NOVINKY V HEMOFILII

Antonín Hluší

seminář HOK FNOL 18. září 2017

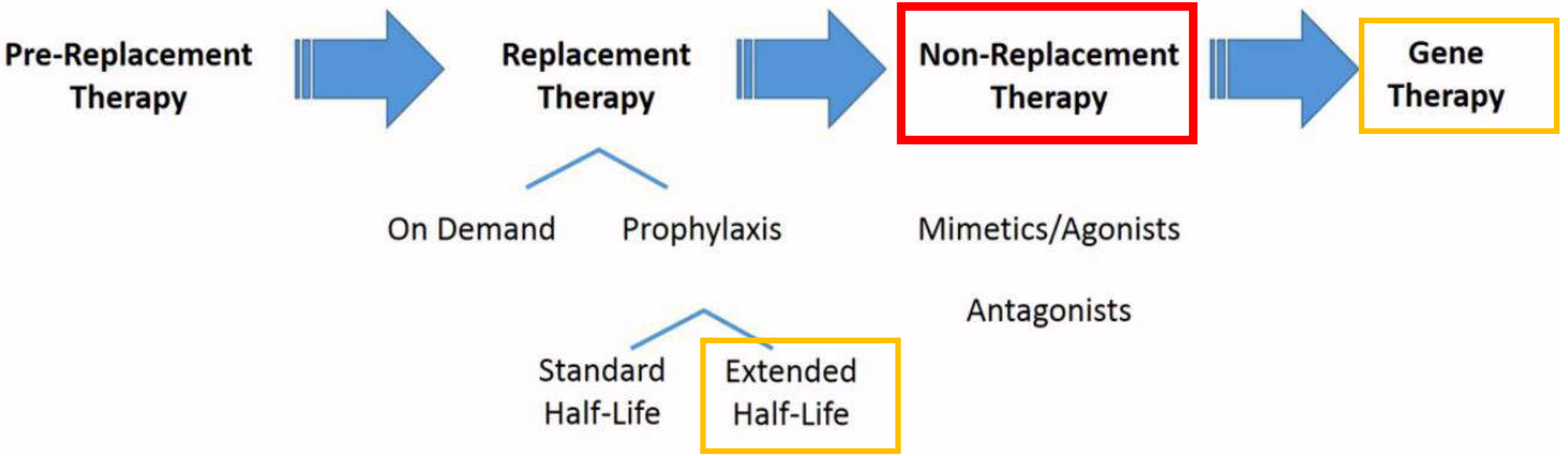
Hemato-onkologická klinika
Fakultní nemocnice Olomouc

český národní hemofilický program

ISTH 2017 CONGRESS JULY 8-13
BERLIN GERMANY
WWW.ISTH2017.ORG
TRANSCENDING SCIENTIFIC BOUNDARIES


CityCube Berlin

Current and Future Approaches to Care



Terapeutické možnosti u hemofilie

Koncentráty faktorů
Fúzní molekuly
Syntetické molekuly
Porcinní

FVIII mimetika Ab – **emicizumab**

Non-factor terapie - cílená pro antitrombinu – **fitusiran** (ALN-AT3)
- cílená proti TFPI
- cílená proti APC
- cílená proti proteinu S

Genová terapie – Hemophilia A - **AAV5-hFVIII-SQ**
Hemophilia B - **SPK-9001, AMT-060**

HAEMOPHILIA

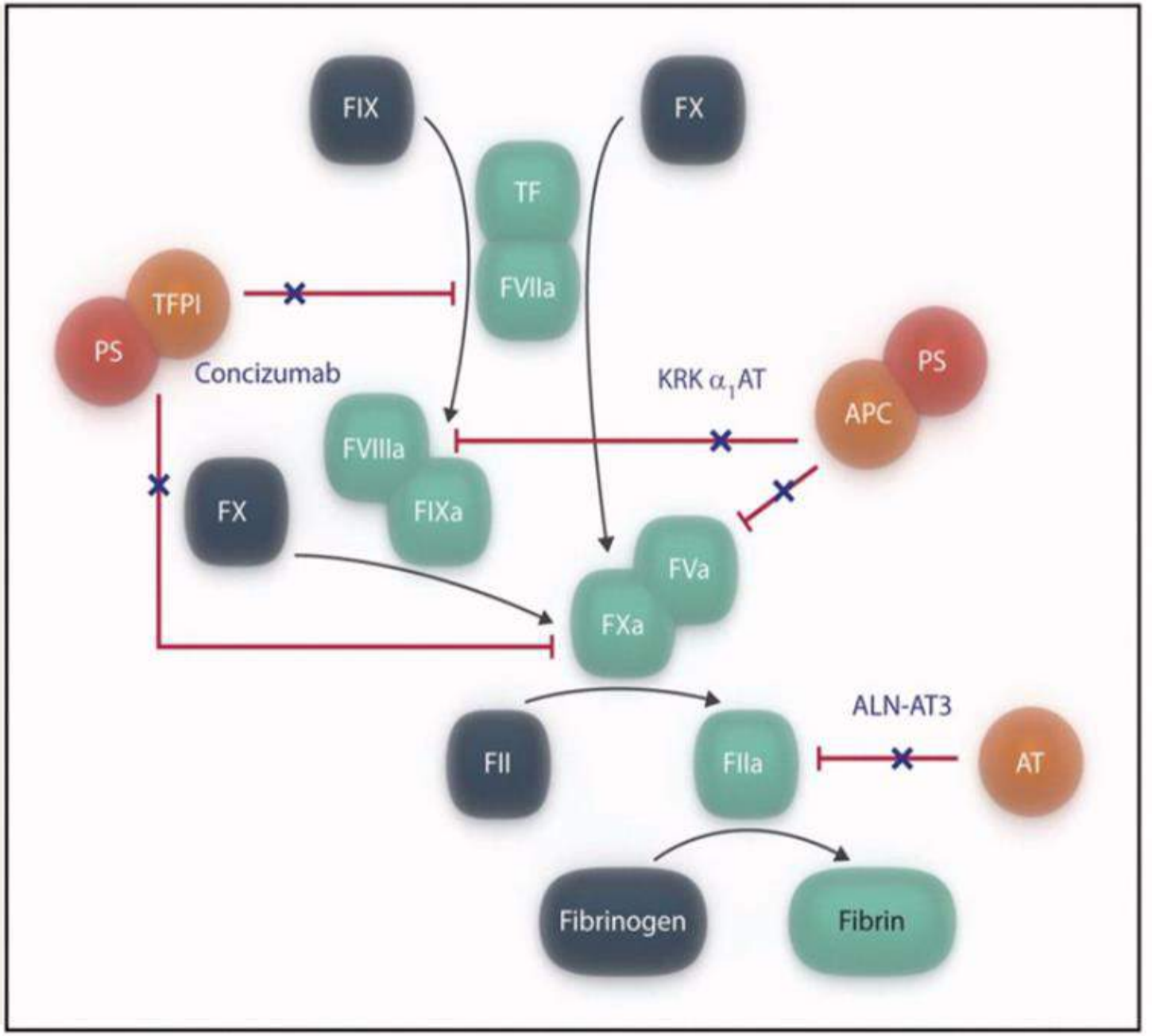
People with haemophilia do not produce enough factor VIII or factor IX, proteins that play a crucial part in clotting.

FACTOR REPLACEMENT TREATMENT

To prevent and staunch bleeding, physicians typically give patients with haemophilia infusions of the factors they lack. Adding these extra factors restores the balance between bleeding and clotting.

ANTICOAGULANT INHIBITION TREATMENT

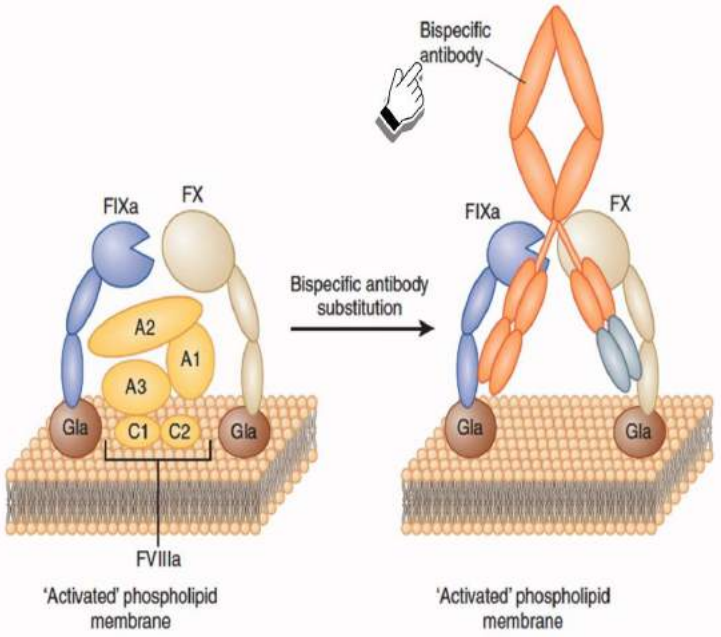
An approach under development restores balance instead by inhibiting the proteins that prevent clotting – natural anticoagulants such as tissue factor pathway inhibitor (TFPI) and antithrombin.



HAVEN 1: Emicizumab (ACE910) prophylaxis in patients with hemophilia A with inhibitors – a randomized, multicenter, open-label, phase 3 study to investigate efficacy, safety and pharmacokinetics

J. Oldenburg, J. Mahlangu, B. Kim, C. Schmitt, M. Callaghan, G. Young, E. Santagostino, R. Kruse-Jarres, C. Negrier, C. Kessler, N. Valente, E. Asikanius, G. Levy, J. Windyga, M. Shima
Germany, South Africa, United States, Switzerland, Italy, France, Poland, Japan

See also: **N Engl J Med**. 2017 Jul 10. doi: 10.1056/NEJMoa1703068. [Epub ahead of print]; editorial: D. Lillicrap. July 10, 2017DOI: 10.1056/NEJMe1707802



Humanizovaná bispecifická monoklonální Ab

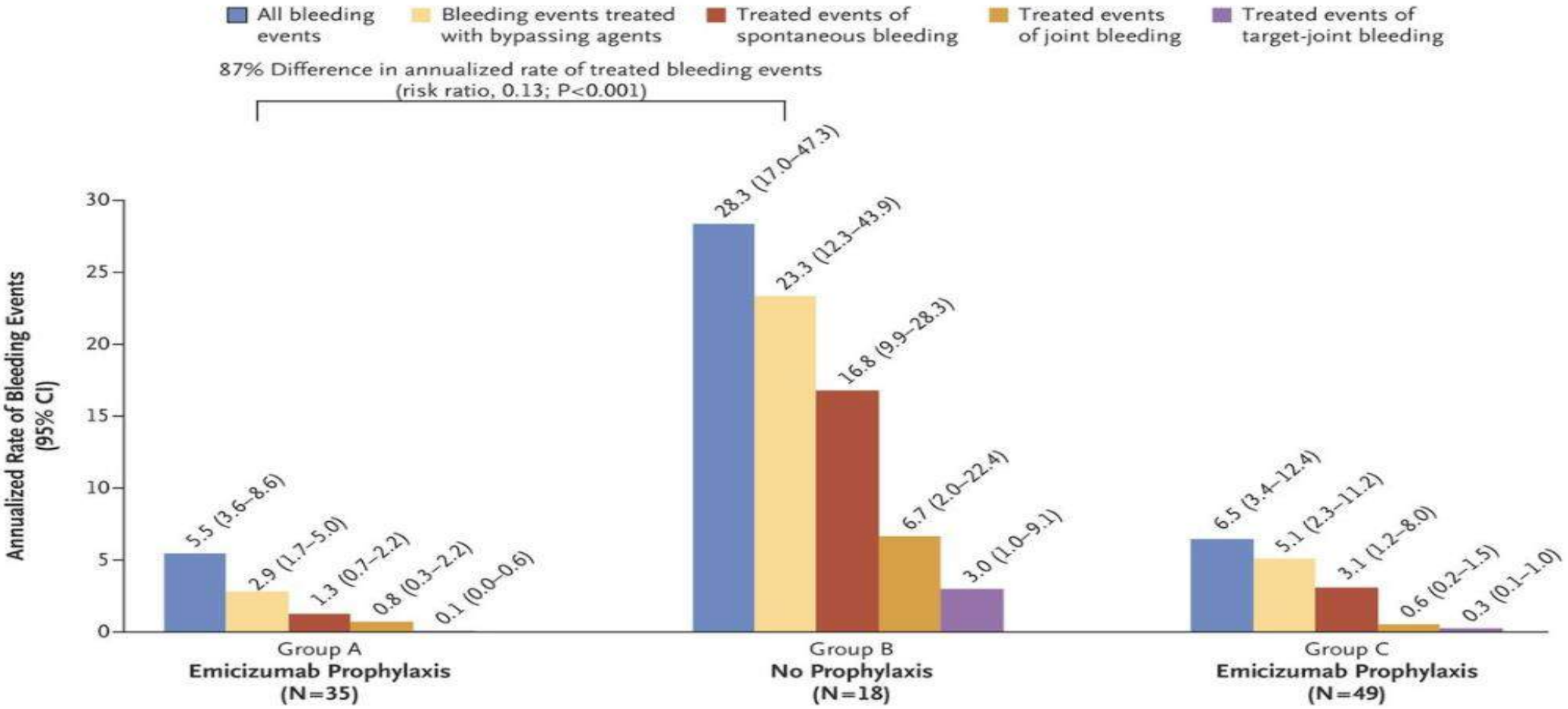
Bez strukturální homologie k FVIII

Nahrazuje chybějící FVIIIa přemostěním FIXa a FX

Neindukuje ihnibitor FVIII

Subkutánní podání (1w)

- emicizumab snižuje výskyt krvácení o 87% v porování s bypassing přípravky podávánými OD
- emicizumab snižuje výskyt krvácení o 79% v porovnání s předchozí profylaxí bypassing přípravky



Phase III Studies with Emicizumab

- HAVEN 1 is a randomized, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis versus no prophylaxis in people (**adolescents and adults**) with **hemophilia A and inhibitors** to factor VIII
- HAVEN 2 is a single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of once weekly subcutaneous administration of emicizumab in **children** <12 years old with **hemophilia A and inhibitors** to factor VIII
- HAVEN 3 is evaluating emicizumab prophylaxis dosed **once weekly or once every other week** in people **≥12 years** with hemophilia A **without inhibitors**
- HAVEN 4 is evaluating emicizumab prophylaxis dosed **every 4 weeks** in people **≥12 years** with hemophilia A **without inhibitors**

Emicizumab …?

- normalizace aPTT krátce po podání
- laboratorní hodnocení odpovědi (?) – chromogenní FVIII, TGA
- korelace klinického efektu s aktivitou FVIII?
- testování inhibitoru

- potenciál u hemofilie B ?
- Typ 2N vWCH ?

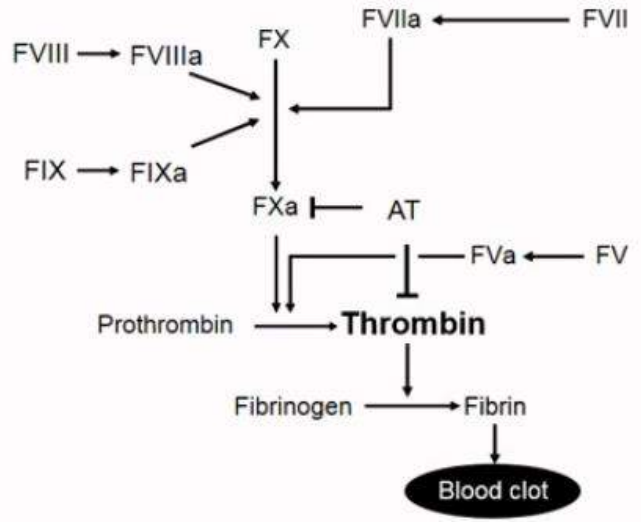
Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Interim Results from a Phase 2 Extension Study in Patients with Hemophilia A and B with and without Inhibitors

K.J. Pasi, P. Georgiev, T. Mant, M.D. Creagh, T. Lissitchkov, D. Bevan, S. Austin, C. Hay, I. Hegemann, R. Kazmi, P. Chowdary, S. Rangarajan, C.-H. Soh, A. Monpara, H.V. Nguyen, K. Madigan, M.V. Ragni
United Kngdom, Bulgaria, Switzerland, United States

Fitusiran (ALN-AT3)

SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)

- Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—site of AT synthesis
- Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels



Therapeutic hypothesis

Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation

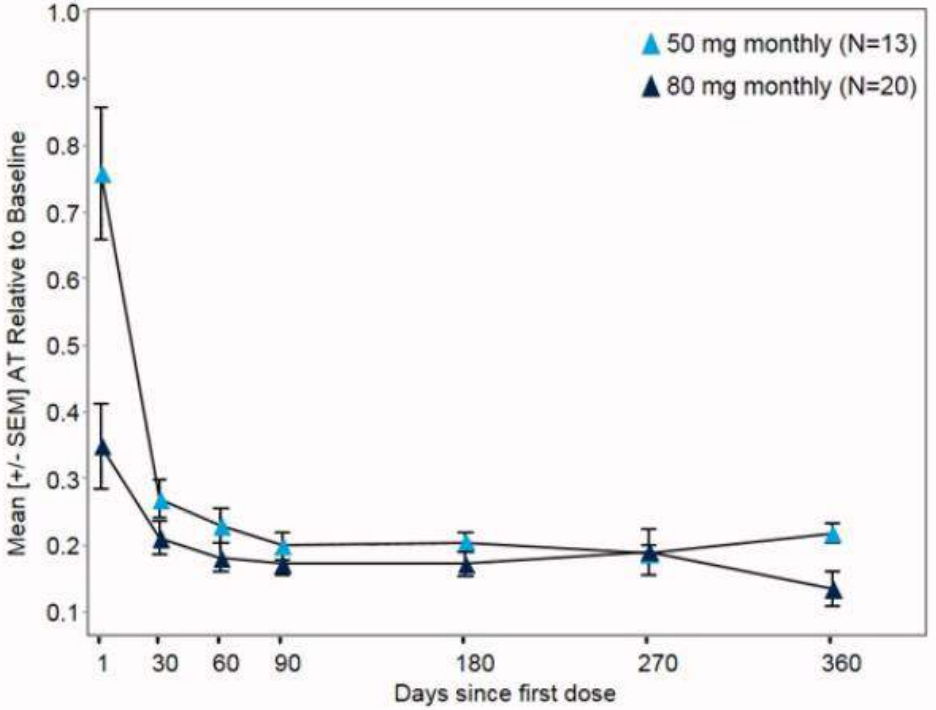
Fitusiran is designed to lower AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding

- Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia[1-4]
- Supported by pre-clinical data[5] and emerging Phase 1 clinical results[6-7]

[1]Kurnik K, et al. *Haematologica*. 92:982-985 (2007); [2]Ettingshausen E, et al. *Thromb Haemost*. 85:218-220 (2001); [3]Negrier C, et al. *Blood*. 81:690-695 (1993); [4]Shetty S, et al. *Br J Haematol*. 138:541-544 (2007); [5]Seghal A, et al. *Nat Med*. 21:492-497 (2015); [6]Pasi KJ et al. *Blood*. 2016, 128: 1397; [7]Pasi KJ, et al. *N Engl J Med. 2017; DOI 10.1056/NEJMoa1616569*.

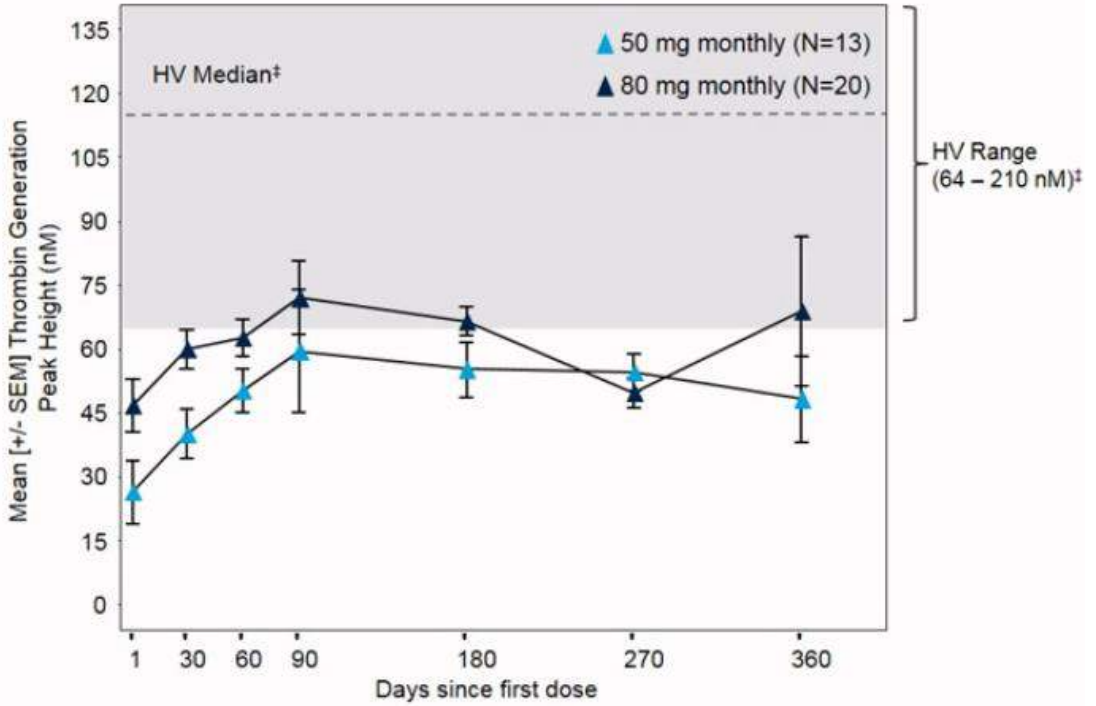
Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Antithrombin Levels



Days since first dose:	1	30	60	90	180	270	360
▲ N†=	13	13	13	13	10	10	6
▲ N†=	19	19	17	16	12	9	4

Thrombin Generation



Days since first dose:	1	30	60	90	180	270	360
▲ N†=	12	10	11	11	9	8	5
▲ N†=	17	17	15	13	12	7	4

*Data transfer 15June2017
OLE, open-label extension; AT, antithrombin; SEM, standard error of the mean; HV, Healthy Volunteer
†Only patients with >56 days in OLE included in analysis; patients excluded from TG analysis if theyadministered factor or bypassing agent within 48 hours
‡Healthy volunteers with AT lowering <25% (Pasi KJ, et al. *N Engl J Med. 2017; epub ahead of print.*)

Pasi et al., ISTH 2017

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

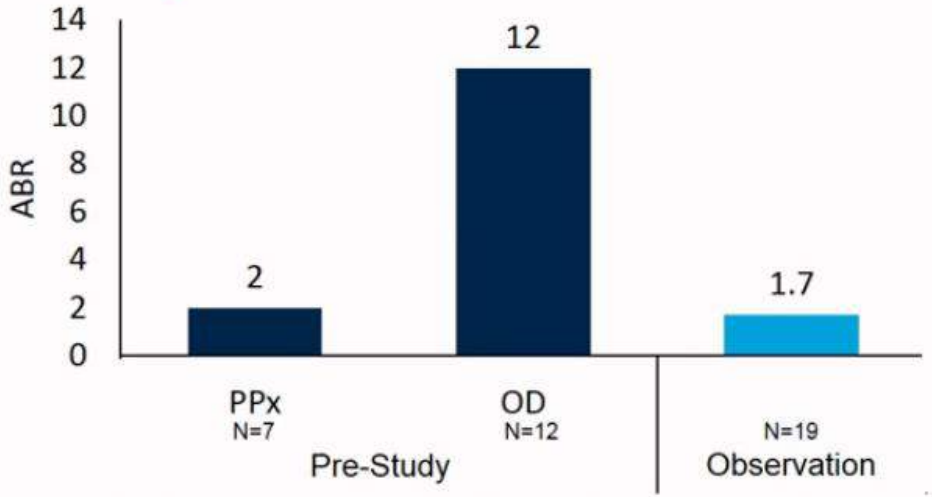
Increasing patient safety experience, with up to 20 months of dosing in Phase 2 OLE

- Majority of AEs were mild or moderate in severity; ISRs most common non-laboratory AE, all mild and transient
- No thromboembolic events; no clinical or laboratory evidence of pathologic clot formation
- Asymptomatic ALT increases >3X ULN observed in HCV Ab+ patients; most cases improved without dose interruption; 1 case led to discontinuation

Summary of Median ABRs in all Patients

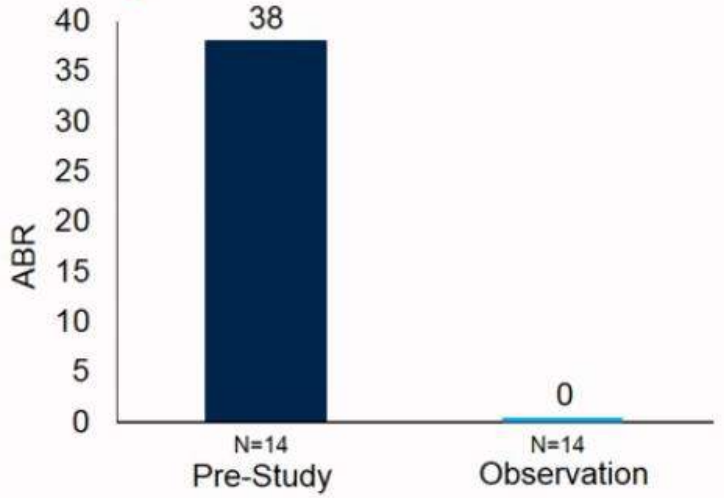
- 48% (16/33) of patients bleed free during observation period†; overall median ABR in observation period = 1
- 67% (22/33) of patients reported no spontaneous bleeds; overall median AsBR in observation period = 0

Summary of Median ABRs in Patients without Inhibitors



- Median duration in observation period: 13 months [range: 2 –19]
- Mean AT activity in observation period (relative to baseline): 22%

Summary of Median ABRs in Patients with Inhibitors



- Median duration in observation period: 6 months [range: 1 –11]
- Mean AT activity in observation period (relative to baseline): 18%

*Data transfer 15June2017

†Observation period defined as day 29 of treatment to earlier of data transfer or 56 days after last dose

ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; PPx, prophylaxis; OD, on demand

Pasi et al., ISTH 2017

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

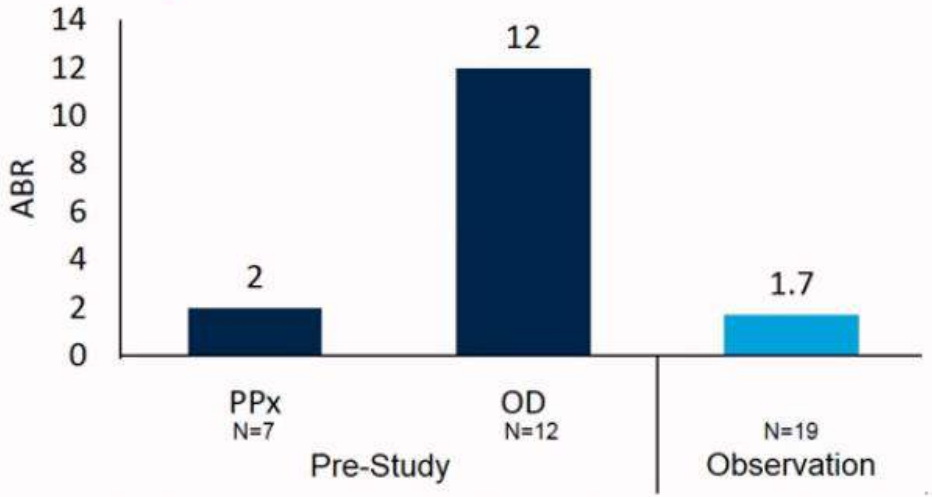
Increasing patient safety experience, with up to 20 months of dosing in Phase 2 OLE

- Majority of AEs were mild or moderate in severity; ISRs most common non-laboratory AE, all mild and transient
- No thromboembolic events; no clinical or laboratory evidence of pathologic clot formation
- Asymptomatic ALT increases >3X ULN observed in HCV Ab+ patients; most cases improved without dose interruption; 1 case led to discontinuation

Summary of Median ABRs in all Patients

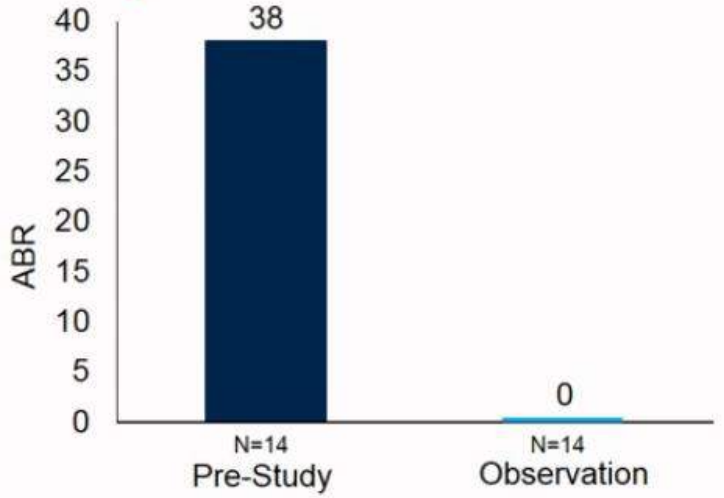
- 48% (16/33) of patients bleed free during observation period†; overall median ABR in observation period = 1
- 67% (22/33) of patients reported no spontaneous bleeds; overall median AsBR in observation period = 0

Summary of Median ABRs in Patients without Inhibitors



- Median duration in observation period: 13 months [range: 2 –19]
- Mean AT activity in observation period (relative to baseline): 22%

Summary of Median ABRs in Patients with Inhibitors



- Median duration in observation period: 6 months [range: 1 –11]
- Mean AT activity in observation period (relative to baseline): 18%

*Data transfer 15June2017

†Observation period defined as day 29 of treatment to earlier of data transfer or 56 days after last dose

ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; PPx, prophylaxis; OD, on demand

Pasi et al., ISTH 2017

Summary and Next Steps

Increasing patient safety experience, with up to 20 months of dosing in Phase 2 OLE

- Majority of AEs were mild or moderate in severity; ISRs most common non-laboratory AE, all mild and transient
- No thromboembolic events; no clinical or laboratory evidence of pathologic clot formation
- Asymptomatic ALT increases >3X ULN observed in HCV Ab+ patients; most cases improved without dose interruption, 1 case (SAE) led to discontinuation

Encouraging results in patients with hemophilia A and B, with and without inhibitors

- Approximately 80% AT lowering with low inter-patient variability achieved with once-monthly subcutaneous dosing
- Exploratory post-hoc analysis of bleed events demonstrates median ABR = 1 for all patients[†]
  - 48% (16/33) patients bleed-free and 67% (22/33) patients experiencing zero spontaneous bleeds

All bleed events in patients successfully managed with replacement factor or BPA

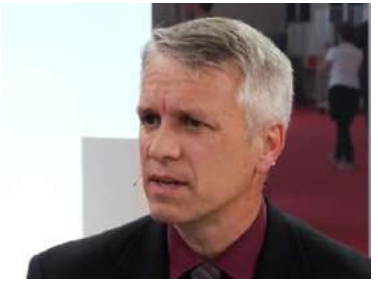
ATLAS Phase 3 program initiated

Anti-TFPI

- regulace iniciální fáze hemostázy
- vliv aktivity TFPI na „krvácivý“ fenotyp hemofilie
- inhibice TFPI zlepšuje koagulační potenciál v plasmě hemofiliků
  - non-antikoagulační polysacharidy
  - aptamery a peptidy
  - humanizované anti-TFPI protilátky
    - concizumab
    - BAY1093884

Small Molecules in the Treatment of Hemophilia

Steven Pipe, MD
University of Michigan



otázky

- bioekvivalence k FVIII/FIX, a je nezbytná pro klinický efekt?
- laboratorní bioekvivalence, shoda s klinickou korelací
- ignoruje přístup potenciální funkční/tkáňovou distribuci FVIII/FIX
- ovlivnění protrombotického rizika při dalších klinických okolnostech, příp. potřebě BPA
  - velké chirurgické zákroky
  - sepse
  - žilní přístupy / centrální linky
- alterace prokoagulační / antikoagulační rovnováhy