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HEALTH TECHNOLOGY BRIEFING
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Bentracimab for reversal of the antiplatelet activity of ticagrelor

NIHRIO ID	28457	**NICE ID**	10550
Developer/Company	PhaseBio Pharmaceuticals Inc	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical development.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Bentracimab is in clinical development for reversal of the antiplatelet activity of ticagrelor. Ticagrelor binds to platelets to prevent them from forming blood clots that could restrict blood flow. The risk of blood clots is higher in people who have had a heart attack or chest pain, and are often prescribed ticagrelor alongside aspirin. Ticagrelor can significantly increase the risk of blood loss when undergoing bleeding or emergency surgery as the blood does not clot as easily, leading to complications. Prior to surgery, it is recommended to stop ticagrelor for five days, however this is not an option for urgent procedures.

Bentracimab is designed as an intravenous infusion to rapidly reverse the effect of ticagrelor by binding to ticagrelor and its target receptor in order to reduce blood thinning and allow blood clotting. If licensed, bentracimab will be the first medicine for ticagrelor-treated people who have uncontrolled major or life-threatening bleeding, or need urgent procedures that might result in severe blood loss.

PROPOSED INDICATION

For adult ticagrelor-treated patients with uncontrolled major or life-threatening bleeding, or in need of surgery or invasive procedure.[1]

TECHNOLOGY

DESCRIPTION

Bentracimab (PB2452) is a novel monocloncal antibody that binds to both ticagrelor and its active metabolite resulting in a rapid return of platelet aggregation. Bentracimab binds to ticagrelor's target receptor (P2Y12) with approximately 100-fold greater affinity than ticagrelor. Bentracimab only binds to free ticagrelor and continues binding to it as it dissociates from the P2Y12 receptor or plasma proteins.[2]

Bentracimab is in a pivotal phase III clinical trial (NCT04286438) for tigagrelor-treated patients with uncontrolled major or life-threatening bleeding, or requiring urgent surgery or invasive procedure. Infusion of 18g betracimab will be initiated on day 1 and will continue for approximately 16 hours. It will be comprised of an initial intravenous (IV) bolus of 6g infused over 10 minutes for rapid reversal, followed immediately by a 6g IV loading infusion over 4 hours and then a 6 g IV maintenance infusion over 12 hours. This bentracimab 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.[1]

INNOVATION AND/OR ADVANTAGES

Bentracimab is a first-in-class technology for the reversal of potent P2Y12 inhibitors, ticagrelor included. The addition of bentracimab will increase the safety of patients requiring reversal of ticagrelor for acute uncontrolled or life-threatening major bleeding events.[2]

In a phase I clinical trial (NCT03492385) in healthy volunteers, the administration of bentracimab provided immediate and sustained reversal of the antiplatelet effects of ticagrelor, as measured by multiple assays.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bentracimab does not currently have Marketing Authorisation in the EU/UK for any indication.

Bentracimab has the following regulatory designations:

- a PRIME status for reversal of the antiplatelet effects of ticagrelor in patients with uncontrolled major or life-threatening bleeding or requiring urgent surgery or an invasive procedure by the EMA in January 2020.[4,5]

- a Breakthrough Therapy by the US FDA for the reversal of the antiplatelet activity of ticagrelor in April 2019.[6]

PATIENT GROUP

DISEASE BACKGROUND

Ticagrelor is an antiplatelet medicine that makes blood flow more freely through veins. It acts by reducing blood clotting.[7] It is often prescribed in combination with aspirin (acetylsalicyclic acid) to people who have had a heart attack or unstable angina, in order to reduce the risk of having another heart attack, stroke or dying from coronary syndromes.[8,9]

Due to the action of ticagrelor, undergoing surgery can increase the risk of bleeding complications, as such it is recommended ceasing the medication 5 days prior to surgery.[8,9] This is feasible for elective surgeries, however not always possible for non-elective urgent procedures or emergencies. When possible, postponing non-elective invasive procedures for at least a few hours until the elimination of the active compound, or a few days to reduce the antiplatelet effect is recommended. Ticagrelor's peak concentration occurs within 1.5-3 hours and its half-life is 6.7-9.1 hours, whereas its first metabolite has a 8.5-12.4 hours half-life.[10]

CLINICAL NEED AND BURDEN OF DISEASE

Patients exposed to ticagrelor within 72 hours prior to surgery have a substantial risk of major bleeding.[11] Periopeative bleeding is a major complication during and after surgery that results in increased morbidity and mortality.[12,13]

The population likely to be eligible to receive bentracimab could not be estimated from available published sources.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Multiple factors are associated with surgical bleeding and risks are identified and managed on a case-by-case basis by a perioperative team.[14] Discontinuing ticagrelor prior to surgical procedures is recommended to reduce antiplatelet effect and risk of bleeding.[8,9] Preoperative teams can assess the risk of bleeding complications in ticagrelor-treated patients using platelet function tests to help treatment strategies.[10,15] Haemostatic agents and platelet transfusion may be used to try to reduce the antiplatelet effect of ticagrelor.[10]

CURRENT TREATMENT OPTIONS

The following pharmacological treatments may be used for ticagrelor-treated patients with severe bleeding or undergoing non-elective procedures:[10]

- Haemostatic agents e.g. recombinant activated factor VIIa (rFVIIa)
- Desmopressin may reduce red blood cell transfusion, blood loss and potential reoperations due to bleeding.
- Tranexamic acid

PLACE OF TECHNOLOGY

If licensed, bentracimab will provide the first ever specific treatment option for ticagrelor-treated patients with uncontrolled major or life-threatening bleeding, or in need of urgent surgery or invasive procedure.

CLINICAL TRIAL INFORMATION

Trial	**REVERSE-IT;** NCT04286438; A Phase 3, Multicenter, Open-Label, Single-Arm Study of Bentracimab (PB2452) in Ticagrelor-Treated Patients With Uncontrolled Major or Life-Threatening Bleeding or Requiring Urgent Surgery or Invasive Procedure **Phase III -** Recruiting **Location(s):** 7 EU countries, UK, USA, Canada and Switzerland **Primary completion date:** December 2023
Trial design	Open label, single group assignment, multicentre.
Population	N=200; aged 18 years and older; Ticagrelor-treated patients with uncontrolled major or life-threatening bleeding requiring urgent reversal of the antiplatelet effects of ticagrelor.
Intervention(s)	Bentracimab 18g intravenous (IV) infusion over a 16 hour duration.
Comparator(s)	No comparator.
Outcome(s)	Primary outcome measure: • Reversal - Platelet Reactivity Units (PRU) [Time Frame: 4 hours post-initiation of infusion] Minimum % inhibition of PRU within 4 hours of the initiation of study drug as assessed by VerifyNow™ PRUTest™ platelet function assay See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04122170; A Phase 2B, Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy of PB2452 in Reversing Ticagrelor in Subjects Aged 50 to 80 Years Old **Phase II –** Completed **Location(s):** USA and Canada **Study completion date:** September 2021
Trial design	Randomised, quadruple masked, parallel assignment, placebo-controlled, multicentre.
Population	N=200; aged 50 and 80 years; Subjects in good general health
Intervention(s)	• Pre-treatment: Ticagrelor 90 mg oral tablet; administered as 180 mg (2 × 90 mg tablet) loading dose plus 90 mg every 12 hours for 4 additional doses

	• Pre-treatment: Aspirin 81 mg oral tablet; administered daily between day -7 to the morning before receiving study medication on day 1, for a total of 8 tablets only • Bentracimab 18g IV infusion over a 16 hour duration
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome measure: Reversal effect of intravenous infusion of PB2452 compared to baseline - Minimum % inhibition of PRU (Verify Now) [Time frame: Four hours after the start of infusion (compared against pre-dose sample)] Reversal of anti-platelet effects of ticagrelor with intravenous infusion of PB2452 or placebo. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03928353; A Phase 2A, Randomized, Double-blind, Placebo-controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 With Ticagrelor Pretreatment in Older and Elderly Subjects and With High-Dose Ticagrelor Pretreatment in Healthy Younger Subjects **Phase II –** Completed **Location(s):** USA **Study completion date:** October 2019
Trial design	Randomised, quadruple masked, sequential assignment, placebo-controleed.
Population	N=23; aged 18 and 80 years; Subjects in good general health
Intervention(s)	5 dose levels of bentracimab infusion + ticagrelor oral tablet See trial record for full list of doses
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome measure: • Incidence and severity of adverse events [Time frame: 73 days - Starting up to 45 days prior to dosing] See trial record for full list of other outcomes.
Results (efficacy)	Statistically significant reversal of ticagrelor was achieved within 5 minutes of initiation of PB2452 infusion and sustained for over 20 hours. Platelet function was normalised by 15 minutes following initiation of PB2452 infusion and remained normal for over 20 hours.[16]
Results (safety)	PB2452 was generally well tolerated, with only minor adverse events reported.[16]

ESTIMATED COST

The cost of bentracimab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- French Working Group on Perioperative Haemostasis (GIHP) and French Society of Anaesthesia and Intensive Care Medicine (SFAR). Management of antiplatelet therapy for non-elective invasive procedures of bleeding complications. June 2019.[10]

ADDITIONAL INFORMATION

PhaseBio Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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