; FVIII, factor VIII; SHL, standard half-life.
SHL (octocog alfa), EHL (rurioctocog alfa pegol and efmoroctocog alfa), and high-sustained (efanesoctocog alfa) FVIII replacement therapies. The reported perioperative period was during hospitalization for octocog alfa, 7 days for rurioctocog alfa pegol, and 14 days for both efmoroctocog alfa and efanesoctocog alfa.

Postpartum Hemorrhage in Hemophilia a and B Carriers after Enhanced Prophylactic Clotting Factor Suppletion: The Pregnancy and Inherited Bleeding Disorders Study (PRIDES) (de Vann A, et al)

Female hemophilia carriers at risk for PPH (>500ml) to severe (>1000ml) Severe PPH (12.5% vs 7.7%)

New Dutch guideline in 2018

- The third trimester cut-off value for clotting factor suppletion increased from < 50 IU/dL to < 80 IU/dL
- Target FVIII/FIX levels at delivery were increased from > 100 IU/dL to > 150 IU/dL
  - Thought to be more physiological

170 deliveries were recorded, 88.3% (n=150/170) in hemophilia A carriers.

- (47.6% primipara | 24.1% cesarean)

20% (34/170) had third trimester levels < 80 IU/dL

- 73.5% (n=25/34) received prophylactic clotting factor suppletion during delivery

The incidence of PPH in the < 80 IU/dL group was 29.4% (n=10/34) vs. in the ≥ 80 IU/dL group 34.6% (n=47/136) p-value 0.57 (adjusted OR 1.11, 95% CI 0.48-2.71)

The incidence of severe PPH was similar in the < 80 IU/dL group was 11.8% (n= 4/34) vs. the ≥ 80 IU/dL group 12.5% (n= 17/136) p-value 0.91 (adjusted OR of 1.07, 95% CI 0.36-0.93)

Many Thanks

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