NXT007：ISTH勉強会

2025年6月24日

中外製薬株式会社

重要な注意事項

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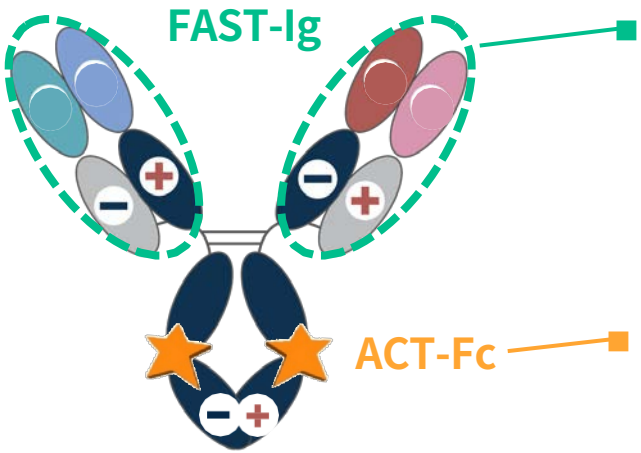
NXT007：血友病Aの方々への新たな価値提供

- **自社の抗体エンジニアリング技術を適用。現在実施中のP2試験成績は、25年の学会で発表予定**
- **ヘムライブラ®との直接比較試験も含め、26年に3本のP3試験開始予定**



当社のFAST-Ig™を適用した抗FIXa/FXバイスペシフィック抗体：ヘムライブラ®の可変領域を最適化し、より高い有効性を期待

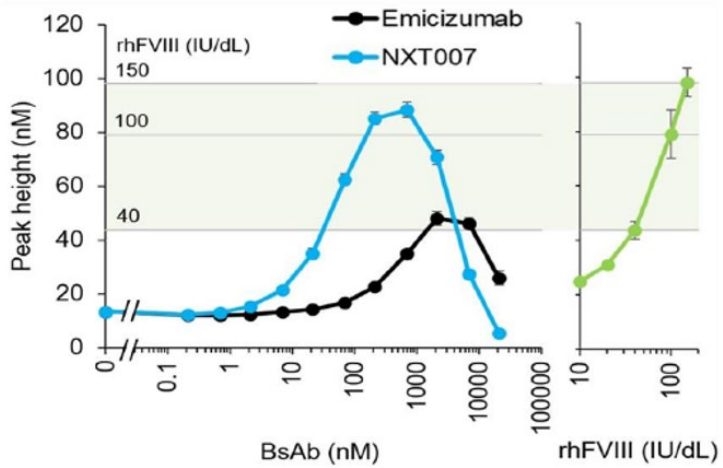
ACT-Fc®の適用により、PKプロファイルを改善し、より高い利便性を期待

P1	P2	P3	
P1/2			25年 学会発表予定
FVIII製剤との直接比較			P3 26年開始予定
ヘムライブラ®との直接比較			P3 26年開始予定
小児対象			P3 26年開始予定

ヘムライブラ®をベースにエンジニアリングし、結合親和性の最適化、血中半減期の延長により、少量かつ低頻度の皮下注射を可能に

- ヘムライブラ®よりも約30倍効力が高く、*in vitro*アッセイで、トロンビン生成が血友病Aではない人の範囲内であることが示唆*
- 投与時の高い利便性　（約10週の半減期**、皮下注射）

***in vitro* トロンビン生成試験** [1,a]



*A bispecific antibody NXT007 exerts a hemostatic activity in hemophilia A monkeys enough to keep a non-hemophiliac state（https://doi.org/10.1016/j.jtha.2023.09.034）

**NXT001JG試験 健康成人パートでのデータ（2023 ISTH発表）

[1] *Yuri Teranishi-Ikawa et. al Journal of Thrombosis and Haemostasis 2023*　[a] tissue factor triggered

®登録商標

(OC 20.3)

NXT007 Prophylaxis in Emicizumab-Naive Persons with Hemophilia A without Inhibitor: Phase I/II Study (NXTAGE)

Midori Shima[1], Chur-Woo You[2], Young-Shil Park[3], Yeu-Chin Chen[4], Ming-Ching Shen[5], Jiaan-Der Wang[6], Masahiro Takeyama[7], Kagehiro Amano[8], Sheng-Chieh Chou[9], Takuya Miwa[10], Chun-An Chen[10], Takeshi Miyake[10], Keisuke Iwasaki[10], Keiji Nogami[11]

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Overview of NXTAGE Part B

Multiple ascending dose part in emicizumab-naïve PwHA to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and efficacy of NXT007

Key Inclusion Criteria:
- Severe Hemophilia A
- Without FVIII inhibitors
- Ages ≥12 to <65 years

Patients received NXT007 via subcutaneous (SC) administration every 4 weeks (Q4W) in ascending dose cohorts after loading doses

(N=6-8/cohort*1)

- B-4: 4 weeks loading dose → Maintenace dose: **1.08** mg/kg **Q4W SC**
- B-3: 4 weeks loading dose → Maintenace dose: **0.7** mg/kg **Q4W SC**
- B-2: 6 weeks loading dose → Maintenace dose: **0.28** mg/kg **Q4W SC***2
- B-1: 4 weeks loading dose → Maintenace dose: **0.072** mg/kg **Q4W SC**

*1 For B-1, 10 patients were enrolled.
*2 Dosing regimen was switched from 0.14 mg/kg Q2W to reflect study protocol amendment.

Timing of the primary analysis:
- At least 6 patients completed 16 weeks of NXT007 treatment in all Part B cohorts
- First patient in: 1-Feb-2022
- Data cutoff date: 6-Nov-2024

PwHA, patients with hemophilia A; FVIII, factor VIII; Q2W, every 2 weeks

Concept of Dose Setting

- NXT007 doses were adapted by population PK simulations using the PK data from healthy volunteers who participated in NXTAGE to achieve the target FVIII-equivalent activity predicted based on FIX-NXT007-FX ternary complex concentrations.
- FVIII-equivalent activity was predicted to reach non-hemophilic level in B-2 onwards.

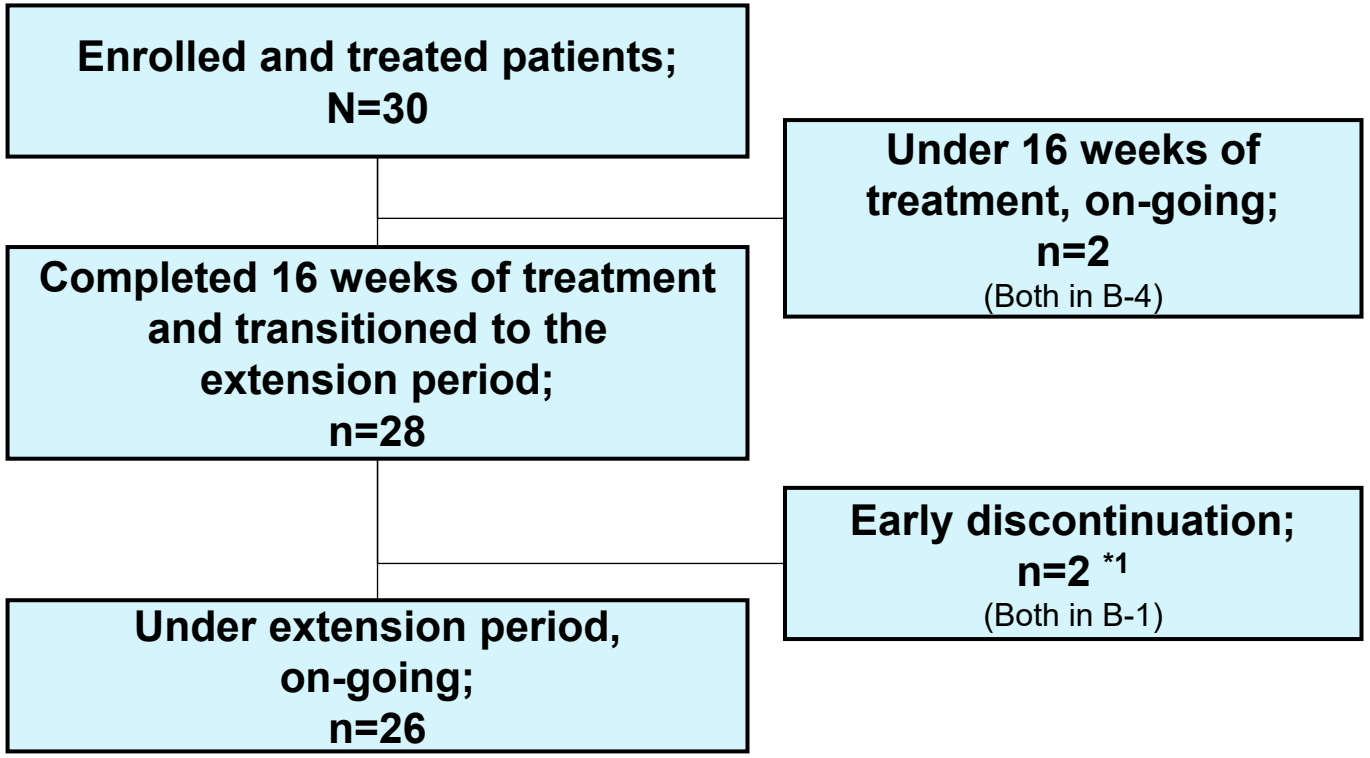
Cohort	Maintenance dose	Predicted trough levels at steady state	
		Plasma NXT007 concentration	FVIII-equivalent activity*1
B-4	1.08 mg/kg Q4W	24.8 µg/mL	**93.1 IU/dL**
B-3	0.7 mg/kg Q4W	16.1 µg/mL	**73.8 IU/dL**
B-2	0.28 mg/kg Q4W	7.27 µg/mL	**40.1 IU/dL**
B-1	0.072 mg/kg Q4W	2.29 µg/mL	**13.8 IU/dL**

*1 The FVIII-equivalent activity prediction was performed based on Yoneyama et.al., Blood (2022) 140 (Supplement 1): 11295–11296

FIX, factor IX; FVIII, factor VIII; FX, factor X; PK, pharmacokinetics; Q4W, every 4 weeks

Patient Disposition and Duration of Exposure

Patient Disposition



*1 One patient discontinued NXT007-treatments due to unrelated adverse event, lower limb fracture. Another patient discontinued NXT007-treatments due to development of anti-drug antibody (ADA) impacting PK. Both discontinued the study due to consent withdrawal thereafter.

Duration of NXT007 Exposure by Cohort

Cohort	Duration of Exposure; week (median, min-max)
B-1 (N=10)	114.1 (29-140)
B-2 (N=6)	96.4 (88-112)
B-3 (N=6)	58.1 (52-72)
B-4 (N=8)	22.2 (4-28)
Total (N=30)	**68.4 (4-140)**

PK, pharmacokinetics

Patient Demographics

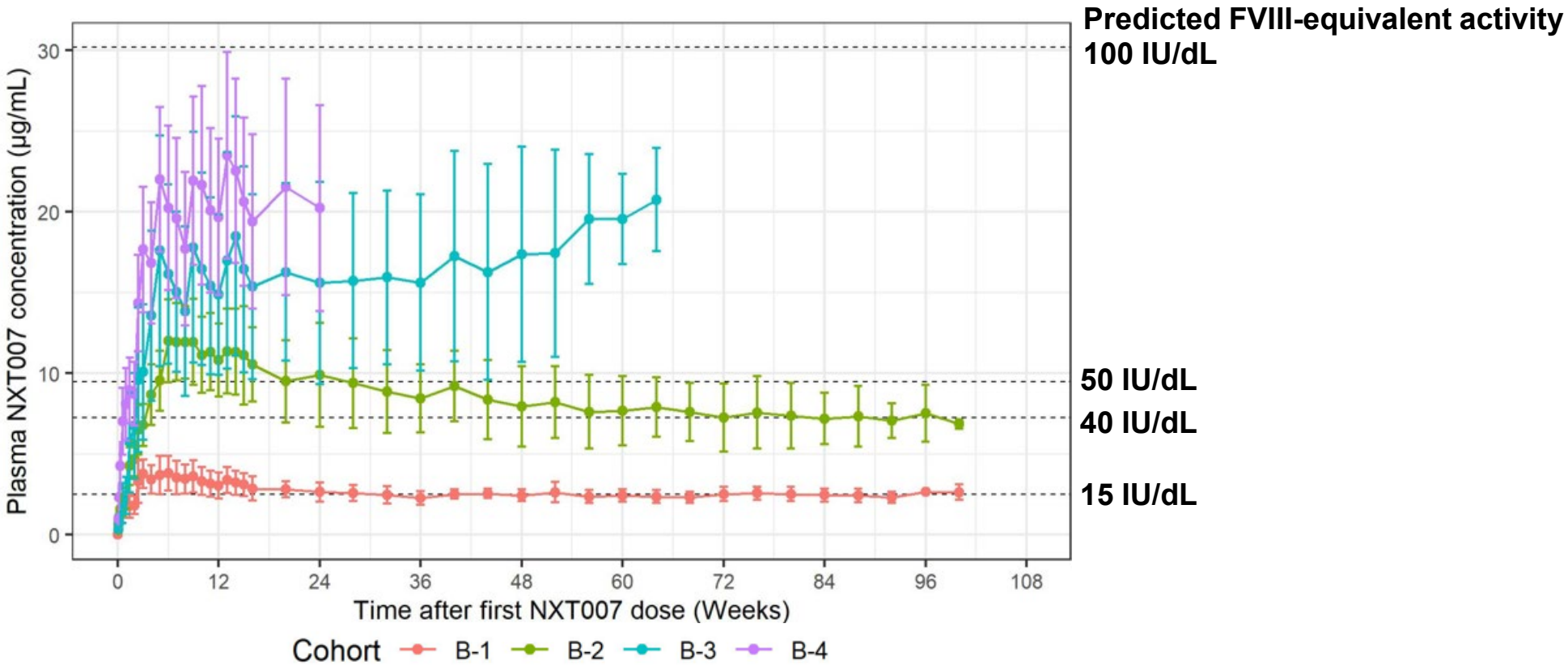
Most of the patients (96.7%) received FVIII prophylaxis before enrollment.

	B-1 (N=10)	B-2 (N=6)	B-3 (N=6)	B-4 (N=8)	Total (N=30)
Age, years, median (range)	39.5 (20 - 57)	22 (12 – 54)	37 (18 - 52)	51.0 (25 - 56)	39.5 (12-57)
Weight, kg, median (range)	68.75 (53.8 – 93.9)	78.30 (40.6 – 89.6)	60.70 (52.6 – 82.0)	70.55 (56.2 – 81.5)	69.65 (40.6-93.9)
Patients with Target joint, n (%)	3 (30.0%)	1 (16.7%)	1 (16.7%)	1 (12.5%)	6 (20.0%)
Prior treatment regimen					
Prophylaxis, n (%)	**9 (90%)**	**6 (100%)**	**6 (100%)**	**8 (100%)**	**29 (96.7%)**
Episodic, n (%)	**1 (10%)**	**0**	**0**	**0**	**1 (3.3 %)**

FVIII, factor VIII

PK and Predicted FVIII-equivalent Activity

- Dose-dependent increase of NXT007 plasma concentration was observed.
- In B-3 and B-4, plasma concentrations beyond non-hemophilic levels of FVIII-equivalent activity were maintained, consistent with the dose setting concept.

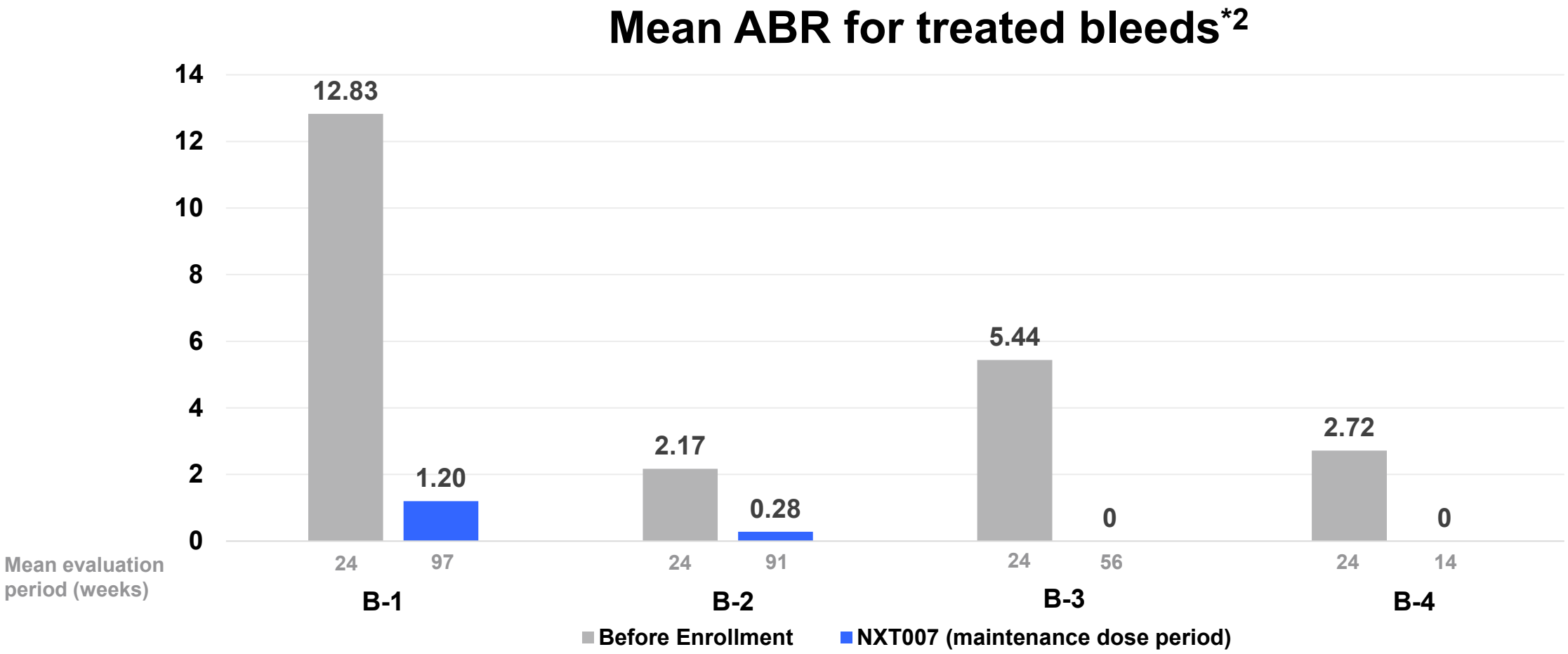


Excluding 4 PK outliers, and 2 patients with PK decrease presumably due to anti-drug antibody. The PK data after up-titration in 3 B-1 patients were also excluded. Data not shown if the number of measured values is less than two.

PK, pharmacokinetics; FVIII, factor VIII

Efficacy: Annualized Bleed Rate (ABR)

ABR decreased during NXT007 prophylaxis compared to baseline*[1].



*1 96.7% of patients received prophylactic therapy with FVIII agents.

*2 Bleeding information before study was collected from 24 weeks before the study in a retrospective manner. Calculated ABR is displayed.

FVIII, factor VIII

Safety and Tolerability

NXT007 was well tolerated:

- No dose-dependent increases in AEs were observed.
- All serious AEs were NOT related to NXT007.
- **No thromboembolic events were observed**.
- Injection site reactions were reported in 4 patients (13.3%), all of which were mild.

	B-1 (N=10)	B-2 (N=6)	B-3 (N=6)	B-4 (N=8)	Total (N=30)
Total No. of patients with at least one AE	7 (70.0%)	5 (83.3%)	3 (50.0%)	6 (75.0%)	21 (70.0%)
Total No. of AEs	17	51	10	11	89
Total No. of patients with at least one:					
Serious AE *1	3	0	0	0	3
Leaded to treatment discontinuation *1	1	0	0	0	1
NXT007-related *1	0	0	0	0	0
Thromboembolic event	0	0	0	0	0
NXT007-related AE *2	2	1	0	3	6
Injection site reactions	2	0	0	2	4

*1 Serious AEs include lower limb fracture, ankle fracture, and carbon monoxide poisoning, among which the lower limb fracture leaded to study drug discontinuation.

*2 Injection site erythema (1 event in B-1, 1 event in B-4), injection site reaction (2 events in B-1), rash (1 event in B-2) , hepatic function abnormal (1 event in B-4), and injection site rash (1 event in B-4).

AE, adverse event

Immunogenicity: Anti-Drug Antibody (ADA)

- ADA was observed in 22 out of 30 patients; the number of ADA positive patients at the final observation before the data cutoff was 9.
- ADA impacting PK was observed in 2 patients.
  - One patient in B-1 completely lost NXT007 plasma concentration due to ADA, and discontinued treatment.
  - The other patient in B-3 experienced a decrease in plasma concentration to B-1 levels, and was continuing NXT007 treatment without bleeding events.
- No ADA cross-reacting with emicizumab was observed.

	B-1 (N=10)	B-2 (N=6)	B-3 (N=6)	B-4 (N=8)	Total (N=30)
ADA post-baseline incidence *1	**7**	**6**	**4**	**5**	**22**
ADA impacting PK	1	0	1	0	2
ADA cross-reacting with emicizumab	0	0	0	0	0

*1 No patients were ADA positive at baseline.

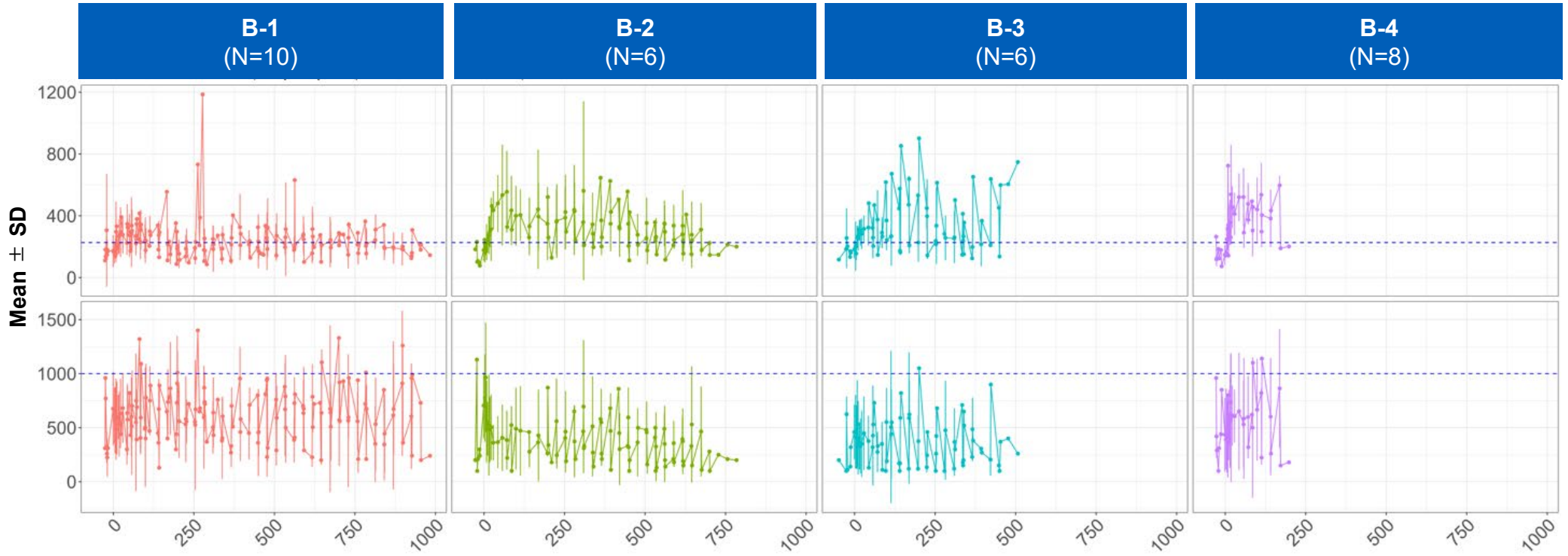
PK, pharmacokinetics

Coagulation Markers

- Prothrombin fragment 1+2 levels showed an increasing trend above the reference range, suggesting increased coagulation potential.
- No increasing trend was observed in D-dimer, suggesting no significant systemic hypercoagulability.

Prothrombin fragment 1+2

D-dimer



Blue lines represent upper limit of reference ranges

AE, adverse event

Conclusions

NXTAGE Part B examined NXT007, the emicizumab-based next generation bispecific antibody, in PwHA with Q4W SC dosing for the first time.

NXT007 prophylaxis led to a decrease in ABR compared to baseline.

No treated bleeds were observed during maintenance dose period in B-3 and B-4 with predicted FVIII-equivalent activity beyond the non-hemophilic level.

No safety concerns were observed up to the highest dose cohort (B-4).

The results suggest that NXT007 has a potential to provide a hemostatic normalization in PwHA with acceptable safety profile, supporting advancement to next phase clinical studies. The efficacy and safety of NXT007, including hypercoagulability and ADA, should be further investigated.

PwHA, patients with Hemophilia A; Q4W, every 4 weeks; SC, subcutaneous; FVIII, factor VIII

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