BTG Pharmaceuticals
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Administration of bentracimab

ICD-10 Coordination & Maintenance Committee Meeting

March 2024

$P2Y_{12}$ Inhibitors: Increased risk for major bleeding and bleeding associated with surgery

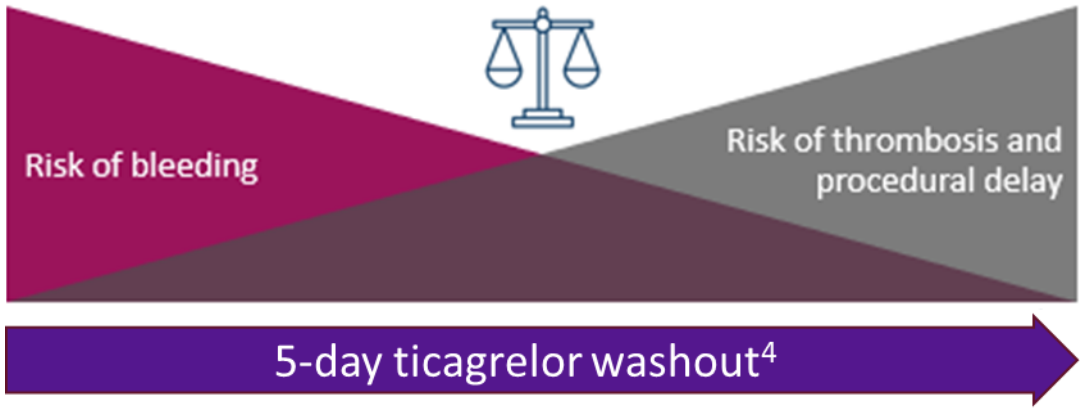
Significant unmet need for reversal of antiplatelet effect of ticagrelor, an oral $P2Y_{12}$ inhibitor[1,2]

Patients Requiring Surgery

- Recommendations include a ~3 to 5-day washout prior to surgery. In non-deferrable cases, this is not possible; washout exposes patients to incremental and steadily increasing thrombotic risk[3]
- There is no known treatment to reverse the antiplatelet effects of Brilinta® (ticagrelor), a $P2Y_{12}$ inhibitor[4]
- Discontinuation of $P2Y_{12}$ is not recommended because of thrombosis risk[3]
- Clinical challenge is to balance risks of bleeding and thrombosis and risk of procedural delay with clinical judgment alone[1]

Risk Factors for Major Bleeding

- Advanced age, chronic kidney disease, diabetes; all are also factors for ischemic risk[5]
- Anemia, heart failure, medications (oral anticoagulant therapy, chronic steroid, and chronic NSAID), among others[5]



Unlike other $P2Y_{12}$ inhibitors, Brilinta® (ticagrelor) is a reversible inhibitor, which made the development of a specific reversal agent for ticagrelor feasible and warranted

NSAID, nonsteroidal anti-inflammatory drug

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Bentracimab: A novel, investigational reversal agent for ticagrelor

Bentracimab is the only specific reversal agent in development to reverse the antiplatelet effects of ticagrelor; studied for use in both patients requiring non-deferrable surgery and with major bleeds

- Bentracimab clinical data to date have demonstrated both immediate (~5 minutes) and sustained (~24 hours) reversal of ticagrelor antiplatelet effects[1,2,6]
- Phase 3 REVERSE-IT (NCT04286438) pre-specified interim results published in December 2021[1]


NEJM Evidence

EVALUATE THE REASONS. EVIDENCE UNDERSTAND THE RESULTS.

Digital journal from the *New England Journal of Medicine* Group.
First issue, January 2022.
Article is posted at https://evidence.nejm.org/

Bentracimab for Ticagrelor Reversal in Patients Undergoing Urgent Surgery

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- Regulatory status:
  - US FDA Breakthrough Therapy designation and EMA PRIME designation
  - US Biologics License Application (BLA) expected to be submitted 1H 2024
    - On May 11, 2023, SERB Pharmaceuticals (SERB) and SFJ Pharmaceuticals (SFJ) announced that SERB had acquired exclusive US rights to bentracimab from SFJ.
    - BTG International Inc, a SERB company, will be responsible for manufacturing and commercialization of bentracimab in the US.

EMA, European Medicines Agency; PRIME, PRIority MEdicines designation; REVERSE-IT, Rapid and SustainEd ReVERSal of TicagrElor – Intervention Trial

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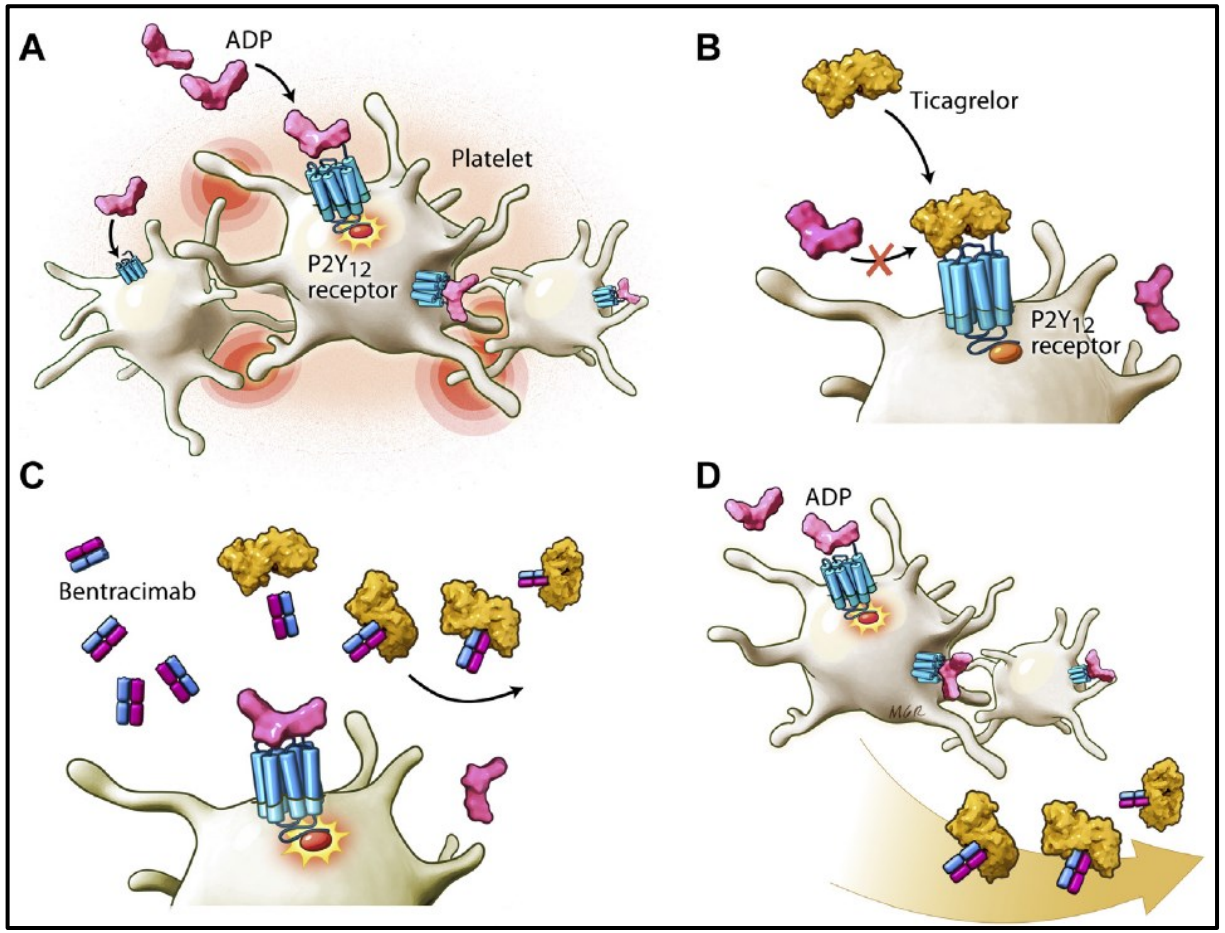
Bentracimab: An intravenous monoclonal antibody fragment designed to reverse the antiplatelet activity of ticagrelor[6]

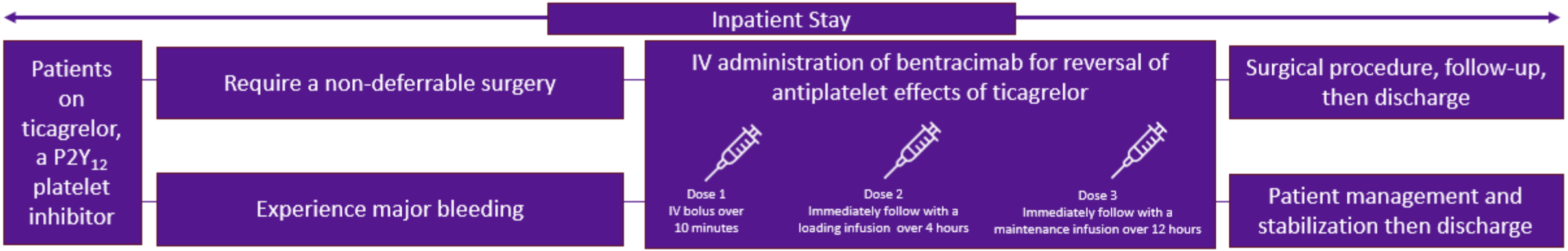
- The $P2Y_{12}$ receptor is activated by adenosine diphosphate (ADP) **(A)**, an important and potent platelet activator. Activated platelets are required to generate a stable blood clot.
- On platelets, ticagrelor reversibly binds to the $P2Y_{12}$ receptor. This induces a conformational change that prevents ADP from signaling through to the $P2Y_{12}$ receptor, inhibiting platelet activation **(B)**.
- Bentracimab is a recombinant human IgG1 monoclonal antibody fragment that binds to free ticagrelor with high affinity and specificity. This allows ADP to activate platelets while the bentracimab:ticagrelor complex is eliminated from the bloodstream **(C and D)**.



There Is no ICD-10-PCS procedure code to identify the inpatient intravenous (IV) administration of bentracimab

Proposed indication: Bentracimab is a human monoclonal antibody fragment (Fab) indicated when reversal of antiplatelet effects of ticagrelor is needed:

- in patients experiencing major bleeding
- in patients requiring non-deferrable surgery or invasive procedure



- Bentracimab will be available in single-use 6g dose glass vials (ready for infusion, no reconstitution needed). For each patient, the administration regimen will use 3 x 6g dose vials.
- Bentracimab is expected to be primarily administered in the inpatient setting; its use will be documented in the patient's medical record in the same manner as other therapies that are administered via IV infusion. Clinical documentation may also appear in the surgeon's notes in the operating room or procedure room medical record and in the nurses' notes.

REVERSE-IT: A global Phase 3, multi-center, open-label prospective single-arm trial

Pre-specified interim analysis[1,6]

REVERSE-IT: **R**apid and Sustain**E**d ReVer**S**al of Ticagr**E**lor – **I**ntervention **T**rial

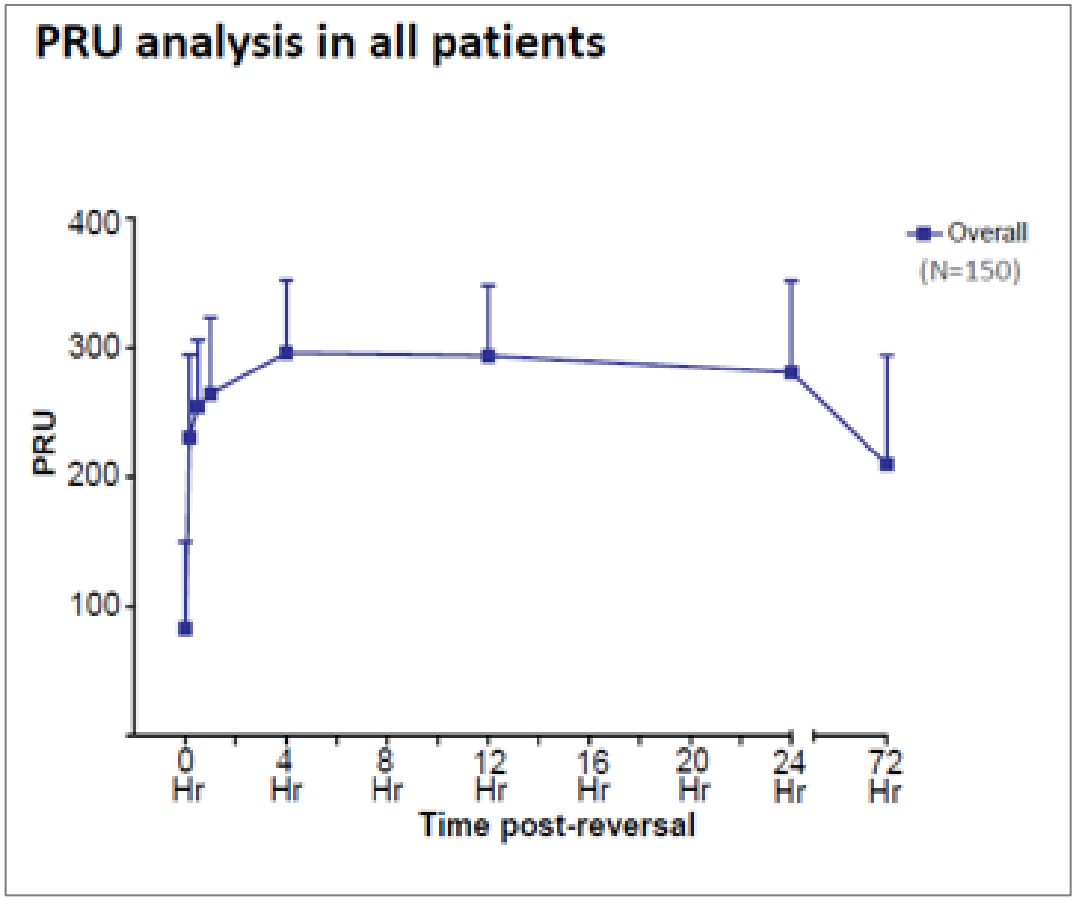
- Open-label, single-arm study in patients treated with ticagrelor who present with major bleeding or who require non-deferrable surgery
- 200 patients targeted for total enrollment; pre-specified interim analysis (n=150)[1]
- Primary reversal endpoint: The minimum % inhibition of $P2Y_{12}$ reaction units (PRU) within 4 hours of bentracimab initiation as assessed by the Verify Now™ PRUTest™ platelet function assay
- Primary hemostasis endpoint: Achievement of effective hemostasis within 24 hours after start of bentracimab infusion assessed in each population (surgery and major bleed) separately[7,8] and then pooled for primary endpoint analysis

REVERSE-IT Baseline Characteristics[1]

Characteristic	Surgical (N=142)	Bleeding (N=8)	Total (N=150)
Age (years), Mean (SD)	64.8 (10.46)	67.0 (13.40)	65.0 (10.59)
Sex, n (%)			
Male	112 (78.9)	4 (50.0)	116 (77.3)
Female	30 (21.1)	4 (50.0)	34 (22.8)
Weight (kg), Mean (SD)	85.2 (19.33)	76.9 (29.72)	84.8 (19.87)
Height (cm), Mean (SD)	170 (8.62)	169 (11.69)	171 (8.75)
BMI (kg/m^2), Mean (SD)	29.1 (6.21)	27.8 (11.46)	29.1 (6.49)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.7)	2 (25.0)	3 (2.0)
Not Hispanic or Latino	141 (99.3)	6 (75.0)	147 (98.0)
Race, n (%)			
White	118 (83.1)	7 (87.5)	125 (83.3)
Black or African American	5 (3.5)	1 (12.5)	6 (4.0)
Asian	16 (11.3)	0 (0)	16 (10.7)
American Indian or Alaskan	1 (0.7)	0 (0)	1 (0.7)
Other	2 (1.4)	0 (0)	2 (1.3)
Hypertension	114 (80.3)	6 (75.0)	120 (80.0)
Diabetes	57 (40.1)	2 (25.0)	59 (39.3)
Myocardial infarction	118 (83.1)	4 (50.0)	122 (81.3)
Baseline eGFR (MDRD)			
eGFR < 60, n (%)	32 (22.5)	0 (0)	32 (21.3)
Time from last ticagrelor, n (%)			
0-1 days	100 (70.4)	7 (87.5)	107 (71.3)
2 days	29 (20.4)	1 (12.5)	30 (20.0)
3 days	13 (9.2)	0 (0)	13 (8.7)

Bentracimab provided immediate and sustained reversal of ticagrelor's antiplatelet effects

REVERSE-IT pre-specified interim analysis[1]



- A highly significant 135% reduction in inhibition of $P2Y_{12}$ reaction units (PRU) was observed with bentracimab in the overall cohort (n=150), indicating achievement of the primary reversal end point (P<0.001) across all timepoints (P<0.001)
  - Ticagrelor reversal occurred within 5 to 10 minutes of initiation of bentracimab infusion and remained significant through 24 hours before declining modestly by 72 hours
- Platelet function was restored for adequate hemostasis
- Benefits were consistent in all pre-specified subgroups including those undergoing surgery and with major bleeding

Adjudicated surgical and bleeding hemostasis

REVERSE-IT: pre-specified interim analysis[1,6]

Adjudicated and Investigator-Reported Surgical Outcomes

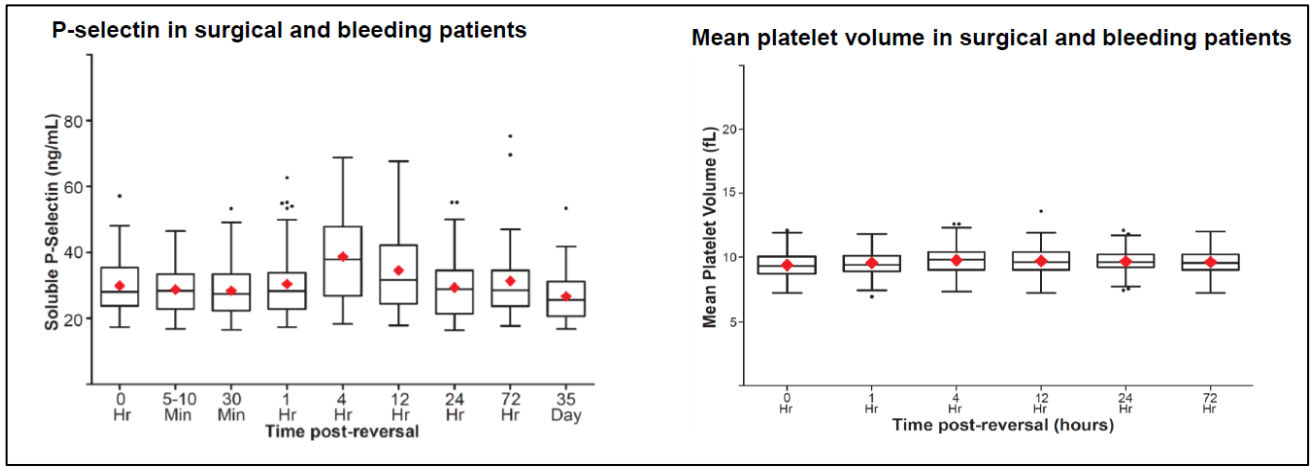
Hemostasis in Surgical Patients	n (%)
Adjudicated achieved hemostasis (N=113)	113 (100.0)
GUSTO Mild	75 (66.4)
GUSTO Moderate	38 (33.6)
GUSTO Severe	0 (0)
Investigator-reported achieved hemostasis (N=142)	135 (95.1)
Normal or mildly abnormal bleeding	110 (77.5)
Moderately abnormal	25 (17.6)
Severely abnormal or unknown	7 (4.93)
Blood Product Transfusions	**n (%)**
Total blood transfusions (pRBCs or whole blood)	56 (39.04)
Blood transfusions for bleeding event	10 (7.04)
Total platelets transfusions	19 (13.4)
Platelet transfusions for bleeding event	6 (4.22)
Other Surgical Outcomes	
Restarted $P2Y_{12}$ inhibition, n (%)	111 (74%)
Time to restart (median), days (min, max)	2 (0, 22)
Total mortality, n (%)	4 (2.8)

pRBC, packed red blood cells. Investigators were required to specify in case report forms whether allogeneic blood and platelet products were transfused for bleeding events or other routine perioperative use. Total transfusions and transfusions for bleeding events are shown above.

Adjudicated and Investigator-Reported Bleeding Outcomes

Hemostasis in Bleeding Patients	n (%)
Adjudicated achieved hemostasis (N=9)	7 (77.8)
Excellent hemostasis	6 (66.7)
Good hemostasis	1 (11.1)
Poor hemostasis	1 (11.1)
Unable to determine	1 (11.1)
Investigator-reported achieved hemostasis (N=8)	7 (87.5)
Median time to hemostasis, hrs (min, max)	23 (112, 7)
Blood Product Transfusions	**n (%)**
Total blood transfusions (pRBCs or whole blood)	5 (62.5)
Blood transfusions for bleeding event	5 (62.5)
Total platelet transfusions	2 (25.0)
Platelet transfusions for bleeding event	1 (12.5)
Other Outcomes in Bleeding Patients	
Restarted $P2Y_{12}$ inhibition, n (%)	5 (62.5)
Time to restart (median), days (min, max)	5 (0, 8)
Total mortality, n (%)	0 (0.0)

Safety Summary
REVERSE-IT: pre-specified interim analysis[1,6]



Effect of Bentracimab Treatment on P-Selectin and Mean Platelet Volume (MPV). Soluble P-selectin and MPV were measured pre-dose and at multiple timepoints post-initiation of bentracimab treatment to assess for a potentially prothrombotic rebound increase in platelet reactivity post-reversal. Shown are the soluble P-selectin levels in surgical and bleeding patients treated with bentracimab (left). MPV was measured in surgical and bleeding patients treated with bentracimab (right).

Adjudicated Thrombotic Events Occurring Post-Reversal

Type of Event	Patient Type	Days from Bentracimab and Surgery	P2Y12 Restarted Before Event	Related to Bentracimab
51 yr old man, s/p CABG	Myocardial infarction	7	Yes	No
78 yr old woman, s/p CABG	Transient ischemic attack	2	Yes	No
70 yr old man, s/p CABG	Lacunar stroke	1	No	No
58 yr old man, s/p CABG	Anterior, inferior STEMI with total graft occlusion	1	No	No
69 yr old man, s/p CABG, intraortic balloon pump, and thrombectomy	RLE arterial thromboembolism	1	No	No
73 yr of woman, s/p CABG	Acute ischemic stroke	5	No	No
44 yr old male, s/p CABG	Acute coronary syndrome with graft failure	29	Yes	No
47 yr old man, s/p CABG +aortic dissection repair	Acute ischemic right leg immediately post-op	1	No	No

- A total of 45 patients (30%) experienced serious but not drug-related AEs, including sepsis (3%) and septic shock (2%)
- There were no drug-related serious adverse events (AEs) or allergic or infusion-related reactions

With bentracimab as a new standard of care, the benefit-risk profile in ticagrelor treated patients requiring non-deferrable surgery or with major bleed will be enhanced

- Results from the pre-specified interim analysis of the Phase 3, REVERSE-IT study demonstrate clinically meaningful and potentially life-saving benefits of bentracimab for patients taking ticagrelor who are in need of non-deferrable surgery or invasive procedure or who experience major bleeding.

- The antiplatelet effect of ticagrelor was rapidly and effectively reversed in both groups of patients.

- With immediate and sustained restoration of platelet function, bentracimab will contribute to an improved, streamlined, and consistent patient care pathway. This will relieve patients and physicians from making difficult choices between accepting the higher bleeding risk to perform non-deferrable procedures while taking ticagrelor and attempting to delay necessary invasive procedures with potential thrombotic risk while ticagrelor is discontinued.

- Patients will be able to remain on ticagrelor for the benefit of platelet inhibition until surgery, risks associated with surgery will be mitigated, and physicians will be able to restart oral antiplatelet therapy once hemostasis is reached, as needed for individual patients.

References

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