24 July 2025
EMADOC-1700519818-2339670
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Jivi

Damoctocog alfa pegol

Procedure no: EMA/PAM/0000267496

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	30 June 2025	27 June 2025
☐	CHMP comments	14 July 2025	14 July 2025
☐	Updated CHMP Rapporteur AR	17 July 2025	17 July 2025
☒	CHMP outcome	24 July 2025	24 July 2025

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1. Introduction

On 17 April 2025, the MAH submitted a completed adult study including adolescents for Jivi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the PREDICT Study (CSP 21924, CSR B003604) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation being used in this study is a powder and solvent for solution for injection. The powder formulation is available as Jivi 250 IU; Jivi 500 IU; Jivi 1000 IU; Jivi 2000 IU and Jivi 3000 IU. In June 2025, the additional strength 4000 IU was approved.

This formulation has an MAA for the use in children from 12 years and older.

Jivi is for intravenous use, and dosing is dependent on the child's weight, factor activity level as well as current bleeding episode or the risk of bleeding.

It is found that this formulation is suitable for the use in children

2.2.1. Introduction

The MAH submitted a final report for:

- PREDICT (CSP 21924, CSR B003604)

2.3. Clinical aspects

2.3.1. Clinical study

PREDICT (CSP 21924, CSR B003604)

Description

A multicenter, prospective, open-label, clinical study to assess the effect of using a new risk score approach to select the most appropriate prophylaxis regimen for reaching a favorable outcome, when hemophilia A patients switch from standard half-life products to Jivi.
The PREDICT study is a Phase 4 study to assess a new risk score approach utilizing the best known phenotypic and biologic variables to select the most appropriate prophylaxis regimen for reaching a favorable outcome when switching treatment.

Methods

Study participants

Participants were ≥ 12 years of age with congenital haemophilia A who had a documented history of at least 150 exposure days with any FVIII product. All participants had received prophylaxis with a licensed standard half-life FVIII product with a stable dosing regimen for at least 6 consecutive months within the previous 12 months prior to the screening visit.

Treatments

All eligible participants were assigned a risk score at baseline and started treatment 2x/week (40 IU/kg/dose) with Jivi for 4 weeks.

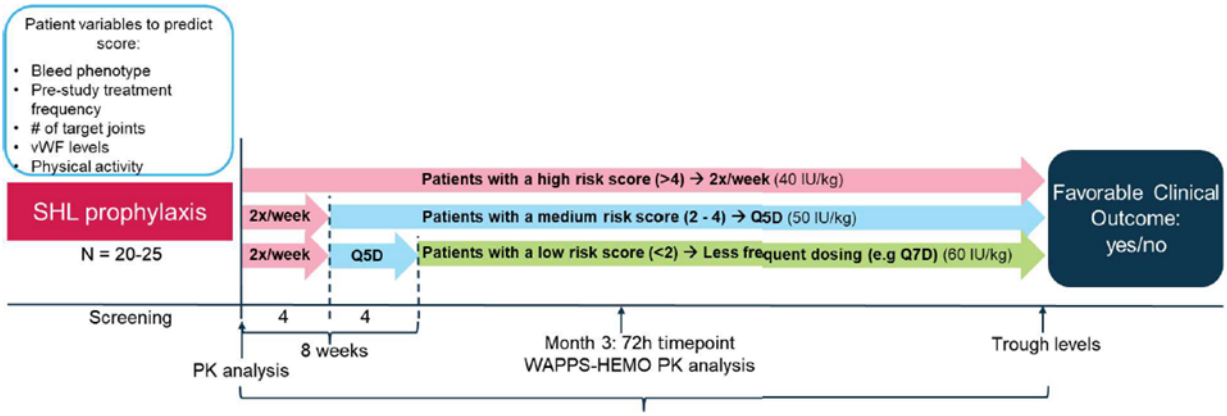
At baseline, participants' total risk scores were determined based on 5 individually weight variables: pre-study bleeding phenotype, previous treatment frequency, number of active target joints, vWF levels and physical activity (Table 1).

Table 1. Parameters for determining participant risk scores

Participant Variables	Score Assignment
Bleed phenotype (total bleeds, occurring during the stable SHL period[a])	
ABR ≤ 1	-2
1 < ABR ≤ 4	+2
ABR > 4	+3
Treatment frequency derived from the stable SHL period[a]	
< 3x/week	-1
3x/week	0
> 3x/week	+1
Number of active target joints[b]	
0	-1
1	0
2	+1
> 2	+2
vWF antigen levels (within previous 12 months)	
vWF ≥ 150%	-1
100% ≤ vWF < 150%	0
vWF < 100%	+2
Physical activity[c]	
Low[d] (non-contact sports)	-1
Sedentary[e]	0
Medium/high[f] (contact sports)	+1

Prophylactic treatment: Treatment was then continued based on their assignment to 1 of the 3 following prophylaxis regimens:

- Participants with a high-risk score (> 4) continued on prophylaxis 2x/week (40 IU/kg/dose)
- Participants with a medium risk score (2 to 4) were to switch after 4 weeks to prophylaxis every 5 days (50 IU/kg/dose)
- Participants with a low risk score (< 2) were to switch after 4 weeks to prophylaxis every 5 days (50 IU/kg/dose) and then after 4 weeks to a less frequent (e.g. every 7 days) regimen (60 IU/kg/dose)



Abbreviations: PK = pharmacokinetics; Q5D = every 5 days; Q7D = every 7 days; SHL = standard half-life; vWF = von Willebrand factor.

[a] Score exception: if ≥2 muscle or joint bleeds (without evident trauma) occur within any given 8-week period during the 6-month study, then the protocol recommends assigning the participant to the next highest frequency regimen. Per protocol, the treating investigator reserves the right to change a participant's regimen at any time if they perceive the risk score-determined regimen is not well-suited for the participant.

Treatment of bleeds: All bleeding events that occur in participants receiving prophylactic infusion after the start of treatment will be treated with Jivi (prescribing information provided).

Objective(s)

It is important to emphasize that the objective of this study is to assess a treatment tool (a risk score) for the use in dose selection of Jivi. The treatment already holds a market authorization for this indication and in this age group.

Table 2. PREDICT study objectives and endpoints

Objectives	Endpoints
Primary	
To assess the effect of using a baseline risk score, based on a participant's phenotypic and biologic variables, to select the most appropriate prophylaxis regimen for reaching a favorable outcome, when switching from an SHL product to Jivi	Occurrence of favorable outcome on the score selected dosing regimen
Secondary	
To assess the effectiveness of Jivi compared to a previous SHL treatment	Annual bleed rate (ABR) (total, joint, spontaneous) and change in total ABR from pre-study
To assess the frequency of Jivi administration	Change in the frequency of pre-study SHL treatment to the frequency of Jivi administration (infusions/month)
To assess the proportion of participants with 0 and ≤ 1 spontaneous bleeds	Occurrence of participants with 0 and ≤ 1 spontaneous bleeds
To assess participant QoL and physical activity, as measured by Patient Reported Outcomes (PROs)	Change in Haemophilia Quality of Life Questionnaire (Haem-A-QoL or Haemo-QoL); Patient's Global Impression of Change (PGI-C); EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire; Treatment Satisfaction Questionnaire for Medication (TSQM); Work Productivity and Activity Impairment (WPAI) questionnaire scores
To assess target joint status, per International Society on Thrombosis and Haemostasis (ISTH) guidelines	Number of target joints and change in target joint status from baseline
Other, Pre-specified	
To assess whether blood type and body mass index (BMI) would have led to a different score allocation	Participant score considering ABO type and BMI
To describe pharmacokinetic (PK) parameters derived from Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) and assess an association with clinical risk score	PK parameters derived from WAPPS-Hemo
To determine participant Jivi trough levels while on a specific regimen	Trough measurement of Jivi levels
To determine the percentage of participants who can maintain > 1%, > 3%, and > 5% FVIII trough levels while on a specific prophylaxis regimen	Occurrence of trough levels above 1%, 3% and 5%, stratified by prophylaxis regimen

Outcomes/endpoints

Objectives	Endpoints
Primary	
To assess the effect of using a baseline risk score, based on a participant's phenotypic and biologic variables, to select the most appropriate prophylaxis regimen for reaching a favorable outcome, when switching from a SHL product to Jivi	Occurrence of favorable outcome on the score selected dosing regimen
Secondary	
To assess the effectiveness of Jivi compared to a previous SHL treatment	ABR (total, joint, spontaneous) and change in total ABR from pre-study
To assess the frequency of Jivi administration	Change in the frequency of pre-study SHL treatment to the frequency of Jivi administration (infusions/month)
To assess the proportion of participants with 0 and ≤ 1 spontaneous bleeds	Occurrence of participants with 0 and ≤ 1 spontaneous bleeds
To assess participant quality of life (QoL) and physical activity, as measured by Patient Reported Outcomes (PROs)	Change in Haemophilia Quality of Life Questionnaire (Haem-A-QoL or Haemo-QoL KIDS, depending on age of participant); Patient's Global Impression of Change (PGI-C); EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire; Treatment Satisfaction Questionnaire for Medication (TSQM); Work Productivity and Activity Impairment (WPAI) questionnaire scores
To assess target joint status, per International Society on Thrombosis and Haemostasis (ISTH) guidelines	Number of target joints and change in target joint status from baseline
Other, Pre-specified	
To assess whether blood type and body mass index (BMI) would have led to a different score allocation	Participant score considering ABO type and BMI
To describe PK parameters derived from WAPPS-Hemo and assess any association with clinical risk score	PK parameters derived from WAPPS-Hemo
To determine participant Jivi trough levels while on a specific regimen	Trough measurement of Jivi levels
To determine the percentage of participants who can maintain > 1%, > 3 %, and > 5% FVIII trough levels while on a specific prophylaxis regimen	Occurrence of trough levels above 1%, 3% and 5%, stratified by prophylaxis regimen
Abbreviations: ABR = annualized bleeding rate; EQ-5D-5L = EuroQoL 5 dimensions; FVIII = human coagulation factor VIII; SHL = standard half-life	

Sample size

Initially it was planned to enrol a maximum of 70 participants such that approximately 60 evaluable participants would complete the study. This turned out not to be feasible (slower recruitment than expected). Twenty-one patients were included in the PREDICT study.

Three patients < 18 years were included in the PREDICT study and treated with Jivi.

Randomisation and blinding (masking)

N/A

Statistical Methods

The study is not designed to test any predefined hypothesis. All analyses will be descriptive or exploratory. Confidence intervals, 95%, two-sided, will be reported for the primary endpoint and for selected secondary endpoints, assessed as occurrence rates, mean scores or counts, and change from baseline.

Results

Participant flow

Table 3. Disposition: Flow of participants through study phases (all enrolled participants)

Number of participants	High risk score	Medium risk score	Low risk score	Total
Enrolled				21
Did not complete screening				0
Assigned to treatment regimen	7	9	5	21
Study drug never administered	0	0	0	0
Treated	7 (100.0%)	9 (100.0%)	5 (100.0%)	21 (100.0%)
Treatment period				
Started	7 (100.0%)	9 (100.0%)	5 (100.0%)	21 (100.0%)
Completed	6 (85.7%)	8 (88.9%)	5 (100.0%)	19 (90.5%)
Did not complete	1 (14.3%)	1 (11.1%)	0	2 (9.5%)
Primary reason				
Subject decision	1 (14.3%)	1 (11.1%)	0	2 (9.5%)
Safety follow-up period				
Started	7 (100.0%)	9 (100.0%)	5 (100.0%)	21 (100.0%)
Completed	6 (85.7%)	8 (88.9%)	5 (100.0%)	19 (90.5%)
Did not complete	1 (14.3%)	1 (11.1%)	0	2 (9.5%)
Primary reason				
Adverse event	0	1 (11.1%)	0	1 (4.8%)
Subject decision	1 (14.3%)	0	0	1 (4.8%)

Percentages are based on the safety analysis set.

Recruitment

Slower than expected recruitment led to 'Protocol amendment 3' (2. October 2023), protocol version 4.0 with a change in inclusion criteria and amendment back to recruitment in a single country (United states). Of the three patients < 18 years who were included in the 'PREDICT study', two were enrolled before protocol amendment 3 and one after this amendment.

Baseline data

Age	13 years	15 years	15 years
Risk Score group	Low	High	Low

Prior SHL FVIII product	XYNTHA® 2500 IU, 2 times per week.	AFSTYLA® 2750 IU, 4 times per week	ADVATE® 2000 IU, once a week
Duration prior stable SHL FVIII product	901 days	1266 days	4060 days

Number analysed

Three participants < 18 years of age

Efficacy results

Extracted from clinical overview.

Jivi treatment dose	40 IU/kg/dose 2x/week	40 IU/kg/infusion 2x/week	40 IU/kg/dose 2x/week
Change in dose	Yes, reduction	No	Yes, reduction
Treatment duration	183	173 days	163
ABR baseline	1	8	20
ABR study period	5.99	2.11	0
Dosing frequency baseline	8.7/month	17.4/month	Not included in CO/CSP
Dosing frequency study period	4.32/month	8.27/month	Unchanged
Bleeding episodes	3 (not treated)	1 (treated)	-
Improvement QoL scores	No	Yes	Improvement/No change

ABR=Annual bleeding rate

Listings of efficacy data are included in the clinical study protocol.

Safety results

One reported adverse event in the three patients < 18 years who were included in the PREDICT study: one patient presented mild headache starting 3 months after enrolment which resolved after 3 months without change in dose and any remedial therapy.

There were no unexpected safety outcomes during the study.

2.3.2. Discussion on clinical aspects

The aim of the presented PREDICT study was to assess the use of a clinical tool for the conversion of treatment and dose-adjustment in patients with congenital haemophilia A and receiving prophylactic treatment with a FVIII product. The applied risk score is an approach to select the most appropriate prophylaxis regimen for reaching a favorable outcome, when switching from standard half-life products to Jivi.

The treatment applied in the study is within the SmPC current at the time the study was conducted which holds the following indication and posology:

Indication: Treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency).

Posology: The dose and duration of substitution therapy depends on the severity of the factor VIII deficiency, the location and extent of the bleeding and on the patient's clinical condition.

Under the current posology test, the dose is decided based on Factor VIII activity in plasma and clinical judgement based on individual patient characteristics and treatment response (including bleeding episodes). It is the same elements that are included in the 'risk score'-calculation applied in the PREDICT Study in a standardized way.

The SmPC states 'On demand and prophylactic treatment dosing in adolescent patients is the same as for adult patients.'

Three participants < 18 years of age are included in the study. All participants are > 12 years of age. Therefore, the treatment exposure is within the MA for Jivi current at the time the study was conducted. The number of adolescents treated is too low to extract specific new treatment recommendations in this age group, but there are no safety or efficacy data in this study that lead to concerns that could affect the benefit-risk ratio for Jivi in patients under 18 years of age. Nor are there findings that suggest changes in the current SmPC.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.