SYNOVIIIUS: Prospective Interventional Study of Effectiveness of Efanesoctocog Alfa Prophylaxis on Synovial Hypertrophy in Patients with Hemophilia A — Study Design

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Introduction

- Hemophilia A is a rare X-linked inherited bleeding disorder caused by deficiency in coagulation factor VIII (FVIII). The most common symptom is recurrent joint bleeding (hemarthrosis), which, if not properly managed, can lead to synovitis and hemophilic arthropathy.[1,2]
- These conditions involve joint remodeling, chronic pain, reduced quality of life, and may eventually require joint replacement.[1-3]
- Evidence suggests that FVIII activity levels of up to 50% may be needed to achieve a near-zero joint bleed rate. However, achieving high FVIII activity levels with current standard and extended half-life FVIII replacement therapies is associated with a high treatment burden.[4]
- Efanesoctocog alfa (ALTUVIIIO; formerly BIVV001) is the first-in-class high-sustained FVIII replacement therapy designed to decouple recombinant FVIII from endogenous von Willebrand factor (VWF) and overcome the VWF-imposed half-life ceiling.
- Weekly prophylaxis with efanesoctocog alfa in severe hemophilia A patients was well tolerated and has demonstrated superior bleed prevention compared to pre-study prophylaxis and meaningful improvement in joint health in the Phase 3 XTEND-1 (NCT04161495) study.[5]
- Although the Phase III study confirms the effectiveness and safety of weekly efanesoctocog alfa in preventing bleeds and enhancing joint health in patients with severe hemophilia A, comprehensive information on subclinical joint changes over time is limited.

Objective

Primary Objective:

- To assess the improvement of synovial hypertrophy during the 12 months of weekly efanesoctocog alfa prophylaxis in joints with existing evidence of synovial hypertrophy in patients with hemophilia A.

Secondary Objectives:

- To evaluate the impact of 12 months of weekly efanesoctocog alfa prophylaxis on the index joints in patients with hemophilia A, using Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) domain scores, Hemophilia Joint Health Score (HJHS), magnetic resonance imaging (MRI), and assessments of pain and quality of life (QoL) questionnaires.
- To determine the effectiveness, safety, and tolerability of weekly efanesoctocog alfa prophylaxis over 12 months.

Methods

Overview

- SYNOVIIIUS is a prospective, 12-month, multicenter, open-label, single-arm interventional study assessing the effectiveness of once weekly efanesoctocog alfa prophylaxis (50 IU/kg) on synovial hypertrophy in hemophilia A patients receiving pre-study prophylaxis in the previous 12 months. (**Figure 1**)

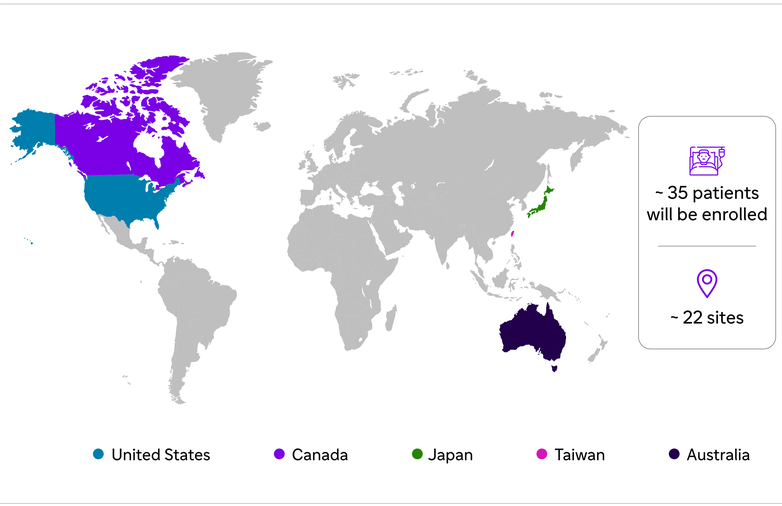
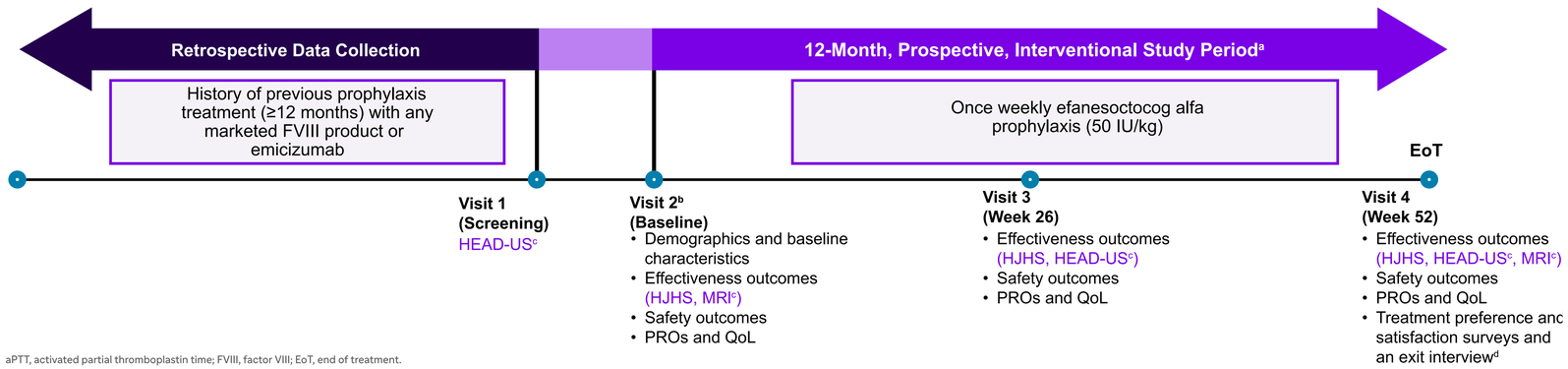
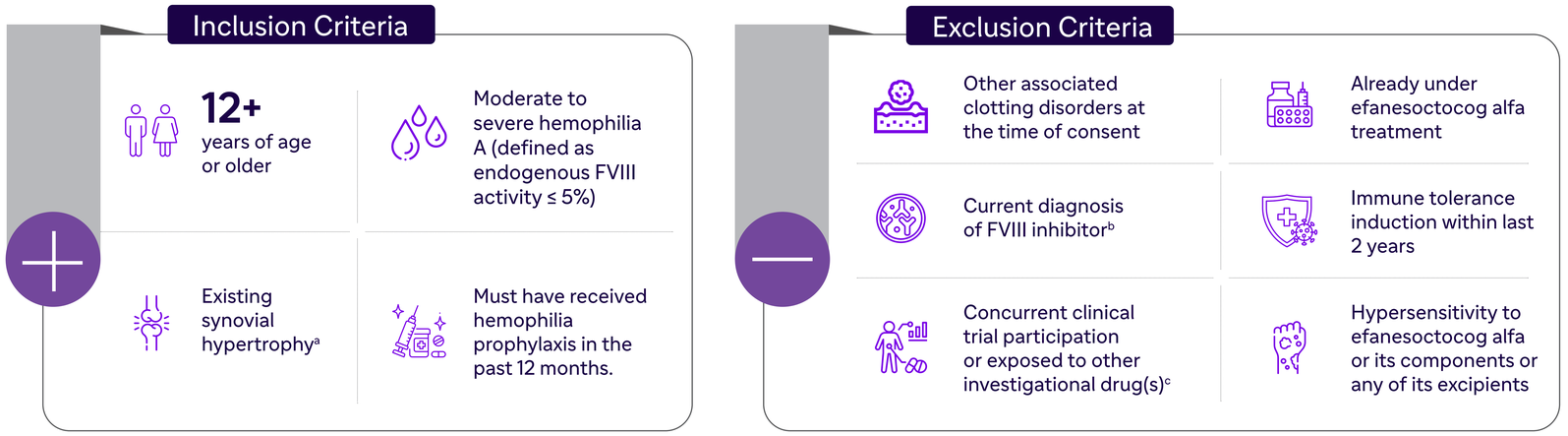


Figure 1: Schematic of SYNOVIIIUS study design



aPTT, activated partial thromboplastin time; FVIII, factor VIII; EoT, end of treatment.
[a]At any "unscheduled visit," a safety evaluation; assessment of FVIII inhibitors, FVIII levels, and aPTT; recording of prior concomitant therapy and procedures; and the pregnancy test will be done, as needed.
[b]Baseline visit (Visit 2) can be performed once the patient is eligible for study enrollment. A maximum window of 28 days between the screening visit (Visit 1) and baseline visit (Visit 2) will apply.
[c]MRI and HEAD-US of the index joints will be performed, and the images will be sent for the central reading assessment. MRI scans will be assessed using the IPSG MRI scale. The JADE ultrasound score (v2.0) will be assessed post hoc to the HEAD-US images. The initial MRI assessment can be done at the baseline visit (Visit 2) or up to 28 days thereafter. For Week 26 and Week 52/EoT visits, these assessments can be performed at any time during the visit window of ±10 days independent of when the actual study visit is scheduled.
[d]A single telephone interview following the Week 52/EoT visit

Patient Eligibility



[a]In at least one of six index joints (ankles, elbows, knees) with Hemophilia Early Arthropathy Detection with Ultrasound´ (HEAD-US) synovitis score of 1 or 2.
[b]Defined as inhibitor titer ≥0.6 BU/mL
[c]within 3 months prior to screening for this study

Study Duration

- The study will include a series of visits: a screening visit (Visit 1), a baseline visit (Visit 2), clinic/on-site visit at Week 26 (Visit 3) and Week 52/end of treatment (Visit 4).
- Each patient's treatment will last for approximately 12 months (each month = 28 days).

Dosing:

- The prophylaxis regimen is 50 IU/kg efanesoctocog alfa once weekly (every 7 days).

Efficacy Assessments:

- HEAD-US and MRI Assessments
- HJHS
- Annualized bleeding rate (ABR) and annualized joint bleeding rate (AjBR)
- Joint Health Biomarkers
- Assessment of patient-reported outcomes (PROs) and QoL
- Target joints assessment.

Safety Assessments:

- Demographics and medical, surgical, and hemophilia history
- Physical examination
- Clinical safety laboratory assessment – will be done at the investigator's discretion anytime during the study. If used for AE evaluation, results must be entered into the eCRF.
- Serious adverse event (SAEs) including adverse event of special interest (AESI) and adverse events (AEs).

Conclusions

- The Phase 3 study (XTEND-1; NCT04161495) in patients with severe hemophilia A (>12 years of age) demonstrated that once-weekly efanesoctocog alfa prophylaxis achieved normal to near-normal factor VIII levels, superior bleed protection, and improved physical health, pain relief, and joint health.[5]
- The SYNOVIIIUS study will investigate the potential of efanesoctocog alfa to improve synovitis by maintaining high sustained FVIII levels.
- New insights from this study will provide clinicians with valuable data on the impact of efanesoctocog alfa on synovial hypertrophy.

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ES is an employee of Sobi and may hold shares and/or stock options in the company. **JD**, **AW**, **AY** and **NT** are employees of Sanofi and may hold shares and/or stock options in the company.
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