Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Updated Results from Phase 1 and Phase 2 Extension Studies in Patients with Inhibitors

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Fitusiran

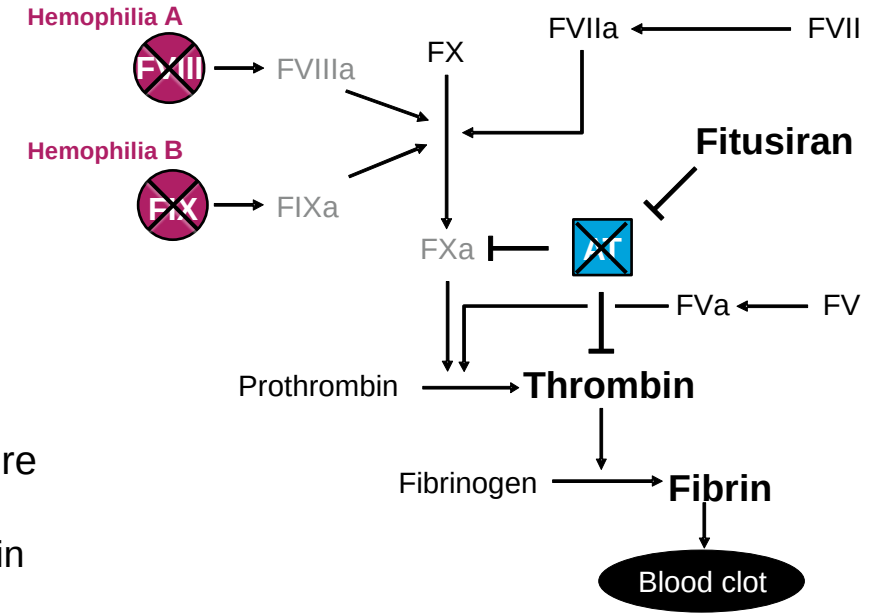
Investigational RNAi Therapeutic for Treatment of Hemophilia

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. 2015, 126:551*; [7]Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)

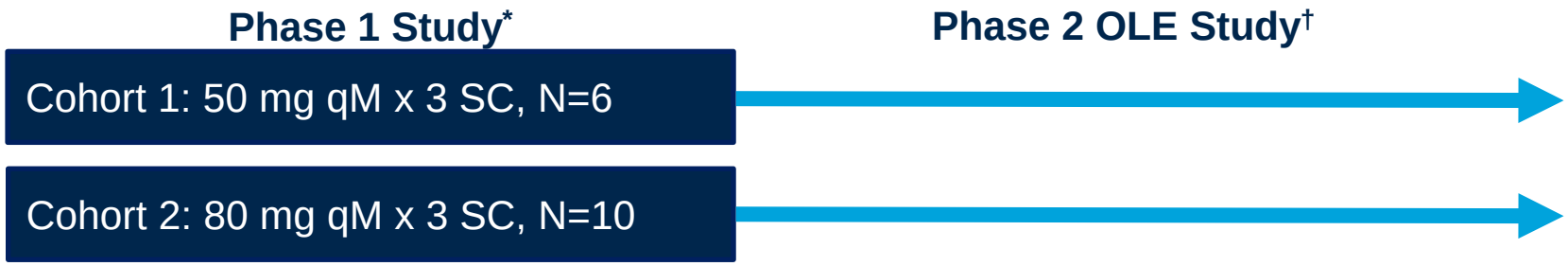
Fitusiran Phase 1 and Phase 2 OLE Study Design

Part A: Single-Ascending Dose (SAD) │Randomized 3:1, Single-blind, Placebo-Controlled, Healthy Volunteers

Part B: Multiple-Ascending Dose (MAD), Weekly dosing │ Open-label, Patients with Hemophilia A or B

Part C: MAD, Monthly dosing │ Open-label, Patients with Hemophilia A or B*

Part D: MAD – Monthly dosing │ Open-label, Patients with Hemophilia A or B with Inhibitors



- Patients eligible to roll over onto Phase 2 OLE starting on Day 84
- Individual patient dose adjustment may be allowed (per Safety Review Committee)

OLE, Open-Label Extension; qM, monthly; SC, subcutaneous
*ClinicalTrials.gov Identifier: NCT02035605; Pasi KJ, et al. Haemophilia. 2016, 22(Suppl 4)
†ClinicalTrials.gov Identifier: NCT02554773

Interim Fitusiran Phase 1 (Part D) Study Results*

Demographics & Baseline Characteristics in Patients with Inhibitors

	50 mg N=6	80 mg N=10
Age, years; mean (range)	32 (22-41)	37 (21-65)
Weight, kg; mean (range)	73 (55-100)	73 (52-108)
Hemophilia A with Inhibitors Hemophilia B with Inhibitors	5 1	10 0
Severe Moderate	6 0	10 0
Medical history of hepatitis C	3	9

*Data cut-off 06Oct2016

Interim Fitusiran Phase 1 (Part D) Study Results*
Safety/Tolerability† in Patients with Inhibitors

Fitusiran generally well tolerated in inhibitor patients

- No discontinuations due to AEs or drug-related SAEs
- No thromboembolic events
- All AEs mild or moderate in severity
  - Non-laboratory AEs reported in ≥2 patients: injection site reactions (ISRs) 7/16 (44%) and cough 2/16 (13%)
  - ISRs all mild; mostly pain and/or erythema at injection site
- ALT increases >3x ULN observed in 3 patients
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - All patients had medical history of HCV
  - Reversible, all patients currently with ALT <3x ULN
- Non-clinically significant D-dimer increases observed in some patients; none associated with laboratory signs of pathological clot formation (changes in platelets, fibrinogen, and/or PT/INR)
- No clinically significant changes in other laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- All bleed events successfully managed with bypassing agents (rFVIIa, aPCC)
- As of data cut-off, 7 patients transitioned to Phase 2 OLE; fitusiran continues to be generally well tolerated

*Data cut-off 06Oct2016
AE, adverse events; SAE, serious adverse events
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events

Interim Fitusiran Phase 1 (Part D) Study Results*

Patient Characteristics in Patients with Inhibitors

Patient	Hemophilia	Prescribed BPA†	Dose (qM)
D1-1	HA	aPCC	50 mg
D1-2	HB	rFVIIa/aPCC	50 mg
D1-3	HA	rFVIIa	50 mg
D1-4	HA	aPCC	50 mg
D1-5	HA	rFVIIa/aPCC	50 mg
D1-6	HA	rFVIIa	50 mg
D2-1	HA	aPCC	80 mg
D2-2	HA	aPCC	80 mg
D2-3	HA	rFVIIa	80 mg
D2-4	HA	rFVIIa/aPCC	80 mg
D2-5	HA	rFVIIa	80 mg
D2-6	HA	rFVIIa	80 mg
D2-7	HA	rFVIIa	80 mg
D2-8	HA	rFVIIa	80 mg
D2-9	HA	rFVIIa	80 mg
D2-10	HA	rFVIIa	80 mg

Follow-up of patients in Phase 1 ranged from 43-147 days

*Data cut-off 06Oct2016
HA, Hemophilia A, HB, Hemophilia B; BPA, bypassing agent; qM, monthly
†All patients previously prescribed on demand BPA treatment

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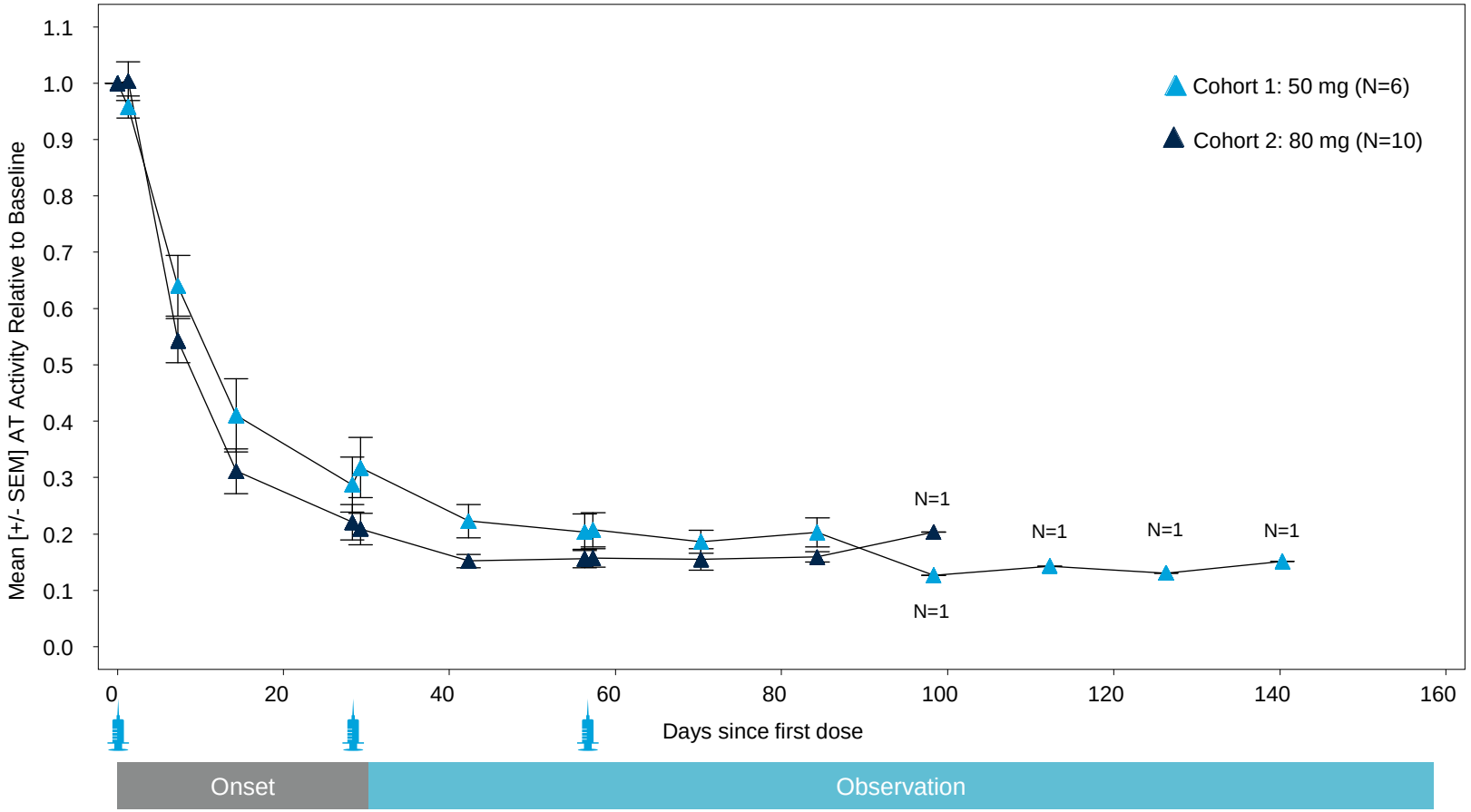
Interim Fitusiran Phase 1 (Part D) Study Results*
AT Lowering in Patients with Inhibitors

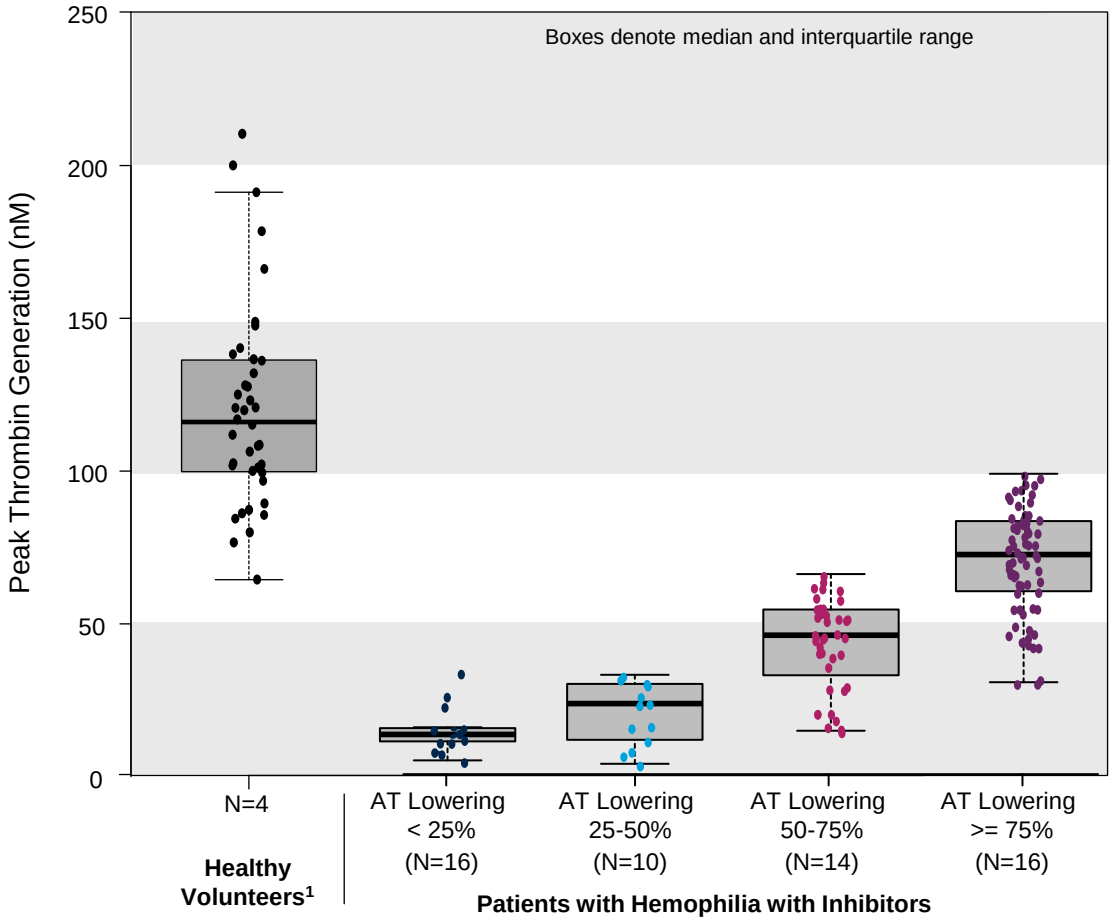
AT lowering after monthly dosing in hemophilia patients with inhibitors



*Data cut-off 06Oct2016

Interim Fitusiran Phase 1 (Part D) Study Results*
AT Lowering is Correlated with Increased Thrombin Generation

Post hoc analysis of thrombin generation by AT lowering quartiles



*Data cut-off 06Oct2016

[1]Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4),

Interim Fitusiran Phase 1 (Part D) and OLE Study Results*

Exploratory Analysis of Bleed Events†

Patient	Pre-study ABR‡	Onset ABR	Observation Period				
			Days in Obs Period	All Bleeds, N	ABR	Spontaneous Bleeds, N	AsBR
D1-1^	40	13	191	3	**5.7**	2	**3.8**
D1-2^	26	13	180	5	**10.1**	3	**6.1**
D1-3	0	0	84	0	**0**	0	**0**
D1-4^	52	38	162	11	**25**	9	**20**
D1-5^	80	38	160	20	**46**	12	**27**
D1-6^	16	13	156	0	**0**	0	**0**
D2-1	48	0	48	1	**7.6**	0	**0**
D2-2	48	0	41	0	**0**	0	**0**
D2-3	8	0	72	0	**0**	0	**0**
D2-4^	48	13	56	0	**0**	0	**0**
D2-5	36	0	69	0	**0**	0	**0**
D2-6	20	0	69	1	**5.3**	0	**0**
D2-7^	14	13	55	0	**0**	0	**0**
D2-8	20	38	55	2	**13.3**	2	**13.3**
D2-9	12	0	13	0	**0**	0	**0**
D2-10	44	0	13	0	**0**	0	**0**

*Data cut-off 06Oct2016
OLE, open-label extension; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleed rate
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier); ‡Pre-study ABR derived from medical records; ^Patients transitioned to Phase 2 OLE as of data cut-off;

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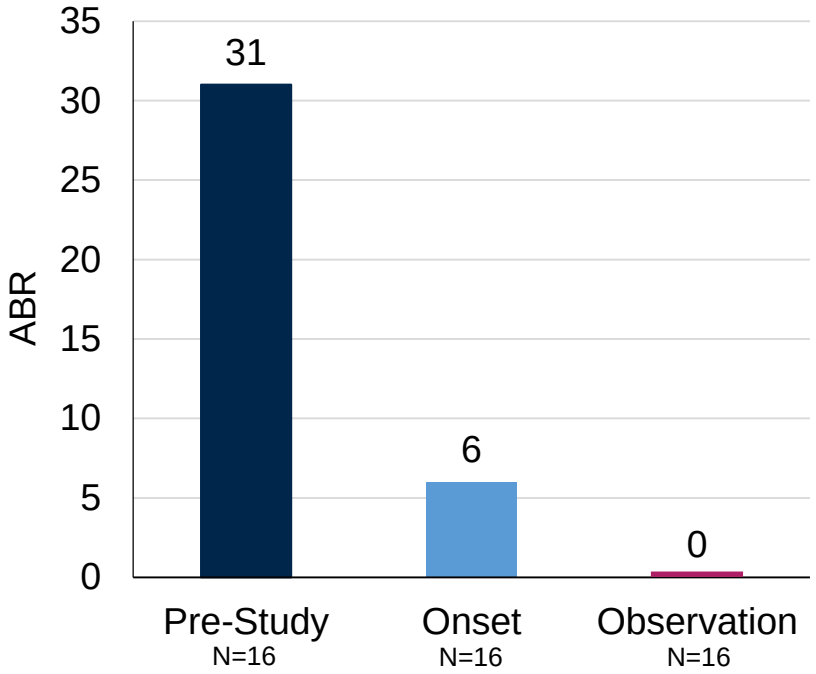
Interim Fitusiran Phase 1 (Part D) and OLE Study Results*

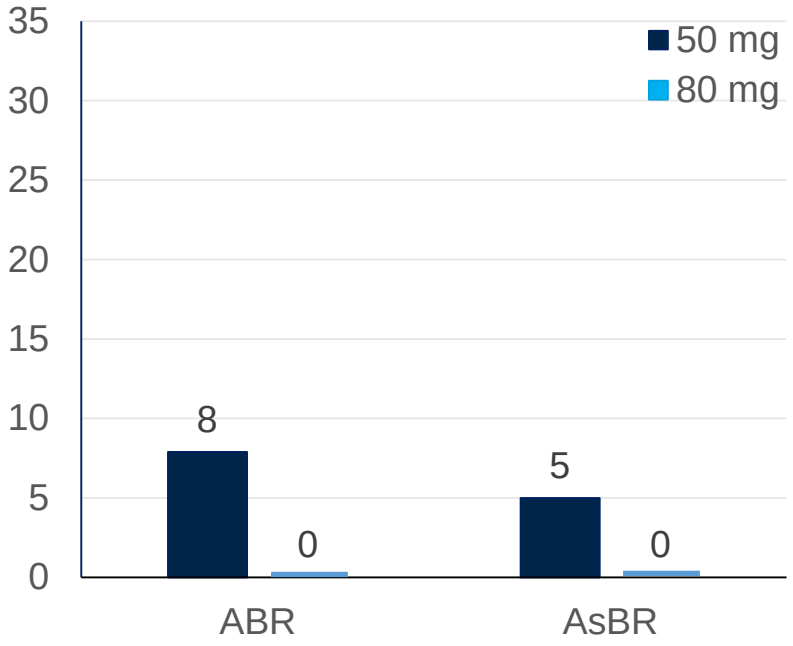
Summary of Median ABRs

All Inhibitor Patients



- Median ABR, Pre-study period: 31
- Median ABR, Observation period: 0
  - Patients reporting no bleeds: 9/16 (56%)
  - Patients report no spontaneous bleeds (AsBR = 0): 11/16 (69%)

Observation Period, 50 mg vs 80 mg



- 50 mg: Median ABR = 8, median AsBR = 5
- 80 mg: Median ABR = 0, median AsBR = 0
  - Patients reporting no bleeds: 7/10 (70%)
  - Patients report no spontaneous bleeds (AsBR = 0): 9/10 (90%)

*Data cut-off 06Oct2016
OLE, open-label extension; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleed rate

Interim Fitusiran Phase 1 (Part D) and OLE Study Results*
Summary and Next Steps

Fitusiran generally well tolerated in hemophilia A and B patients with inhibitors
- No SAEs related to study drug; no thromboembolic events
- All AEs were mild or moderate in severity; ISRs most common AE, all mild

Encouraging results in hemophilia patients with inhibitors
- Once-monthly subcutaneous dosing at 50 mg and 80 mg achieves dose-dependent AT lowering of ~80%
- Exploratory post-hoc analysis of bleed events demonstrates median ABR = 0 for all patients
  - 9/16 (56%) patients bleed-free and 11/16 (69%) patients experiencing zero spontaneous bleeds
- Data suggest 80 mg may provide greater bleed prevention
  - 7/10 (70%) patients bleed-free and 9/10 (90%) patients experiencing zero spontaneous bleeds

Dosing in hemophilia patients with inhibitors continues in Phase 2 OLE
- 7 inhibitor patients now enrolled
- Up to 7 months of continuous dosing

Plan to advance fitusiran to pivotal studies in early 2017

*Data cut-off 06Oct2016
OLE, open-label extension; SAE: serious adverse events; AE, adverse events; ISR, injection site reactions; AT, anti-thrombin; ABR, annualized bleeding rate;

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	John Pasi	London – The Royal London Haemophilia Centre
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