A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Single Ascending Dose Study to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of DS-1040b when Added to Standard of Care Anticoagulation Therapy in Subjects with Acute Submassive Pulmonary Embolism.

Published: 04-10-2016
Last updated: 31-12-2024

The primary objective of this study is to evaluate the safety and tolerability using bleeding as the primary endpoint. Secondarily, this study will serve as a proof-of concept by evaluating the effect that DS-1040b administration has on total...

Ethical review	Approved WMO
Status	Completed
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON47535

Source
ToetsingOnline

Brief title
DS1040-B-U107

Condition

- Embolism and thrombosis

Synonym
Pulmonary embolism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anticoagulation, DS-1040b, pulmonary embolism

Outcome measures

Primary outcome

Primary Objective: To assess the safety and tolerability of ascending doses of DS-1040b given as a single intravenous (IV) infusion over 12, 24, 48 and 72 hours (h), respectively, when added to standard of care (SOC) anticoagulation therapy compared to placebo by evaluating the rate of adjudicated clinically relevant bleeding (International Society of Thrombosis and Haemostasis (ISTH) major or clinically relevant nonmajor (CRNM) bleeding).

Secondary outcome

Secondary Objectives:

To assess the following efficacy endpoints as evaluation of proof-of-concept:

1. Relative reduction (% reduction) in total thrombus volume from baseline to <= 12h from end of DS1040b infusion, assessed by computed tomography angiography

(CTA) in segmental or larger pulmonary arteries;

2. Proportion of subjects who achieve a >= 20%

greater relative reduction in total thrombus volume

assessed by CTA in segmental or larger pulmonary

arteries, from baseline to <= 12h from end of DS-1040b infusion and compared to

placebo;

3. Proportion of subjects who achieve a >= 50% greater relative reduction in

total thrombus volume assessed by CTA in segmental or larger pulmonary

arteries, from baseline to <= 12h from end of DS1040b infusion and compared to

placebo;

4. Recurrence of adjudicated venous thromboembolism [VTE] (Composite of

recurrent PE, new or recurrent deep vein thrombosis (DVT),

VTE-related death; as well as the individual components) up to hospital

discharge and up to Day 30 Visit after dosing;

5. Death, major cardiovascular events (MACE: defined as a composite of

cardiovascular death or non-fatal myocardial infarction, stroke, or systemic

embolic events [SEE]), hemodynamic decompensation, treatment escalation

(defined as catecholamine infusion, secondary thrombolysis, endotracheal

intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or

thrombus fragmentation by catheter) up to hospital discharge and up to Day 30

Visit after dosing;

6. Overall safety evaluation (serious adverse events [SAEs], treatment-emergent

adverse events [TEAEs], clinical laboratory parameters);

7. Pharmacokinetics (PK) of DS-1040b in subjects with PE.

8. Assess the pharmacodynamic (PD) effect of DS-1040b on thrombin-activatable

fibrinolysis inhibitor (TAFIa) activity, TAFI antigen and Ddimer

fibrinolysis biomarkers, in subjects with PE.

Exploratory Objective:

Assess the effect of DS-1040b on clot lysis as a biomarker for TAFIa activity

in subjects with PE.

Study description

Background summary

Thrombin-activatable fibrinolysis inhibitor (TAFI) is a plasma procarboxypeptidase that, upon activation by thrombin, thrombinthrombomodulin complex or plasmin, turns into an antifibrinolytic enzyme termed activated form of TAFI (TAFIa). In a thrombus, TAFIa removes lysine residues at the carboxy terminal of fibrin degradation products, which prevents effective binding of plasminogen and tissue plasminogen activator (t-PA), resulting in impaired thrombolysis

Study objective

The primary objective of this study is to evaluate the safety and tolerability using bleeding as the primary endpoint. Secondarily, this study will serve as a proof-of concept by evaluating the effect that DS-1040b administration has on total thrombus volume reduction from baseline to the end of infusion, assessed by contrast enhanced computed tomography scan (CT angiography or CTA). This study will also evaluate the pharmacokinetic/pharmacodynamic (PK/PD) and biomarker activity of DS-1040b in subjects with acute PE and the correlation with imaging.

Study design

This will be a randomized, double-blind, placebocontrolled, multi-center, single ascending dose study in subjects with acute PE characterized as low-risk or intermediate-risk or submassive PE. This study will follow an adaptive design and include up to six sequential, ascending-dose/continuous infusion time cohorts, organized in three pairs (1-2, 3-4, and 5-6) and up to two dose

optimization evaluations planned in between the first and second pair of cohorts. All subjects participating in this study will receive SOC anticoagulation therapy as per the current treatment guidelines and local practice for patients with acute PE, to ensure an effective therapeutic background. Due to the early stage of development and in order to minimize variability, the initial background anticoagulation regimen for this study will be standardized for all subjects to enoxaparin 1 mg/kg, subcutaneous, every 12 hours during which the blinded study drug (DS-1040b or placebo) will be administered. At the time of randomization, eligible subjects must initiate or be transitioned to the study specified enoxaparin regimen.

Randomized subjects will receive an IV infusion with study drug (either DS-1040b or placebo) over a period of time ranging from 12h to 72h depending on the cohort. All subjects within a cohort will receive the same dose of study drug administered via IV infusion of the same duration. The assignment to either active drug or placebo will be blinded to the subjects and study site staff who may come in direct contact with the subjects as well as to the Sponsor and Medpace study team. Following the end of the enoxaparin/blinded study drug administration period, study subjects will be switched to the anticoagulant treatment of choice, at the Investigator*s discretion. Subject participation in the study will end on Day 30. The study may be stopped at any time for safety reasons.

Efficacy will be evaluated by measuring total thrombus volume via CTA scans at baseline, at <= 12h post end of blinded study drug infusion, and optionally at Day 30. All CTA scans will be read centrally by the Core Imaging Laboratory; however, confirmation of measurable PE lesion(s) in a segmental or larger pulmonary artery by the site radiologist is essential and mandatory prior to randomization.

An independent, unblinded, Data Monitoring Committee DMC) will review key safety parameters for each cohort and provide its endorsement for the continuation of the study and the dose escalation decisions. A blinded Clinical Events Committee (CEC) will be established to adjudicate bleeding events.

Study enrollment will be done in pairs of cohorts, beginning with Cohorts 1 and 2, followed by Cohorts 3 and 4, then 5 and 6.
This allows for dose optimization assessments after cohort pairs 1 and 2 and 3 and 4.
Randomization within a cohort pair will occur
sequentially, that is randomization within the initial cohort
will be completed and safety monitored by the DMC
before randomization in the subsequent cohort will begin.

Within each pair of cohorts, subject enrollment will be staggered for safety. Enrollment in Cohorts 2, 4, and 6 will begin after the first 10 subjects in Cohorts 1, 3, and 5, respectively have successfully completed study drug

administration and have reached 72 hours post the end of study drug infusion (when the sample collection for PK/PD measurements ends) without any increase in the primary safety endpoint (clinically relevant bleeding) or other relevant safety concerns emerging, as assessed by the independent, unblinded DMC.

In Cohorts 1 and 2 eligible subjects will be randomized in a 2:1 ratio to either DS-1040b or placebo. Beginning with Cohort 3 the randomization ratio will change to 3:1. A dose optimization evaluation is planned after all subjects in Cohorts 1-2 reach 72h post end of infusion, which will include imaging (total thrombus volume reduction from baseline to <= 12 hours post end of study drug infusion), pharmacokinetic, and select biomarker data. The optimized dose(s) and dosing regimens will be then used for the subsequent cohorts. If necessary, a second dose optimization evaluation may be carried out after Cohorts 3-4 are completed, to further optimize the dose(s) and dosing regimens for Cohorts 5-6.
The dose optimization evaluation(s) will be carried out in an unblinded fashion by a separate, designated team with the appropriate firewalls in place to prevent accidental unblinding of the study team. The study may end after Cohorts 3-4 are completed, should the optimized dose(s)
and dosing regimens tested yield a clinically meaningful reduction in thrombus size/volume and have acceptable safety and tolerability.

Intervention

All patients will receive Enoxaparin 1mg/kg for 3-6 days (depending on the Cohort) and anticoagulant (chosen by the investigator) starting from the end of the IP infusion until Day 30.

Study burden and risks

Risks: possible side effects of the medication and study procedures

Burden: a maximum of 5 visits to the investigator; at 3 visits a blood sample is taken. A urine sample is taken on visits Baseline and after the end of the infusion. A CT scan is performed on visits Baseline and Day 30 (the CT scan on Day 30 is not mandatory). An ECG is performed on visits Baseline, Double blind treatment period and After end of infusion visit.
Subjects are required to stay in the hospital until the end of the study medication infusion.

Contacts

Public
Daiichi Sankyo, Inc

Thornall Street 399
Edison NJ 08837
US
Scientific
Daiichi Sankyo, Inc

Thornall Street 399
Edison NJ 08837
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female subjects, age 18 to 75 years and body weight between 50 and 130 kg, inclusive;
2. Subjects admitted to the hospital with a clinical diagnosis of acute PE with an onset of symptoms
in the 5 days prior to diagnosis categorized as low risk or intermediate-risk or submassive PE and for whom
catheter-based therapy is not planned;
a. Subjects must have a CTA scan confirming the PE diagnosis and with at least one measurable index lesion in a segmental or larger pulmonary artery prior to randomization;
b. Subjects should be in otherwise satisfactory health in the opinion of the Investigator;
c. Subjects may have concurrent DVT and have an inferior vena cava (IVC) filter placed prior to randomization;
d. Subjects may already be on SOC low molecular weight (Heparin) [LMW (Heparin)] at the time of randomization but for no longer than 36 hours.
3. Able to provide written informed consent.

Exclusion criteria

1. Subjects with acute PE categorized as high-risk or massive, or who are hemodynamically unstable, evidenced by a heart rate > 120 /min and a systolic blood pressure (SBP) of < 90 mmHg for more than 15 consecutive minutes or a drop in SBP of > 40 mmHg since presentation;
2. Subjects for whom use of a thrombolytic, either systemic or via catheter, is planned;
3. Subjects with PE lesions only in the sub-segmental or smaller arteries, which due to limitations of the imaging method may not be consistently identified and measured;
4. Subjects unable or unwilling to take the required SOC anticoagulation therapy;
5. Subjects receiving more than 36 hours of SOC anticoagulants (eg, unfractionated heparin, LMW
heparin, Vitamin K antagonists or novel oral anticoagulants) for treatment of the index PE event
prior to randomization. Study drug infusion will ideally begin within 6 hours after randomization;
6. Subjects who had prior intracranial hemorrhage, known arteriovenous malformation or aneurysm, or evidence of active bleeding;
7. Subjects with bleeding diathesis, a platelet count < 100,000, international normalized ratio (INR) > 1.7, or a clinically significant elevated activated partial thromboplastin time (aPTT) that is not explained by use of LMWH;
8. Subjects with active endocarditis;
9. Subjects with < 6 month history of acute coronary syndrome (ACS) whether or not they have undergone percutaneous coronary intervention (PCI);
10. Subjects who require ongoing dual antiplatelet therapy or treatment with aspirin alone in a dosage of more than 100 mg/per day;
11. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for >= 4 days/week anticipated to continue during the study;
12. Subjects with uncontrolled hypertension at randomization, evidenced by SBP > 180 mm Hg or diastolic blood pressure>120 mmHg, or who require parenteral medication to maintain blood pressure below these limits;
13. Subjects who within 3 months prior to randomization have had intracranial surgery, clinically significant head trauma (in the opinion of the Principal Investigator), a stroke, or have received thrombolytic treatment;
14. Subjects with ECG evidence of 2 nd degree or higher atrioventricular (AV) block or with QTcB or QTcF> 450 ms;
15. Subjects who within 21 days prior to randomization have had gastrointestinal or genitourinary bleeding;
16. Subjects who within 14 days prior to randomization have had major surgery or a lumbar puncture (or epidural steroid injection);
17. Subjects with hemoglobin < 10 g/dL;
18. Subjects with an estimated creatinine clearance < 60 mL/min;
19. Subjects with diagnosed active liver disease or with elevation of liver enzymes/bilirubin:
a. Alanine transaminase (ALT) or aspartate transaminase (AST) >= 2 times upper limit of normal (ULN)

b. Total bilirubin (TBL) >= 1.5 times ULN (except due to confirmed Gilbert*s syndrome)
20. Subjects with known history of testing positive for Hepatitis B antigen or Hepatitis C antibody before randomization;
21. Subjects with known history of testing positive for the human immunodeficiency virus (HIV);
22. Subjects with active cancer defined as recurrent, regionally advanced, metastatic disease, or a
hematologic malignancy not in complete remission
and subjects with malignancy diagnosed within 2 years prior to randomization,
except for adequately treated non-melanoma skin cancer or other non-invasive or insitu neoplasm (eg, cervical cancer in situ);
23. Subjects currently receiving chemotherapy or radiation therapy or having received any treatment
for cancer during the 12 months prior to randomization or expected to initiate such therapy during study participation;
24. Subjects with NYHA Class III or IV congestive heart failure (ie, subjects with marked limitations
in physical activity or unable to engage in normal activity);
25. Subjects with moderate to severe chronic obstructive pulmonary disease (ie, subjects incapable of ordinary activity without dyspnea/shortness of breath or requiring routine oxygen in
the month prior to randomization);;26. Female subjects of child bearing potential with a positive pregnancy test, lactating women, or women unwilling to use highly effective methods of birth control (see protocol for the methods).
27. Subjects currently participating in another investigational study or who have participated in an investigational drug study within 30 days or prior to randomization;
28. Subjects unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the investigator to be unlikely to complete the study);
29. Subjects with any condition (including laboratory abnormalities) that, in the opinion of the Investigator, would potentially place the subject at increased risk of harm through participation in this study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-07-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DS-1040B
Generic name:	DS-1040B

Ethics review

Approved WMO Date:	04-10-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-005211-32-NL
CCMO	NL58056.018.16

Study results

Date completed:	03-08-2019
Results posted:	11-09-2020
Actual enrolment:	22

First publication
13-03-2020