Observational Study of Prophylactic Efanesoctocog Alfa for Joint Health in Hemophilia A: PROTECT-ALT

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BACKGROUND

- Repeated bleeding in people with hemophilia A (PwHA) may cause joint deterioration, leading to chronic pain, impaired physical functioning, joint replacement, and reduced health-related quality of life (QoL)[1]
- Normalization of factor VIII (FVIII) levels can provide effective bleeding prevention and help prevent joint deterioration in PwHA[2]
- Efanesoctocog alfa (ALTUVIIIO®; formerly BIVV001) is a 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[2]
  - It is designed to sustain normal to near-normal factor activity levels (>40%) for most of the week with a once-weekly prophylactic regimen[3-5]
- Weekly prophylaxis with efanesoctocog alfa in severe PwHA is well tolerated, has demonstrated superior bleed prevention compared to previous FVIII prophylaxis, and has shown meaningful improvement in joint health in the Phase 3 XTEND-1 (NCT04161495) study; this improvement is maintained in the XTEND-ed (NCT04644575) study[2,6]
- However, comprehensive data on subclinical joint changes are still lacking. Additionally, current clinical trials have not widely employed high-sensitivity imaging techniques, such as magnetic resonance imaging (MRI), recognized by the World Federation of Hemophilia as an effective method for detailed joint structure assessment, to explore these subtle effects
- The PROTECT-ALT study aims to investigate the real-world safety, effectiveness, and patient-reported outcomes (PROs) of efanesoctocog alfa prophylaxis in PwHA in Taiwan
- The study seeks to document the progression of hemophilic arthropathy, using both MRI and ultrasound, to assess whether efanesoctocog alfa can protect against or mitigate joint deterioration over time with specific focus on joint health outcomes over a 5-year follow-up period

AIM

- To present the design and methodology of PROTECT-ALT study aimed at investigating the real-world safety, effectiveness, and PROs of efanesoctocog alfa in Taiwan

STUDY OBJECTIVES

Primary Objective

To describe the effectiveness of efanesoctocog alfa prophylaxis on clinical joint status over 5 years

Key Secondary Objectives

To determine the effectiveness and usage of efanesoctocog alfa prophylaxis over a 5-year prospective period in

- Prevention of bleeding episodes
- Joint status
- Improvement of chronic synovitis
- Perioperative period
- Safety and tolerability
- QoL as PROs
- Healthcare resource utilization

Exploratory Objectives

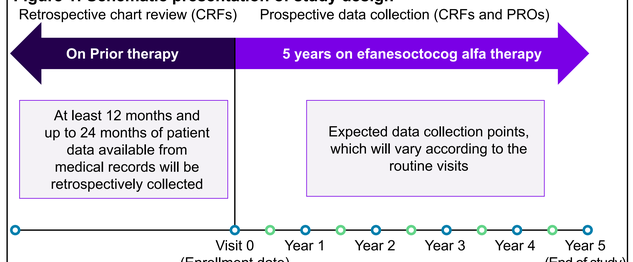
To explore

- Improvement in participants' physical activity
- Relationship between joint health status and participants' PROs

STUDY DESIGN

- PROTECT-ALT (NCT06684314) is a multicenter, retrospective/prospective, longitudinal observational study, enrolling ~100 participants with moderate-to-severe PwHA from 10 medical centers in Taiwan
- The study will collect 5 years of prospective data during routine clinical visits
- Additionally, retrospective data will be collected from ≥12–24 months before efanesoctocog alfa initiation from available medical records (**Figure 1**)

Figure 1: Schematic presentation of study design



The enrollment date is the date when the participants signs the informed consent form. Patients will be followed up until the end of the prospective data collection period, efanesoctocog alfa discontinuation, lost to follow-up, study withdrawal, enrollment in a clinical trial, or death, whichever occurs first.
CRF, case report form; PRO, patient reported outcome.

STUDY ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
Moderate-to-severe hemophilia A (defined as endogenous FVIII levels of ≤5%)	Coagulation disorders other than hemophilia A; other known bleeding disorder
No current inhibitor and/or at least three years with undetectable inhibitor levels (<0.6 BU)	Signs of decreased response to FVIII therapy
Must have initiated efanesoctocog alfa prophylaxis within 1 month before enrolment	Baseline Pettersson score (PS) >6 in both ankles for each joint
Ability to undergo MRI and joint examinations	Enrollment in another trial or intake of an investigational medicinal product within 3 months prior to inclusion
Patients aged >6 years should be able to undergo MRI	Pregnancy

STUDY ASSESSMENTS

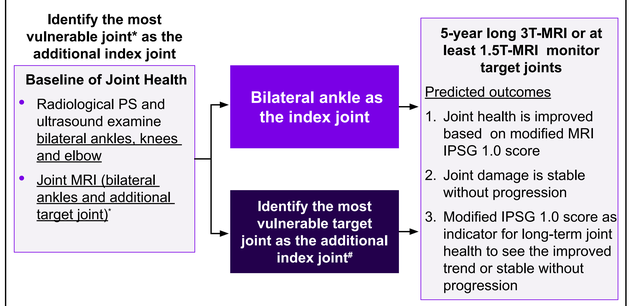
- Structural and functional joint changes in patients under efanesoctocog alfa prophylaxis will be evaluated by integrating routine diagnostic imaging with comprehensive physical assessments
  - Standardized MRI-based modified International Prophylaxis Study Group (IPSG 1.0) score (**Table 1**), developed after reaching consensus by central readers and validated through real cases, will be used along with the Hemophilia Joint Health Score (HJHS) and the Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) for ongoing monitoring (**Figure 2**)
    - The modified IPSG 1.0 score aims to standardize the subjective criteria, by providing objective criteria for scoring and provides a meaningful improvement in scoring reproducibility
  - Owing to challenges with MRI in children <6 years of age, Musculoskeletal Ultrasound (MSKUS) will be employed due to its accessibility and ease of use

Table 1: Modified International Prophylaxis Study Group (IPSG 1.0) MRI scale[7]

Categories	Points
Soft tissue changes	
Effusion	
Absent: thickest length ≤3mm	*0*
Small: thickest length >3mm or ≤5mm	*1*
Moderate: thickest length >5mm or ≤10mm	*2*
Large: thickest length >10mm	*3*
Synovial hypertrophy	
Absent: not measurable	*0*
Small: measurable thickened or increased involvement at different joints	*1*
Moderate: measurable thickened and increased involvement at different joints	*2*
Large: measurable thickened >3mm + increased involvement at different joints	*3*
Hemosiderin	
Absent	*0*
Small: identifiable in at least one place: shown as black under T2 + enhancement at the whitened area under T2*	*1*
Moderate: identifiable in different joints (sum up <10mm at gradient echo)	*2*
Large: enhancement at the existed lesion (sum up >10mm at gradient echo)	*3*
Soft tissue changes subscore	**(Maximum 9 points)**
Osteochondral change	
***Surface erosions* (under T1)**	
Absent	*0*
Any surface erosion	*1*
Half or more of the articular surface eroded in at least one bone: single joint involvement >50% for consecutive 2 images (sagittal/coronal)	*1*
***Subchondral cysts* (under T2_FS)**	
Absent	*0*
At least one subchondral cyst: Only one bone has cyst (regardless of the cyst number but the sum up surface area <1/3 joint surface area and is round-shaped) around the joint (radius=0.5 cm)	*1*
Subchondral cysts in at least two bones, or cystic changes involving a third or more of the articular surface in at least one bone; at least 2 round-shaped lesions around joint (radius=0.5 cm) Within the radius of 0.5 cm around the joint surface: a) at least 1 round-shaped cyst at two bones; or, b) only one bone has cyst and the sum up surface area >1/3 joint surface area	*1*
***Cartilage degeneration* (under T1_SPGR)**	
Absent	*0*
Any loss of joint cartilage height: any irregular thinning at joint surface (definition: obviously looked different from normal appearance, non-consecutive or irregular thinning, but not totally disappeared)	*1*
Loss of half or more of the total volume of joint cartilage in at least one bone: >1/2 length of single joint surface area irregular thinning at 2 consecutive images but not totally disappeared	*1*
Full-thickness loss of joint cartilage in at least some area in at least one bone: full-thickness loss of <1/2 length of single joint surface area at 2 consecutive images	*1*
Full-thickness loss of joint cartilage including at least one half of the joint surface in at least one bone: full-thickness loss of >1/2 length of single joint surface area at 2 consecutive images	*1*
Osteochondral changes subscore	**(Maximum 8 points)**
Total score	**Maximum value: 17**

MRI, magnetic resonance imaging.

Figure 2: Graphical study flow of patients' joint health by 5-year long MRI monitor performed without gadolinium contrast



*At baseline and during routine visits at 5-year follow-up if performed as part of SOC; ankle or additional target joint will be confirmed per physician's judgment.
#The target joint and/or the joint with previous bleeding history or any signs of joint damage based on physician's judgment.
IPSG, International Prophylaxis Study Group; PS, Pettersson score; SOC, standard of care; 1.5T-MRI, 1.5 Tesla magnetic resonance imaging; 3T-MRI, 3 Tesla MRI.

RATIONALE FOR USING BILATERAL ANKLES AS INDEX JOINT

- Ankles remain highly vulnerable to hemophilic arthropathy and soft tissue damage, even in patients with zero or minimal annualized bleeding rates, as shown in studies including the AOZORA study[8,9]
- Using ankles as a primary target for imaging may provide greater sensitivity for detecting subclinical progression, aligning with the study's aim of capturing subtle joint health changes under efanesoctocog alfa prophylaxis

SUMMARY

- PROTECT-ALT is the first study to assess real-world joint health outcomes, effectiveness, and safety of efanesoctocog alfa prophylaxis in PwHA in Taiwan
- By utilizing more precise imaging techniques, this study aims to reveal crucial insights into subclinical joint changes in patients treated with efanesoctocog alfa, and help advance our understanding of long-term joint preservation in PwHA using modern MRI-based evaluations

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CONFLICTS OF INTEREST/ DISCLOSURES:
Te-Fu Weng, Yi-Chih Hsu, Chih-Wei Lee, Da-Ming Yeh have no conflicts of interest to declare; Tong-Ling Chien, Nicole Tsao, and Ching-Min Chang are employees of Sanofi and may hold shares/stock options.

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