A Phase 3, open-label, randomized, multi-center, controlled trial to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard of care anticoagulant therapy in pediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE)

Published: 04-01-2017
Last updated: 15-04-2024

The primary objective is to demonstrate the non-inferiority of edoxaban to standard of care (SOC; including low molecular weight heparin (LMWH), or vitamin K antagonist (VKA)) in the treatment and secondary prevention of VTE in pediatric subjects...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON47183

Source
ToetsingOnline

Brief title
The Edoxaban Hokusai VTE PEDIATRICS Study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
venous thromboembolism, VTE

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Sankyo, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: anticoagulant therapy, Pediatrics, VTE

Outcome measures

Primary outcome

The primary efficacy endpoint is the composite endpoint consisting of incidence of symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden (as defined in the protocol) during the first 3-months period.

Secondary outcome

A composite endpoint consisting of the incidence of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden from randomization to the date of the last dose of study drug + 30 days.

Study description

Background summary

The clinical presentation of pediatric venous thromboembolic (VTE) disease includes
many manifestations, such as catheter-related thrombosis, pulmonary embolism (PE),
deep vein thrombosis (DVT), and sinovenous thrombosis. The majority of pediatric subjects (> 95%) with VTE have at least 1 clinical risk factor.
Edoxaban is an oral direct inhibitor of activated Factor X with predictable pharmacokinetics (PK) and pharmacodynamics (PD). As a result, anticoagulant effects
are more likely to remain within the therapeutic range, thereby decreasing the likelihood
of bleeding, and potentially removing the need for dose adjustment or frequent monitoring. These advantages may result in increased patient satisfaction and adherence compared with existing anticoagulants.

In the EU and Japan, edoxaban has been approved for the following indications:
* Prevention of stroke and systemic embolism in adult subjects with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age * 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA) with no limitation of use.
* Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults
This study will evaluate the benefits and risks of edoxaban in pediatric subjects with
thromboembolic disease.

Study objective

The primary objective is to demonstrate the non-inferiority of edoxaban to standard of care (SOC; including low molecular weight heparin (LMWH), or vitamin K antagonist (VKA)) in the treatment and secondary prevention of VTE in pediatric subjects with regard to the composite efficacy endpoint (ie, symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden) during the first 3-month treatment period.

Study design

This is an event driven Phase 3, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group study in subjects with confirmed VTE. This study is designed to evaluate the PK and pharmacodynamics (PD) of edoxaban and to compare the efficacy and safety of edoxaban after at least 5 days of heparin (LMWH or unfractionated heparin (UFH); with overlapping VKAs if needed) against SOC (LMWH or VKA) in pediatric subjects with confirmed VTE.

Intervention

Edoxaban treatment will be dispensed to the subject on a monthly visit schedule. The oldest cohort (12 to < 18 years of age) will receive tablets. All younger age cohorts (< 12 years) will receive edoxaban granules for oral suspension.

Study burden and risks

As of now, almost 20,000 adults have taken edoxaban (30 mg or 60 mg) in different studies. The most common problem was bleeding. The results of these studies showed that bleeding occurred less with edoxaban compared to warfarin (Coumadin), another medication given to stop blood clots. Right now, edoxaban is prescribed by doctors in US, EU and Japan. However it is not yet approved for pediatric patients. In principle, based on current data obtained on edoxaban, edoxaban is also considered to be suitable for the paediatric population. The DU176b-A-U157 study (currently ongoing in the US, Canada and Europe) will evaluate the pharmacokinetics (PK), the pharmacodynamics (PD), the safety and tolerability of edoxaban in paediatric patients following single-dose oral administration. As of 20th November 2017, 28 subjects have been exposed to doses ranging between 24mg to 60mg. The subjects have been between the ages of 6 to 18. No safety concerns related to study drug have been observed in these subjects. To date 28 subjects with documented VTE have experienced up to 3 months of edoxaban therapy. Serious AEs included pyrexis, asthenia, pulmonary embolism, haematoma, cerviobrachial syndrome. No AEs have led to study drug discontinuation. Any risk in the DU176b-D-U312 trial is minimized as the trial is an open label design, is highly monitored with oversight by a DSMB that meets periodically, and associated risks are controlled and evaluated for the individual patient.

Contacts

Public
Daiichi Sankyo, Inc.

Mt. Airy Road 211
Basking Ridge NJ 07920-2311
US
Scientific
Daiichi Sankyo, Inc.

Mt. Airy Road 211
Basking Ridge NJ 07920-2311
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Subjects must satisfy all of the following criteria to be included in the study:
1. Male or female pediatric subjects between birth (defined as 38 weeks gestational age) and less than 18 years of age at the time of consent.
2. Pediatric subjects with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days.
3. Subjects must have received at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH according to the edoxaban label for VTE treatment) therapy prior to randomization to treat the newly identified index VTE.
In addition, prior to being randomized to edoxaban or SOC, subjects initially treated with VKA are
recommended to have an INR < 2.0.
4. Subject and/or parent(s)/legal guardian(s) or legally acceptable representative is informed and provides signed consent for the child to participate in the study with edoxaban treatment. Pediatric subjects with appropriate intellectual maturity will be required to sign an assent form
in addition to the signed informed consent from the parent(s)/legal guardian(s) or any legally acceptable representative.
5. Female subjects who have menarche must test negative for pregnancy at Screening and must consent to avoid becoming pregnant by using an approved contraception method throughout the study.

Exclusion criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:
1. Subjects with active bleeding or high risk of bleeding contraindicating treatment with LMWH, SP Xa inhibitors, VKAs, or direct oral anticoagulants (DOACs; identified high risk of

bleeding during prior experimental administration of DOACs).
2. Subjects who have been or are being treated with thrombolytic agents, thrombectomy or insertion of a caval filter for the newly identified index VTE.
3. Administration of antiplatelet therapy is contraindicated in both arms except for low dose aspirin defined as 1-5 mg/Kg/day with maximum of 100 mg/day.
4. Administration of rifampin is prohibited during the study and subjects on concomitant use of rifampin are excluded.
5. Subjects with hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk (aPTT > 50 seconds or international normalized ratio [INR] > 2.0 not related to anticoagulation therapy) or ALT > 5 × the upper limit of normal (ULN) or total bilirubin > 2 × ULN with direct bilirubin > 20% of the total at Screening Visit.
6. Subjects with glomerular filtration rate (GFR) < 30% of normal for age and size.
7. Subjects with stage 2 hypertension defined as blood pressure (BP) systolic and/or diastolic confirmed > 99th percentile + 5 mmHg.
8. Subject with thrombocytopenia < 50 × 109/L at Screening Visit.
Subjects with a history of heparin-induced thrombocytopenia may be enrolled in the study at the Investigator's discretion.
9. Life expectancy less than the expected study treatment duration (3 months).
10. Subjects who are known to be pregnant or breastfeeding.
11. Subjects with any condition that, as judged by the Investigator, would place the subject at increased risk of harm if he/she participated in the study including contraindicated medications identified in Appendix 17.4.
12. Subjects who participated in another clinical study or were treated with an experimental therapy with less than a 30-day washout period prior to identifying the qualifying index VTE.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	17-07-2018
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Acenocoumarol Sandoz
Generic name:	Acenocoumarol
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	EDOXABAN TOSYLATE MONOHYDRATE
Generic name:	Edoxaban
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	enoxaparine
Generic name:	Clexane
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fraxiparine
Generic name:	Nadroparine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Marcoumar
Generic name:	Fenprocoumon
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	20-02-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000991-49-NL
CCMO	NL58245.078.16