Extension study with rVIII-SingleChain for treatment of PUPs with severe hemophilia A

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Introduction

- rVIII-SingleChain is a B-domain truncated recombinant factor VIII (rFVIII) approved for on-demand treatment, prophylaxis and perioperative management of patients with hemophilia A[1,2]
- Clinical trials and real-world evidence demonstrated the efficacy and tolerability of rVIII-SingleChain in previously treated patients[3–6]

Objective

To investigate the efficacy and safety of rVIII-SingleChain in previously untreated patients (PUPs)

Methods

- This phase III, open-label, multicenter, extension study was part of the AFFINITY clinical trial program[7]
- PUPs aged <18 years with severe hemophilia A (FVIII <1%) were enrolled to receive either prophylactic or on-demand treatment with rVIII-SingleChain
- PUPs developing FVIII inhibitors were eligible to continue receiving rVIII-SingleChain therapy for up to 24 months, with the aim of eradicating the inhibitor
- Primary endpoints were annualized spontaneous bleeding rates (AsBR) during prophylaxis and on-demand treatment and treatment success (hemostatic efficacy excellent or good) for major bleeds
- Primary safety endpoint was the incidence of high-titer inhibitor formation to FVIII (i.e., inhibitor titer of > 5 BU/mL) in PUPs with at least 50 exposure days (EDs) of rVIII-SingleChain

Results

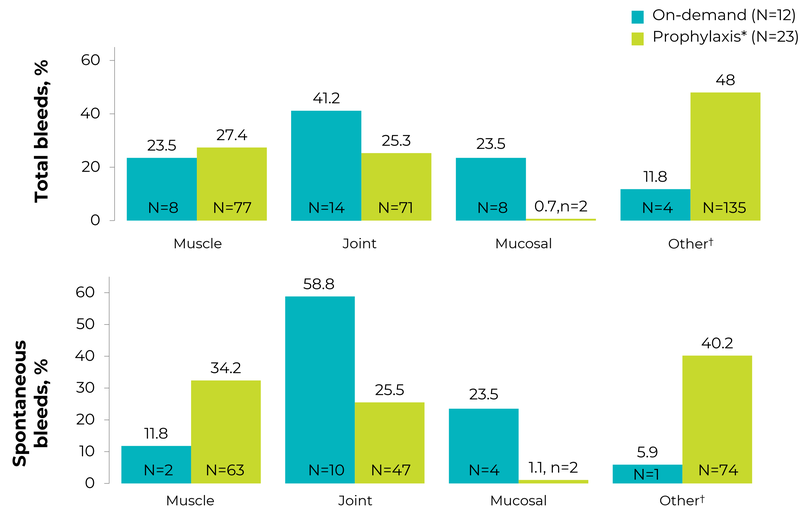
Baseline characteristics

- Of the 24 PUPs enrolled, 12 were assigned to prophylaxis and 12 to on-demand treatment; of the latter 11 then switched to prophylaxis
  - Median age 1 (range 0–5) year
  - Median time on study was 35.0 (range 2.4–54.0) months with 87.5% of PUPs with >50 EDs

Efficacy

- Median time (range) on treatment was 5.0 (0.3–53.3) months for prophylaxis and 25.0 (2.4–48.1) months for on-demand groups
- A total of 315 bleeds required treatment **(Figure 1)**; 99% were treated with rVIII-SingleChain alone
- The overall treatment success rate was 92.1% (95% confidence interval [CI], 87.0–95.3%)
  - Hemostasis was achieved with 1–2 infusions of rVIII-SingleChain in 280 events (88.9%); 17 events (5.4%) required 3 infusions and 11 events (3.5%) required >3 infusions
- Median annualized bleeding rate (ABR) in inhibitor-negative (inhibitor[-]) PUPs was 1.98 (range 0.0–23.6) during prophylactic therapy and 3.76 (0.0–17.1) in on-demand treatment **(Table 1)**
- Median AsBR in inhibitor(-) PUPs during prophylaxis was 0.52 (0.0–19.7) and 1.15 (0.0–5.6) in on-demand therapy

Figure 1. Total and spontaneous bleeding events by rVIII-SingleChain regimen and bleed location



*Prophylaxis subject total included 12 subjects assigned to prophylaxis plus 11 of 12 on-demand subjects who later switched to prophylaxis.
†Included: ankle; elbow; forearm; left gluteal muscle (buttocks); hand back; right hand front; right shoulder; knee; thigh; lower leg; right foot; nasal; oral; and other.

Table 1. Bleeding rates by inhibitor status and rVIII-SingleChain regimen

	While inhibitor(-)		While inhibitor(+)	
	On-demand	Prophylaxis	On-demand	Prophylaxis
N*	10	21	0	11
ABR†	3.76 (0.0, 17.1)	1.98 (0.0, 23.6)	–	0.47 (0.0, 10.1)
AsBR†	1.15 (0.0, 5.6)	0.52 (0.0, 19.7)	–	0.47 (0.0, 10.1)
AjBR†	1.21 (0.0, 4.5)	1.47 (0.0, 4.9)	–	0.00 (0.0, 3.0)

* Includes PUPs who were evaluable and had a minimum of 8 weeks of exposure per inhibitor status and per regimen.
† Reported as median (range).
ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate; inhibitor(+), inhibitor-positive; inhibitor(-), inhibitor-negative; PUP, previously untreated patient.

Safety

- At screening, 5 PUPs (20.8%) were positive for rVIII-SingleChain non-inhibitory anti-drug antibodies (ADAs)
  - Of the 12 (50.0%) PUPs who became positive for non-inhibitory ADAs during the study, 8 (66.7%) developed an inhibitor
  - No allergic reactions or lack of efficacy were associated with ADA positivity
- Twelve PUPs (50.0%, 95% CI 29.1–70.9) developed a FVIII inhibitor, 6 with a high peak titer (25%, 95% CI 9.8–46.7) and 6 with a low peak titer (25%, 95% CI 9.8–46.7) **(Table 2)**
- Successful inhibitor eradication was achieved in 81.8% of inhibitor(+) PUPs; one remained inhibitor(+) throughout the study, and one was withdrawn before the completion of eradication treatment
- Overall, 320 treatment-emergent adverse events (TEAEs) were reported **(Table 3)**
  - 21 treatment-emergent serious adverse events (TESAEs) in 14 PUPs (58.3%)
  - 13 TESAEs (including 12 inhibitor development and one hemorrhage) were related to rVIII-SingleChain

Table 2. Inhibitor development in the study population

	ED of initial inhibitor (+) result (range)	Peak titer BU/mL median (range)	Duration inhibitor (+) months (range)	Time to eradication months (95% CI)	Patients with eradication
High titer (N=6)	9 (4, 23)	34.3 (5.9, 140.0)	13.4 (7.9, 25.5)*	14.8 (3.3–NR)	3
Low titer (N=6)	10 (5, 23)	1.6 (0.7, 3.3)	4.3 (2.5, 15.7)	2.6 (1.8–14.3)	6
All (N=12)	10 (4, 23)	4.6 (0.7, 140.0)	6.0 (2.5, 25.5)*	6.0 (1.9–14.8)	9

* Excluding PUPs who remained inhibitor(+) at end of the study.
BU, Bethesda unit; CI, confidence interval; ED, exposure day; inhibitor(+), inhibitor positive; NR, not reported.

Table 3. Safety outcomes (N=24)

	Safety events
TEAEs, n (%)	320
Mild	208 (65.0)
Moderate	93 (29.1)
Severe	17 (5.3)
No grading	2 (0.6)
Most frequent TEAEs, n (N)	
Pyrexia	44 (15)
URTI	18 (7)
Nasopharyngitis	15 (9)
Cough	13 (6)
Rhinitis	10 (6)
TEAEs related to rVIII-SingleChain, n (%)	17 (5.3)
FVIII inhibitor development	14 (4.4)
TESAEs, n (N)	21 (14)

FVIII, factor VIII; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; URTI, upper respiratory tract infection.

Conclusions

- **rVIII-SingleChain demonstrated favorable efficacy in PUPs, with high treatment success rate and low AsBR during prophylaxis**
- **In 81.8% of inhibitor(+) PUPs, rVIII-SingleChain treatment achieved inhibitor eradication**

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Conflicts of interest

JM, consultancy fees, research funding and/or speaker bureau from Baxalta, Catalyst Biosciences, Chugai, CSL Behring, Novo Nordisk, LFB, Pfizer, Roche, Shire, Spark, Takeda, Biomarin, Freeline Therapeutics, Novartis, Sanofi Genzyme, Sobi, Uniqure and World Federation of Hemophilia. **MEM**, consultancy/advisor fees, research funding and/or speaker bureau from Bayer, BioMarin, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Pfizer, Octapharma, Roche, Sanofi, Spark Therapeutics, Sobi, Takeda and UniQure. **KF**, consultancy fees, research funding and/or speaker bureau from Bayer, Baxter, Biogen, CSL Behring, Freeline Therapeutics, Novo Nordisk, Pfizer, Roche, Sobi. **CDK**, speaker bureau from CSL Behring, LFB, Novo Nordisk, Pfizer and Roche; consultancy fees from Biotest, LFB, Novo Nordisk and Roche. **MC**, consultancy fees from Baxalta (now Takeda), Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Siemens, SOBI and Stago. **FAK**, nothing to disclose. **SJ**, advisory board fees from Sanofi, Octapharma, Spark. **SL**, **BS**, **AS**, **BG**, **WS**, **TC**, CSL Behring employees. **CK**, consultancy fees, speaker bureau and/or research funding from Bayer, Biotest AG, CSL Behring, Intersero, Pfizer, Roche/Chugai, Sobi/Sanofi and Takeda. Editorial assistance was provided by Meridian HealthComms Ltd.

Acknowledgments

Medical writing support was provided by Meridian HealthComms Ltd, funded by CSL Behring. All authors reviewed the results and approved the final version of the poster.
*S. Jobe was at Versiti Blood Research Institute during the time of the study.

Funding

This study was funded by CSL Behring.

Presented at the Annual Meeting of the American Society of Pediatric Hematology/Oncology (ASPHO), Fort Worth, TX, United States, May 10–13 2023.