Clinical Trial Protocol
Iranian Registry of Clinical Trials

18 Sep 2026

A Randomized, Multicenter, Double blind, Single doses Study Comparing the Pharmacodynamic, Pharmacokinetic and Safety of Biosimilar EPTACOG Alfa with Novoseven®, in Patient with Hemophilia A or B with Inhibitors

Protocol summary

Study aim
Bioequivalence according to Pharmacokinetic,Pharmacodynamic parameters.Clinical response in controlling acute bleeding.Immunogenicity,ADRs

Design
Patients enrolled are randomized to receive injections of either doses of AryoSeven or NovoSeven,separated by washout period of 3 days.Blood samples for the PKPD phase(atleast 5 ml) is collected 10 min prior dose administration and at 10, 20min,1,3,5,8,12,24 and 30h after administration.For plasma sample stability study and only for maximum 10 patients,9ml blood instead of 5ml will be drawn during Visit 2 and 3 at timepoints1h and 12h.Before second dose blood is taken for immunogenicity test.Patients hospitalized at time of study medication administration and plasma sampling.Patients will be followed for 12 months to receive AryoSeven for bleedings at center or home(by patient at home or caregiver) with dose and duration of treatment decided by Investigator.Plasma sampling for determination of antibody formation against FVII will be taken every 3 months at the center.

Settings and conduct
Multicenter(Tehran,Shiraz,Zahedan,Istanbul,Adana,Bursa)Randomized,Double blind,crossover.Blinding is performed by independent third party who prepares and labels undistinguishable syringes according to randomization.

Participants/Inclusion and exclusion criteria
Over 12 years with congenital Hemophilia A or B with inhibitors over 5BU with over2 episodes of bleeding oer year requiring treatment with FVII, not in bleeding episode. without inhibitor to FVII and any other type of congenital or acquired coagulopathy

Intervention groups
AryoGEn Eptacog alfa(AryoSeven),IV 90 or 270 mcg perkg. NovoNordisk Eptacog alfa(Novoseven), IV 90 or 270 mcg per kg

Main outcome variables
PK:Area Under Curveinf(AUCinf) PD:Thrombin Generation Assay,D-Dimer,F1.2 prothrombin fragments.

General information

Reason for update
registering patient recruitment start patient recruitment end trial completion date

Acronym
UGA 2014-01

IRCT registration information
IRCT registration number: **IRCT2017021831193N2**
Registration date: **2017-08-05, 1396/05/14**
Registration timing: **prospective**

Last update: **2022-03-02, 1400/12/11**
Update count: **4**

Registration date
2017-08-05, 1396/05/14

Registrant information

Name
Amirhossein Saadatirad
Name of organization / entity
AryoGen Pharmed
Country
Iran (Islamic Republic of)
Phone
+98 26 3610 6480
Email address
saadatirada@aryogen.com

Recruitment status
Recruitment complete

Funding source
AryoGen Pharmed

Expected recruitment start date
2018-09-17, 1397/06/26
Expected recruitment end date
2019-05-31, 1398/03/10
Actual recruitment start date
2018-09-17, 1397/06/26
Actual recruitment end date
2020-10-31, 1399/08/10
Trial completion date
2021-09-23, 1400/07/01

Scientific title
A Randomized, Multicenter, Double blind, Single doses Study Comparing the Pharmacodynamic, Pharmacokinetic and Safety of Biosimilar EPTACOG Alfa with Novoseven®, in Patient with Hemophilia A or B with Inhibitors

Public title
Pharmacodynamic, Pharmacokinetic Study ofAryoSeven with Novoseven®, in Patient with Hemophilia A or B with Inhibitors
Purpose
Treatment
Inclusion/Exclusion criteria
Inclusion criteria:
-Confirmed diagnosis of congenital haemophilia A or B with inhibitors to FVIII or FIX titer >5 Bethesda Units [BU] -With > 2 episodes of bleeding/year requiring treatment with FVII infusions, non in bleeding episode -Male subjects -Adult and children (>12 years) -Patients to be enrolled must also provide voluntary written informed consent to the protocol to be eligible for the study. For minor patients, parent/legal guardian will provide consent and, when possible, patient assent will also be obtained. For compromised patients, their designated proxy must provide informed consent. -For the PK/PD phase, patients will be hospitalized at time of study medication administration for plasma sampling (2 times during the study).
Exclusion criteria:
-Any other type of congenital or acquired coagulopathy, such as: liver disease (hepatitis), vitamin k deficiency, uremia, malignancy. -Antibodies against Factor VII. -Ongoing bleeding prophylaxis regimens with Novoseven or planned to occur during the trial. -Patients who have received routine (prophylactic) treatment with rFVIIa in the period between screening visit (visit 1) and visit 2 of this study (first dose administration). -Platelet count less than 100.000 platelets/mcL (at screening visit). -Any clinical sign or known history of arterial thrombotic event or deep venous- thrombosis or pulmonary embolism. -HIV positive with current CD4+ count of less than 200/µL. -Liver cirrhosis. -Factor VIII/IX immune tolerance induction regimen planned to occur during the trial. -Known hypersensitivity to the study medication. -Parallel participation in another experimental drug trial. -Parallel participation in another marketed drug trial that may affect the primary end point of the study.
Age
From **12 years** old
Gender
Male

Phase
3
Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data and Safety Monitoring Board

Sample size
Target sample size: **48**
Actual sample size reached: **48**
Randomization (investigator's opinion)
Randomized
Randomization description
1:1 manner stratified by center
Blinding (investigator's opinion)
Double blinded
Blinding description
Blinding is performed by an independent third party operator (pharmacist or nurse, unblinded), who will prepare undistinguishable syringes with patient’s dosing and labelling. As soon as the patient is registered (centrally) and randomization code assigned, the central randomization office will inform the pharmacist or nurse through email of the treatment assigned to the patient; the pharmacist or nurse will prepare the study treatment on the basis of the treatment assigned and body weight of patient (defined as weight on the date of admission). The third party operator (pharmacist or nurse) will label the study treatment syringes with with labels supplied by AryoGen.
Placebo
Not used
Assignment
Crossover
Other design features

Secondary Ids

1

Registry name
clinicaltrials.gov
Secondary trial Id
NCT03935334
Registration date
2019-05-02, 1398/02/12

2

Registry name
clinicaltrialsregister.eu
Secondary trial Id
2019-002854-22
Registration date
2020-01-03, 1398/10/13

Ethics committees

1

Ethics committee
Name of ethics committee
Shiraz University of Medical Sciences
Street address
Shiraz University of Medical Sciences
City
Shiraz
Province
Fars
Postal code
7134814336
Approval date
2017-06-19, 1396/03/29
Ethics committee reference number
IR.SUMS.REC.1396.43

2

Ethics committee
Name of ethics committee
Iran University of Medical Sciences
Street address
Iran University of Medical Sciences ,Shahid Hemmat Highway
City
Tehran
Province
Tehran
Postal code
1449614535
Approval date
2018-03-06, 1396/12/15
Ethics committee reference number
IR.IUMS.REC 1396.9-33058

3

Ethics committee
Name of ethics committee
Zahedan University of Medical Sciences
Street address
Zahedan University of Medical Sciences, Dr. Hesabi sq. Zahedan, Iran
City
Zahedan
Province
Sistan-va-Balouchestan
Postal code
9816737789
Approval date
2018-12-19, 1397/09/28
Ethics committee reference number
IR.ZAUMS.REC.1397.356

Health conditions studied

1

Description of health condition studied
Hemophilia A with inhibitor
ICD-10 code
D66
ICD-10 code description
Deficiency factor VIII (with functional defect)

2

Description of health condition studied
Hemophilia B with inhibitor
ICD-10 code
D67
ICD-10 code description
Hereditary factor IX deficiency (with functional defect)

Primary outcomes

1

Description
Pharmacokinetic parameter: the area under the plasma concentration time curve from time 0 to infinity, based on the last observed concentration (AUCinf)
Timepoint
10 min- prior to dose administration and at 10 min, 20 min, 1 h, 3 h, 5 h, 8 h, 12 h, 24 h and 30 h after AryoSeven or NovoSeven injection
Method of measurement
Measurement of plasma level of factor VII clotting activity (FVII:C) determined by commercial Staclot® VIIa–recombinant tissue factor assay (Diagnostica Stago, Asniéres sur Seine, France)performed by a central lab.

2

Description
Pharmacodynamic parameters:Thrombin Generation Assay (TGA), D-Dimer, F1.2 prothrombin fragments
Timepoint
Thrombin Generation Assay:10 min prior to dose administration and at 10 min,20 min,1h,3 h,5 h,8 h,12 h,24 h and 30 h after AryoSeven or NovoSeven injection.D-dimer and F1.2 prothrombin fragments- 10 min- prior to dose administration and at 20 min, 1 h, 5 h, and 12 h and 24 h after on the same samples obtained for TGA
Method of measurement
Validated analytical method performed by central lab

Secondary outcomes

1

Description
Secondary PK parameters:AUClast, Cmax,tmax, AUCextra;First order rate constant associated with the terminal (log-linear) portion of the curve (λz);Elimination half-life; MRT; CL; Vss
Timepoint
10 min- prior to dose administration and at 10 min, 20

min, 1 h, 3 h, 5 h, 8 h and 12 h, 24 h and 30 h after AryoSeven or NovoSeven injection

Method of measurement

Pharmacokinetic assessment by measurement of plasma level of factor VII clotting activity (FVII:C) determined by commercial Staclot® VIIa–recombinant tissue factor assay (Diagnostica Stago, Asniéres sur Seine, France)., performed by a central lab

2

Description

Clinical parameters in controlling acute bleeding after treatment with AryoSeven.

Timepoint

2 h, 6 h and 12 h post infusion (last AryoSeven dose).

Method of measurement

4 point scale (Excellent, Good, Moderate, None) by the investigator

3

Description

Immunogenicity assessment.

Timepoint

At screening visit, after the second drug administration (visit 3) and then every 3 months for a year.

Method of measurement

PT based Bethesda assay

4

Description

Adverse events

Timepoint

at any time during the study

Method of measurement

Adverse events grading for severity, seriousness, expected or unexpected, relationship to the study drug, action taken, outcome.

Intervention groups

1

Description

AryoGen eptacog alfa (AryoSeven 1.2 mg), intravenous 90 microgram per kg single dose. Lyophilized powder for solution with provided solvent

Category

Treatment - Drugs

2

Description

AryoGen eptacog alfa (AryoSeven 1.2 mg), intravenous 270 microgram per kg single dose. Lyophilized powder for solution with provided solvent

Category

Treatment - Drugs

3

Description

Novo Nordisk eptacog alfa (Novoseven 1 mg), intravenous 90 microgram per kg Lyophilized powder for solution with provided solvent

Category

Treatment - Drugs

4

Description

Novo Nordisk eptacog alfa (Novoseven 1 mg), intravenous 270 microgram per kg Lyophilized powder for solution with provided solvent

Category

Treatment - Drugs

Recruitment centers

1

Recruitment center

Name of recruitment center

Iran Comprehensive Hemophilia Care Center

Full name of responsible person

Dr. Mohammadreza Baghaipour

Street address

Tehran, No. 3, N Felestin St

City

Tehran

Province

Tehran

Postal code

1415863675

Phone

+98 21 8891 0001

Email

mrbaghaipour@yahoo.com

2

Recruitment center

Name of recruitment center

Hemophilia Ward Shahid Dastgheib Hospital

Full name of responsible person

Dr. Mohammad Reza Bordbar

Street address

Building no.7, Shahid Dastgheib Hospital, Hafez avenue, Shiraz, Iran

City

Shiraz

Province

Fars

Postal code

714563769

Phone

+98 71 3228 8064

Email

mbordbar@sums.ac.ir

3

Recruitment center

Name of recruitment center
Ali Asghar Hospital

Full name of responsible person
Dr. Majid Naderi

Street address
Ali Ashghar Hospital, Azadi st, Zahedan, Iran

City
Zahedan

Province
Sistan-va-Balouchestan

Postal code
9816743463

Phone
+98 54 3329 5784

Email
majid_naderi2000@yahoo.com

Sponsors / Funding sources

1

Sponsor

Name of organization / entity
AryoGen Pharmed

Full name of responsible person
Amirhossein Saadatirad

Street address
No 140, Corner of Tajbakhsh street, 24th Km of Tehran Karaj Makhsous road

City
Garmdareh

Province
Alborz

Postal code
3164819712

Phone
+98 26 3610 6480

Email
saadatirada@aryogen.com

Grant name

Grant code / Reference number

Is the source of funding the same sponsor organization/entity?
Yes

Title of funding source
AryoGen Pharmed

Proportion provided by this source
100

Public or private sector
Private

Domestic or foreign origin
Domestic

Category of foreign source of funding
empty

Country of origin

Type of organization providing the funding
Industry

Person responsible for general inquiries

Contact

Name of organization / entity
AryoGen Pharmed

Full name of responsible person
Amirhossein Saadatirad

Position
Project Manager of rFVIIa registration in Europe

Latest degree
Ph.D.

Other areas of specialty/work
Medical Pharmacy

Street address
No 140, corner of Tajbakhsh street, 24th Km of Tehran Karaj Makhsous road

City
Garmdareh

Province
Alborz

Postal code
3164819712

Phone
+98 26 3610 6480

Fax

Email
saadatirada@aryogen.com

Web page address

Person responsible for scientific inquiries

Contact

Name of organization / entity
Baqiyatallah Hospital

Full name of responsible person
Dr. Hasan Abolghasemi

Position
Full professor

Latest degree
Subspecialist

Other areas of specialty/work
Pediatrics

Street address
Mollasadra str, south Sheykh Bahaii str, Tehran

City
Tehran

Province
Tehran

Postal code
1465915371

Phone
009828882742

Fax

Email
Abolghasem@bmsu.ac.ir

Web page address

Person responsible for updating data

Contact

Name of organization / entity

AryoGen Pharmed

Full name of responsible person

Amirhossein Saadatirad

Position

Project Manager of rFVIIa registration in Europe

Latest degree

Ph.D.

Other areas of specialty/work

Medical Pharmacy

Street address

No 140, corner of Tajbakhsh street, 24th Km of Tehran Karaj Makhsous road

City

Garmdareh

Province

Alborz

Postal code

3164819712

Phone

+98 26 3610 6480

Fax

Email

saadatirada@aryogen.com

Web page address

Sharing plan

Deidentified Individual Participant Data Set (IPD)

Undecided - It is not yet known if there will be a plan to make this available

Study Protocol

Undecided - It is not yet known if there will be a plan to make this available

Statistical Analysis Plan

Undecided - It is not yet known if there will be a plan to make this available

Informed Consent Form

No - There is not a plan to make this available

Clinical Study Report

Undecided - It is not yet known if there will be a plan to make this available

Analytic Code

Undecided - It is not yet known if there will be a plan to make this available

Data Dictionary

Undecided - It is not yet known if there will be a plan to make this available