A Phase 3, Multicenter, Open-Label, Single-Arm Study of PB2452 in Ticagrelor-Treated Patients with Uncontrolled Major or Life-Threatening Bleeding or Requiring Urgent Surgery or Invasive Procedure (REVERSE-IT Trial)

Published: 09-11-2020
Last updated: 10-01-2025

Primary objectives: • To demonstrate reversal of the antiplatelet effects of ticagrelor after initiation of the intravenous (IV) infusion of PB2452 using the VerifyNow* PRUTest* (VerifyNow*, 2016) platelet function assay in ticagrelor-treated...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54454

Source
ToetsingOnline

Brief title
PB2452-PT-CL-0004 (REVERSE-IT)

Condition

- Other condition

Synonym
Ticagrelor-Treated Patients with Uncontrolled Bleeding

Health condition

blood and lymphatic system disorders, Uncontrolled Major or Life Threatening Bleeding or Requiring Urgent, Surgery or Invasive Procedure

Research involving
Human

Sponsors and support

Primary sponsor: SFJ Pharmaceuticals, Inc.
Source(s) of monetary or material Support: SFJ Pharmaceuticals;Inc.

Intervention

Keyword: Bleeding, Open-Label, Phase 3, Ticagrelor-Treated Patients

Outcome measures

Primary outcome

Primary reversal endpoint:

The minimum % inhibition of PRU within 4 hours of the initiation of study drug as assessed by the VerifyNow* PRUTest* platelet function assay. Percent inhibition of PRU is calculated as 100 * [(180 - PRUtrt)/180]. PRUtrt refers to the PRU value measured posttreatment with the study drug. PRU of 180 is considered the lower limit of normal (LLN) platelet function as described in the VerifyNow* PRUTest* manufacturer*s user guidance.

Primary hemostasis endpoint:

Achievement of effective hemostasis after initiation of PB2452 infusion will be assessed in each population separately and then pooled for primary endpoint analysis. In patients with uncontrolled major bleeding, achievement of effective hemostasis will be assessed using prespecified criteria for effective

hemostasis for visible and non-visible major bleeding adapted from. In patients undergoing urgent surgery or invasive procedure, achievement of effective hemostasis following initiation of PB2452 infusion will be centrally adjudicated using prespecified criteria for effective hemostasis derived from the GUSTO clinical bleeding scale.

Secondary outcome

Secondary endpoints:

• Minimum % inhibition of PRI assessed by VASP within 4 hours after the initiation of study drug. Percent inhibition of PRI is calculated as 100 * [(PRIbsl - PRItrt)/ PRIbsl]. PRItrt refers to the PRI value measured posttreatment with the study drug. PRIbsl is the lower limit of normal obtained from previous studies in healthy volunteers

• Maximum reversal of PRU assessed by VerifyNow® PRUTest® within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 * [(PRUtrt - PRUpre-trt)/(180- PRUpre-trt)]. PRUpre-trt is defined as the PRU value prior to administration of study drug. PRU of 180 is considered as the lower limit of normal (LLN) for platelet function as described in the VerifyNow® PRUTest® package insert

• Maximum reversal of PRI assessed by VASP within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 * [(PRItrt - PRIpre-trt)/(LLN - PRIpre-trt)]. PRIpre-trt is defined as the PRU value prior to administration of study drug. LLN of PRI is obtained from previous studies in healthy volunteers

• Proportion of subjects achieving 60%, 80% or 100% reversal of platelet

inhibition by ticagrelor using PRU and PRI at any time point during the

treatment period

• Duration of at least 60%, 80%, and 100% reversal by PRU and PRI

Study description

Background summary

PB2452 is a specific and selective neutralizing antibody fragment that binds ticagrelor and TAM, the major active circulating ticagrelor metabolite, with high affinity and selectivity. PB2452 is intended to reverse the antiplatelet effects of ticagrelor in patients who experience uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedure, serious but rare conditions that represent an unmet medical need. (reference IB section 2: Introduction)

Study objective

Primary objectives:
• To demonstrate reversal of the antiplatelet effects of ticagrelor after initiation of the intravenous (IV) infusion of PB2452 using the VerifyNow* PRUTest* (VerifyNow*, 2016) platelet function assay in ticagrelor-treated patients presenting with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure.
• To demonstrate the effect of PB2452 on achievement of effective hemostasis after administration of PB2452 in ticagrelor-treated patients presenting with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure

Secondary objective:
• To demonstrate reversal of the antiplatelet effects of ticagrelor with intravenous (IV) infusion of PB2452 by measurement of the platelet reactivity index (PRI) using the vasodilator-stimulated phosphoprotein (VASP) assay in addition to PRU in ticagrelor-treated patients presenting with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure.

Study design

This is a multicenter, open-label, prospective single-arm study of reversal of the antiplatelet effects of ticagrelor with PB2452 in patients who present with

uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedure. Approximately 200 patients will be enrolled from approximately 200 centers in North America, Europe, and Asia-Pacific regions, including mainland China. Patients with reported use of ticagrelor within the prior 3 days who require urgent ticagrelor reversal will be eligible for enrollment.

Study drug will be administered as an intravenous (IV) infusion comprised of an initial IV bolus of 6 grams (g) infused over 10 minutes for rapid reversal, followed immediately by a 6g IV loading infusion over 4 hours and then a 6g IV maintenance infusion over 12 hours. This PB2452 regimen is expected to provide immediate reversal of the antiplatelet effects of ticagrelor within 5 minutes of the initiation of infusion that is sustained for 20-24 hours. The total infusion time of PB2452 will be 16 hours and 10 minutes, and total volume, approximately 180 mL. The dose will be adjusted for patients with known concomitant use of a moderate or strong CYP3A inhibitor.

(see protocol synopsis for more details).

Intervention

This is a multicenter, open-label, prospective single-arm study of reversal of the antiplatelet effects of ticagrelor with PB2452 in patients who present with uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedure.

Study drug will be administered as an intravenous (IV) infusion comprised of an initial IV bolus of 6 grams (g) infused over 10 minutes for rapid reversal, followed immediately by a 6g IV loading infusion over 4 hours and then a 6g IV maintenance infusion over 12 hours.

Study burden and risks

PB2452 has been shown to provide immediate and sustained reversal of the antiplatelet effects of ticagrelor in early phase studies. In this Phase 3 study, this rapid and sustained reversal of ticagrelor by PB2452 is expected to provide clinically meaningful and potentially life-saving benefit to enrolled patients taking ticagrelor who present with uncontrolled major or life-threatening bleeding or who are in need of urgent surgery by supporting rapid hemostasis or prevention of procedure-related bleeding. The risks related to PB2452 administration are expected to be low and infrequent.

Refer to IB (6.5.2.4 Overall benefit-risk summary)

Based on all available information concerning the potential benefits and risks of PB2452, the absence of alternative therapies for the target patient

populations, and the precautions included in this clinical study, the risks are considered acceptable to enroll ticagrelor-treated patients who present with uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedure.

Contacts

Public
SFJ Pharmaceuticals, Inc.

5000 Hopyard Road Suite 330
Pleasanton, CA 94588
US
Scientific
SFJ Pharmaceuticals, Inc.

5000 Hopyard Road Suite 330
Pleasanton, CA 94588
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or female > 18 years of age with documented or verbal informed consent. Emergency consent may be obtained where permitted by local regulations and institutional approval. 2. History or documentation of ticagrelor intake within the prior 3 days 3. Patients described below who require urgent reversal of the antiplatelet effects of ticagrelor: Patients with uncontrolled major or life-threatening bleeding, requiring urgent reversal of the antiplatelet effects of ticagrelor. It is expected that enrolled patients would have

characteristics similar to those described below: • Potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise, e.g., systolic blood pressure < 90 mm Hg and signs or symptoms of low cardiac output not otherwise explained • Bleeding in a critical organ or closed space, such as intracranial, intraspinal, intraocular, retroperitoneal, intra* articular, pericardial, or intramuscular bleed with compartment syndrome • Visible, uncontrolled bleeding associated with a corrected hemoglobin level < 8.0 g/dL, a fall in hemoglobin level of >= 2.0 g/dL (1.24 mmol/L) from a known baseline, or requirement for transfusion of 2 or more units of packed red blood cells (PRBC) Patients requiring urgent surgery or invasive procedure when it is not medically advisable either to proceed urgently with impaired hemostasis or to delay the urgent procedure for 3 or more days due to the high risk of bleeding. These patients may typically be in any of the following clinical situations: • Requires urgent surgery or invasive procedure known to be associated with a risk of significant bleeding (such as cardiac surgery, neurosurgery, or major orthopedic surgery) • Requires urgent surgery or invasive procedure that may have an adverse procedural outcome if hemostasis is impaired (such as neurological, spinal, ophthalmological, urological, or orthopedic surgery) • At risk of experiencing life-threatening events, such as, shock, myocardial infarction, or stroke, if significant intraoperative or postoperative bleeding occurs (such as in elderly patients or patients with underlying cardiac or pulmonary disease who have limited cardiopulmonary reserve)

Exclusion criteria

1. Known sensitivity or contraindication to PB2452 or any of its excipients 2. Patients in whom ticagrelor reversal is not considered urgent, e.g., patients with stable or non-acute conditions who have low hemoglobin due to chronic, low-grade gastrointestinal bleeding or who have stable, remote, or asymptomatic intracranial hemorrhage. 3. Patients expected to be clinically unsalvageable, such as patients with end-stage cancer or patients with overwhelming sepsis. 4. Any condition which, in the opinion of the investigator, would make it unsafe or unsuitable for the patients to participate in this study. This includes assessment of likelihood to cooperate with study follow-up visits and procedures • Known pregnancy may be exclusionary in some regions or countries as directed by national health authorities and/or local IRBs/Ethics Committees 5. Known use of clopidogrel, prasugrel, or ticlopidine within 5 days of study drug administration; known use of antiplatelet GPIIb/IIIa inhibitors, or cangrelor within 5 half-lives of study drug administration; or known use of warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban within 5 half-lives of expected study drug administration 6. Known recent use (< 5 day) of vitamin K, prothrombin complex concentrate, recombinant factor VIIa, idarucizumab, or andexanet-alfa (coagulation factor Xa (recombinant), inactivated-zhzo).

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-08-2021
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PB2452
Generic name:	PB2452

Ethics review

Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	26-02-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	09-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

(Nieuwegein)

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	EUCTR2019-004457-92-NL
ClinicalTrials.gov	NCT04286438
CCMO	NL75256.100.20