Bentracimab Immediately and Significantly Reverses the Antiplatelet Effects of Ticagrelor in Older People

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Disclosures

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This trial was funded by PhaseBio.

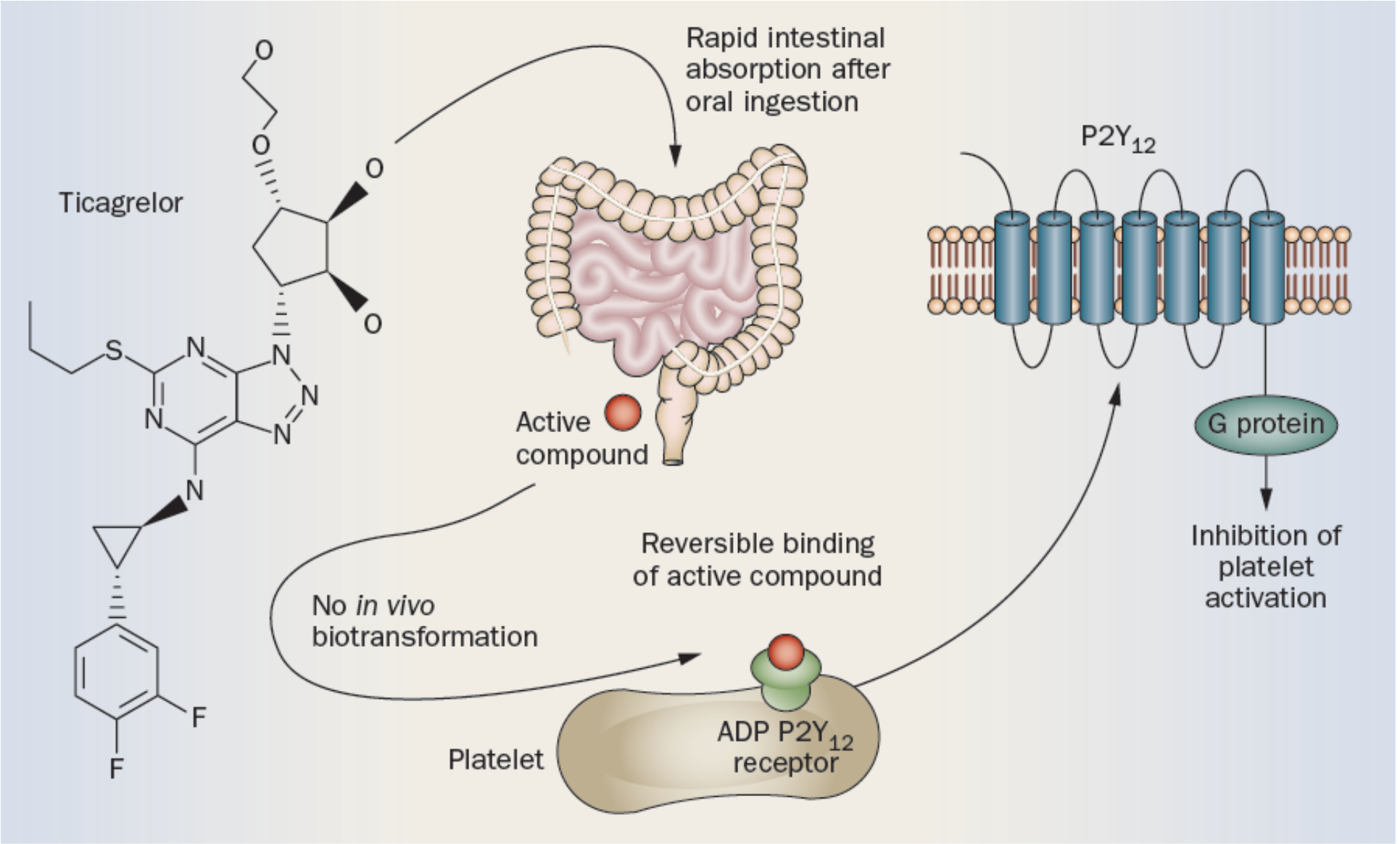
This presentation includes off-label and investigational uses of drugs.

Ticagrelor: Substantial Data, with Broad Label

- Ticagrelor is an oral $P2Y_{12}$ inhibitor that is effective (and FDA-approved) in patients with acute coronary syndromes, prior myocardial infarction, high-risk coronary artery disease, transient ischemic attack, and stroke, based on PLATO,[1,2] PEGASUS,[3,4] THEMIS,[5,6] THEMIS-PCI,[5,7] and THALES.[8]
- As with other antiplatelet drugs, spontaneous major bleeding and bleeding associated with urgent or emergent invasive procedures are concerns.
- The antiplatelet effects of ticagrelor cannot be reversed with platelet transfusion. Therefore, a rapid-acting reversal agent would be useful.

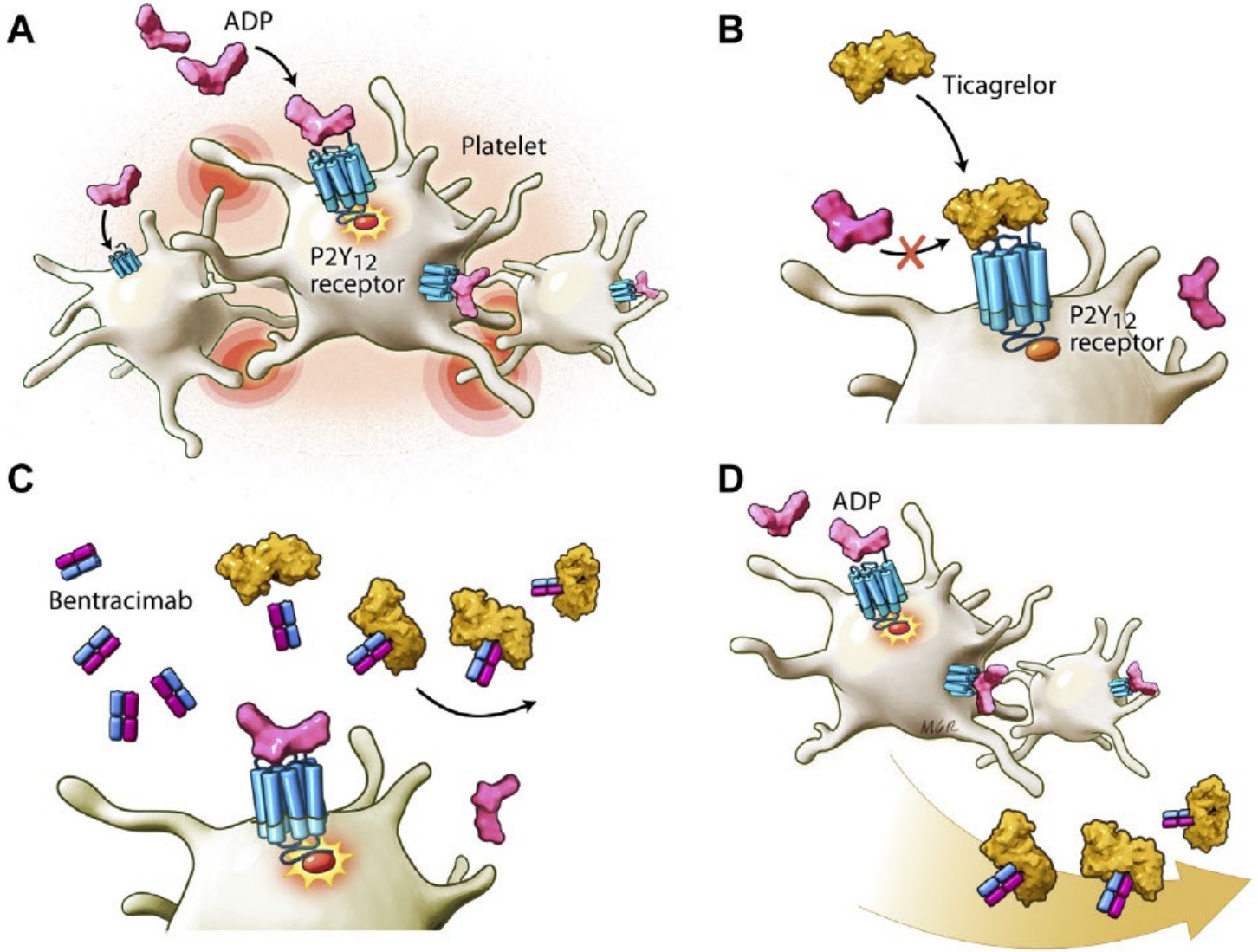
[1]James S, Akerblom A, Cannon CP, et al. *Am Heart J*. 2009;157:599-605.
[2]Wallentin L, Becker RC, Budaj A, et al. *N Engl J Med.* 2009;361:1045-57.
[3]Bonaca MP, Bhatt DL, Braunwald E, et al. *Am Heart J*. 2014;167:437-44.
[4]Bonaca MP, Bhatt DL, Cohen M, et al. *N Engl J Med*. 2015;372:1791-800.
[5]Bhatt DL, Steg PG, et al. *Clinical Cardiology* 2019; 42: 498-505.
[6]Steg PG, Bhatt DL, et al. *N Engl J Med.* 2019;381:1309-1320.
[7]Bhatt DL, Steg PG, et al. *Lancet*. 2019;394:1169-1180.
[8]Johnston SC, Amarenco P, et al. *N Engl J Med* 2020;383:207-217.

Ticagrelor: Reversible Mechanism of Action



Bhatt DL. ***Nature Reviews Cardiology*****. 2009;6:737-38.**

Bentracimab: An Intravenous Monoclonal Antibody



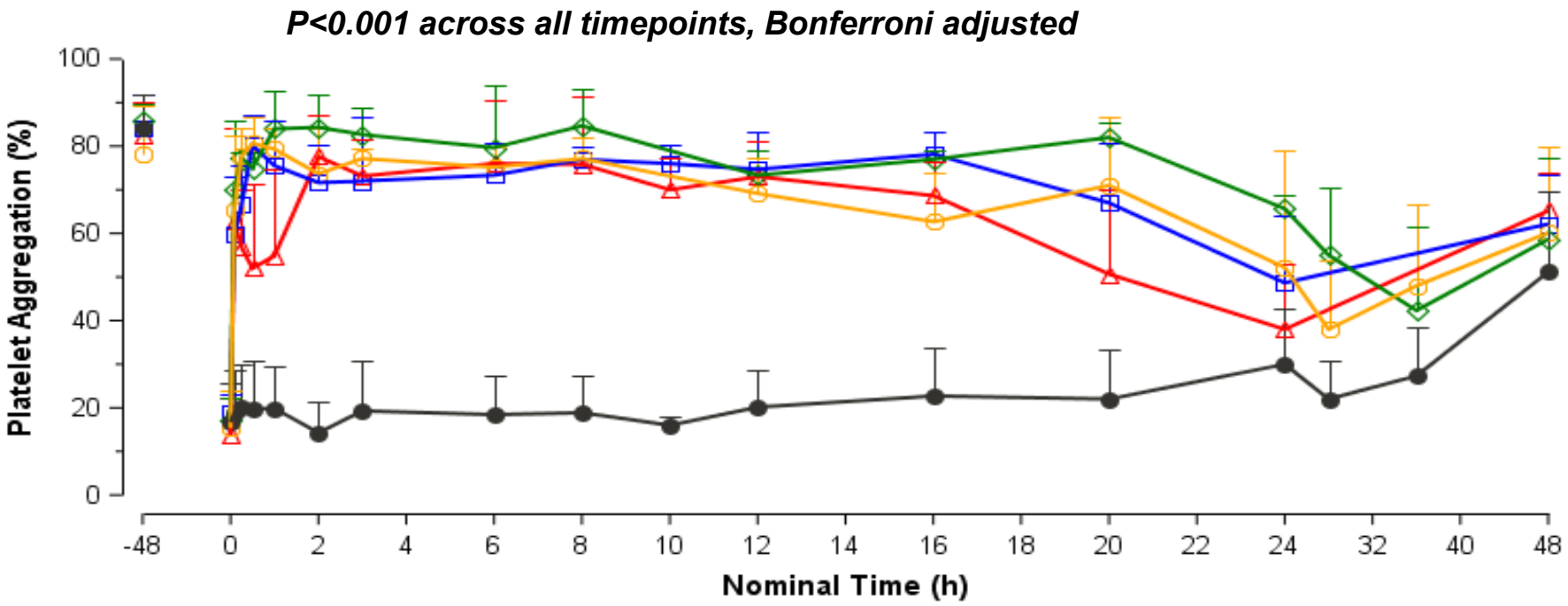
The P2Y12 receptor is activated by adenosine diphosphate (ADP) (A).

On platelets, ticagrelor reversibly binds to the P2Y12 receptor. This induces a conformational change which prevents ADP from signaling through to the P2Y12 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&D).

Ha ACT, Bhatt DL, Rutka JT, Johnston SC, Mazer CD, Verma S. *J Am Coll Cardiol*. 2021;78:1372-1384.

Immediate Onset and Sustained Duration of Ticagrelor Reversal Using Bentracimab (formerly PB2452)



P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h
7	0.040	0.040	0.131	0.037	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.224
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020

Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected. P-values for time point 24 hours or above are not significant.

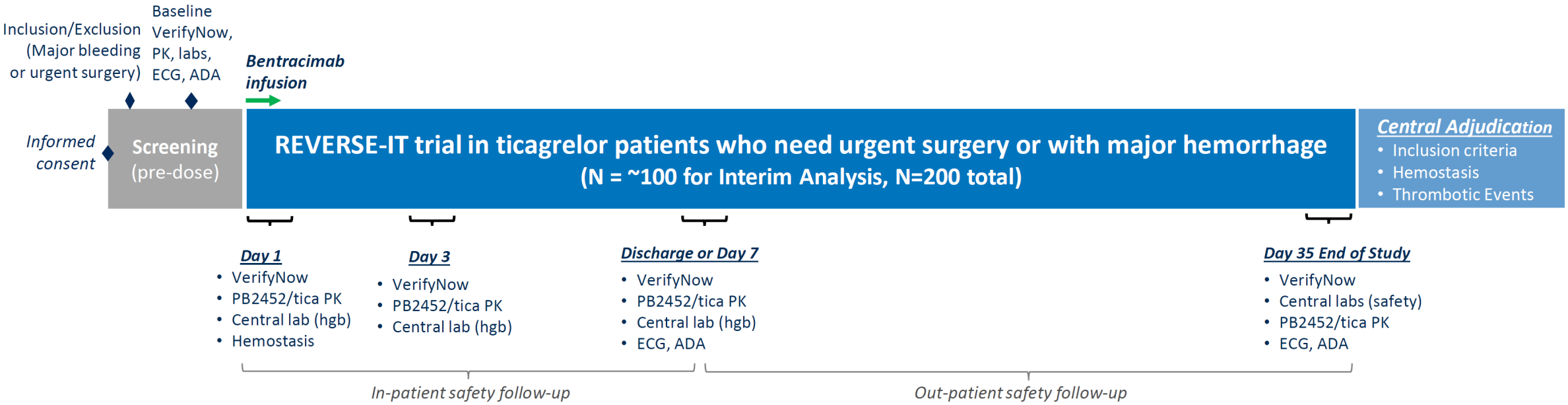
1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion** of 18 g bentracimab.
2. Significant reversal was observed 5 minutes after initiation of bentracimab infusion.
3. Duration of reversal was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion.

PB2452 18g(C7)
PB2452 18g(C8)
PB2452 18g(C9)
PB2452 18g(C10)
Placebo (C7-10)

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019; 380:1825-1833. ACC LBCT 2019.

LTA= light transmittance aggregometry; ADP is the agonist

REVERSE-IT: Phase 3 Interim Analysis Performed



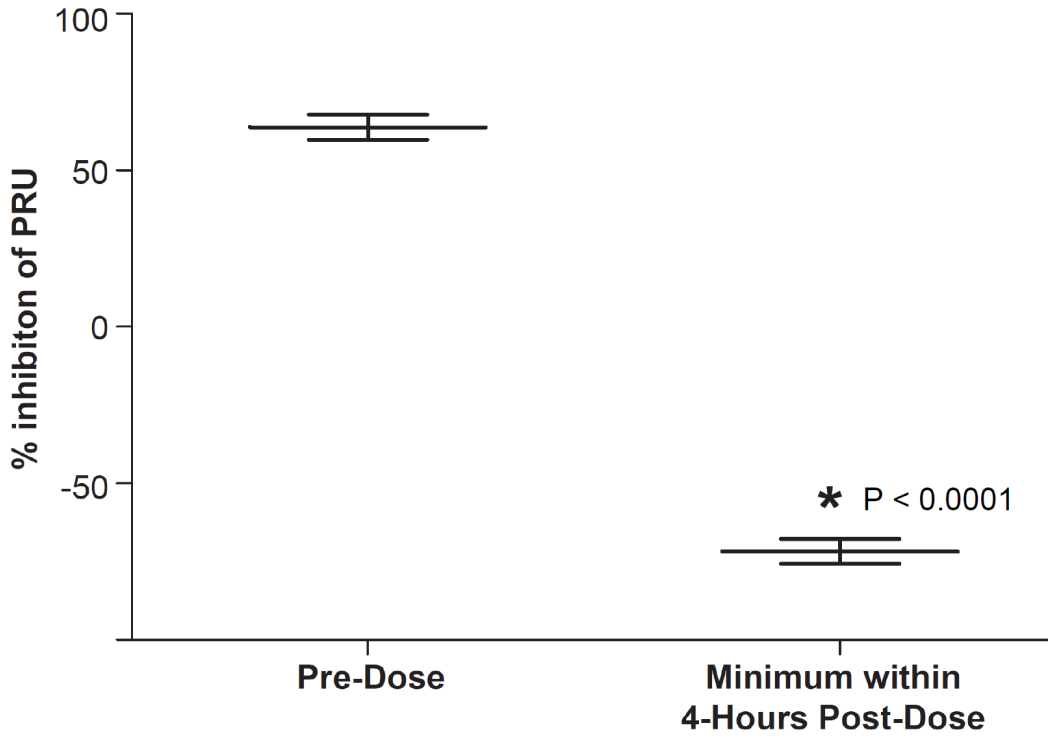
REVERSE-IT Study Design

Multicenter, open-label, prospective single-arm study **of reversal of the antiplatelet effects of ticagrelor with bentracimab in at least 200 patients who present with uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedures. Enrollment is ongoing in North America and Europe. Patients with use of ticagrelor within the prior 3 days who require urgent ticagrelor reversal are eligible for enrollment. Bentracimab was granted Breakthrough Therapy designation by the FDA and PRIME (priority medicines) designation by the European Medicines Agency, and in consultation with them, we performed this *prespecified, interim analysis* to support a BLA submission for an accelerated (conditional) approval.**

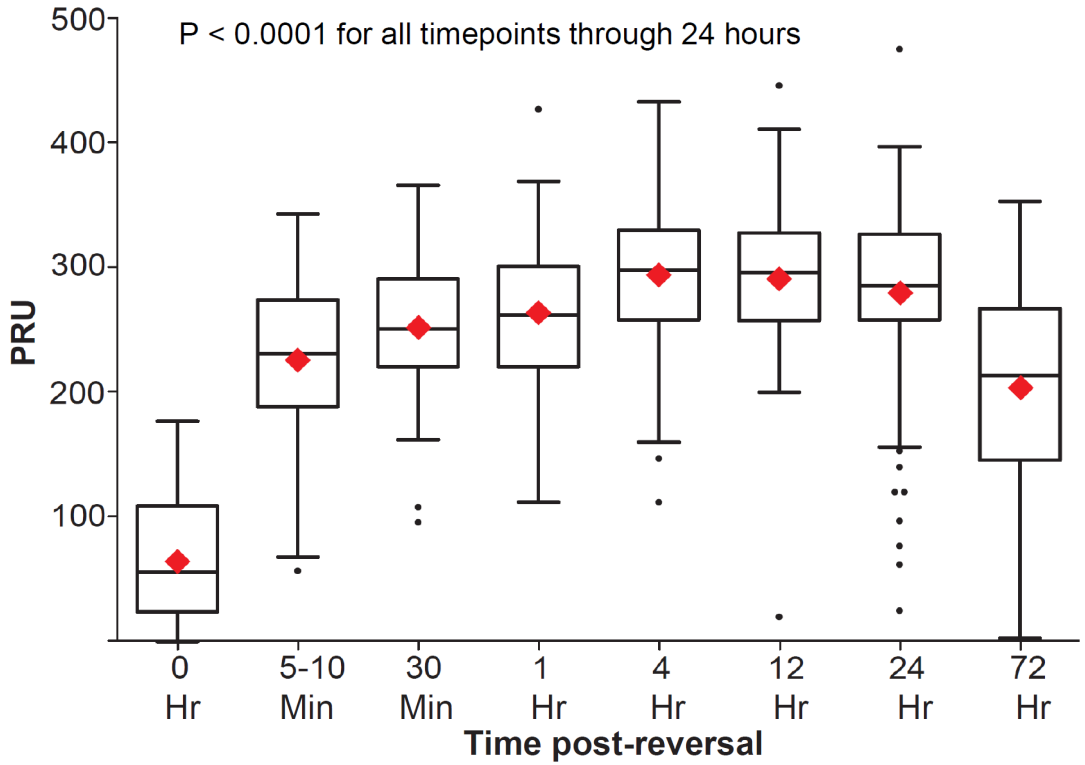
Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Platelet Function Tests

Percent Inhibition of PRU



PRU Analysis of Reversal



Ticagrelor Reversal with VerifyNow PRU. Ticagrelor reversal is shown as a reduction in % inhibition of PRU or PRI and as an increase in PRU or platelet reactivity index at multiple timepoints post-treatment. Shown is the comparison of % inhibition of PRU pre-treatment and the minimum % inhibition of PRU within 4 hours of initiation of bentracimab infusion (left). Onset and duration of ticagrelor reversal in bentracimab-treated patients observed as an increase in PRU with P value at each timepoint Bonferroni adjusted (right).

Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Adjudicated Surgical Hemostasis

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.

Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Adjudicated Thrombotic Events

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

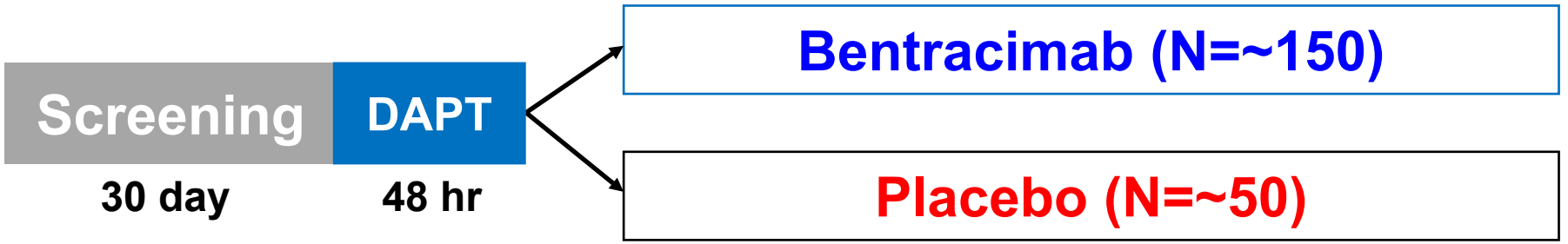
Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

REVERSE-IT: Interim Analysis Summary

- **Bentracimab**, a specific reversal agent for ticagrelor, provided immediate and sustained reversal of ticagrelor's antiplatelet effects, in ticagrelor-treated patients undergoing invasive procedures or with major bleeding.
- Rates of effective hemostasis were adjudicated as good or excellent in >90% of cases, with no drug-related serious adverse events or allergic or infusion-related reactions.
- The benefits were consistent in all prespecified subgroups, including those undergoing surgery or with major bleeding.

Bhatt DL, Pollack CV, Mazer CD, et al. *NEJM Evid*. 2021;1:EVIDoa2100047.

Phase 2B Study Design



Randomized, double-blind, placebo-controlled trial (3 active:1 placebo)

- 50-80 year-old volunteers pretreated with ticagrelor and aspirin for 48 hours
- Primary endpoint - inhibition of PRU

Baseline Characteristics

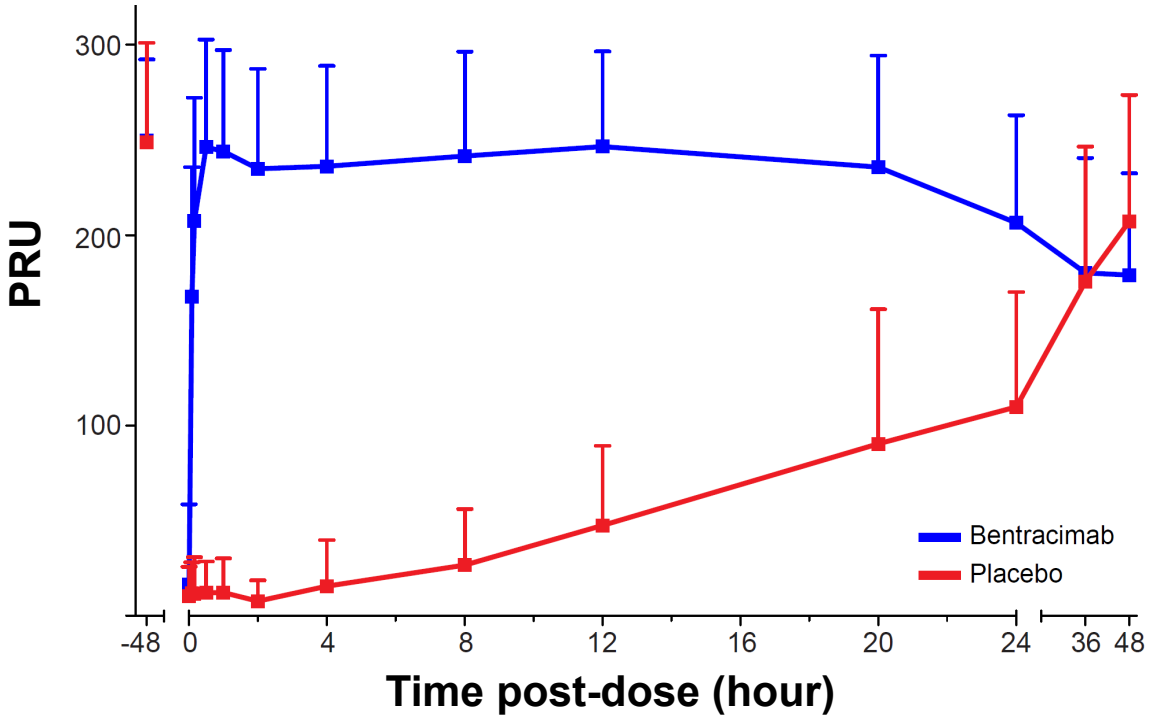
Characteristic Statistic	Placebo (N = 51)	Bentracimab (N = 154)	Total (N=205)
Age* [years]			
n	51	154	205
Mean (SD)	60.9 (6.76)	61.4 (6.90)	61.2 (6.85)
Median	60	61	61
Min, Max	50, 78	50, 80	50, 80
Age Group, n (%)			
<= 65 years	39 (76.47)	107 (69.48)	146 (71.22)
> 65 years	12 (23.53)	47 (30.52)	59 (28.78)
Sex, n (%)			
Male	21 (41.18)	82 (53.25)	103 (50.24)
Female	30 (58.82)	72 (46.75)	102 (49.76)
Ethnicity, n (%)			
Hispanic or Latino	7 (13.73)	18 (11.69)	25 (12.20)
Not Hispanic or Latino	44 (86.27)	136 (88.31)	180 (87.80)
Race, n (%)			
Asian	0	3 (1.95)	3 (1.46)
Black or African American	8 (15.69)	29 (18.83)	37 (18.05)
White	43 (84.31)	121 (78.57)	164 (80.00)
Other	0	1 (0.65)	1 (0.49)

Baseline Characteristics

Characteristic Statistic	Placebo (N = 51)	Bentracimab (N = 154)	Total (N=205)
Renal Group, n (%)			
Normal	16 (31.37)	46 (29.87)	62 (30.24)
Mild	30 (58.82)	91 (59.09)	121 (59.02)
Moderate	4 (7.84)	14 (9.09)	18 (8.78)
Country, n (%)			
Canada	8 (15.69)	23 (14.94)	31 (15.12)
United States	43 (84.31)	131 (85.06)	174 (84.88)
Weight [kg]			
n	51	154	205
Mean (SD)	80.4 (12.93)	80.8 (14.77)	80.7 (14.30)
Median	83.1	81.6	81.6
Min, Max	51.0, 106.0	51.0, 117.5	51.0, 117.5
Height [cm]			
n	51	154	205
Mean (SD)	168.3 (9.99)	169.9 (10.17)	169.5 (10.12)
Median	167.6	170.0	169.5
Min, Max	149.0, 188.2	148.8, 194.5	148.8, 194.5
BMI [kg/m^2]			
n	51	154	205
Mean (SD)	28.3 (3.49)	27.9 (3.71)	28.0 (3.65)
Median	28.3	27.8	27.9

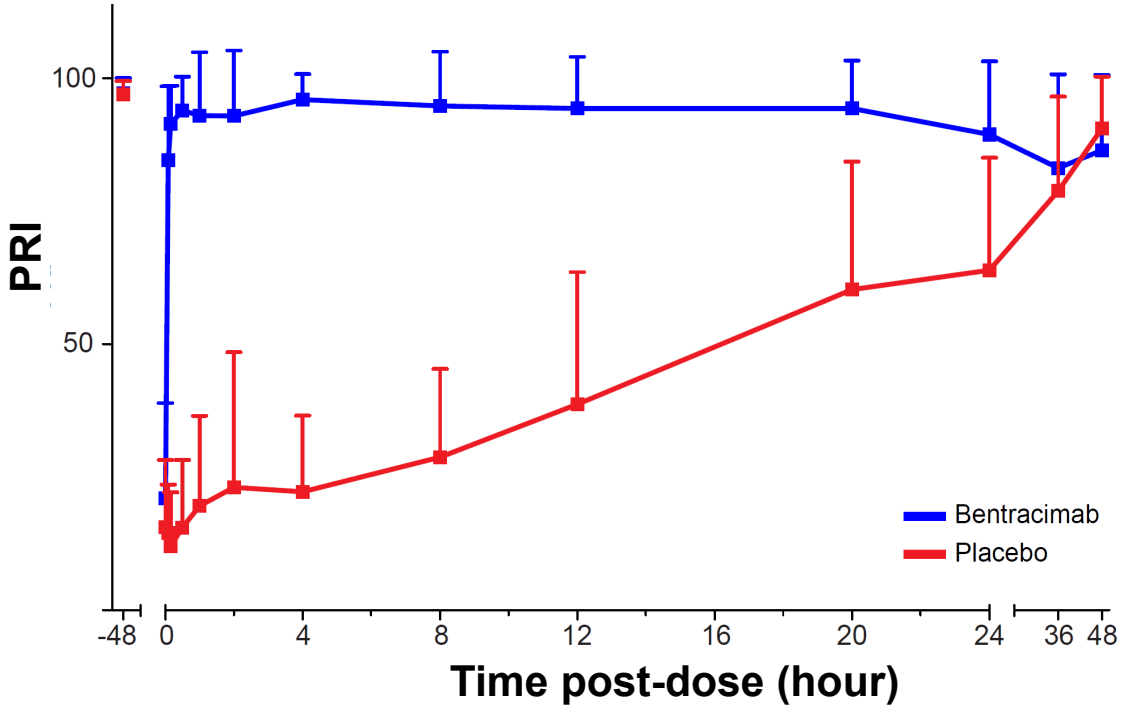
Immediate, Sustained Ticagrelor Reversal with Bentracimab
(VerifyNow PRU and VASP PRI Assays)

PRU analysis
(Bentracimab vs Placebo 0-48 hours)



Timepoint	5 min	10 min	30 min	1 hr	4 hr	12 hr	20 hr	24 hr	36 hr	48 hr
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.1102	0.0127

PRI analysis
(Bentracimab vs Placebo 0-48 hours)

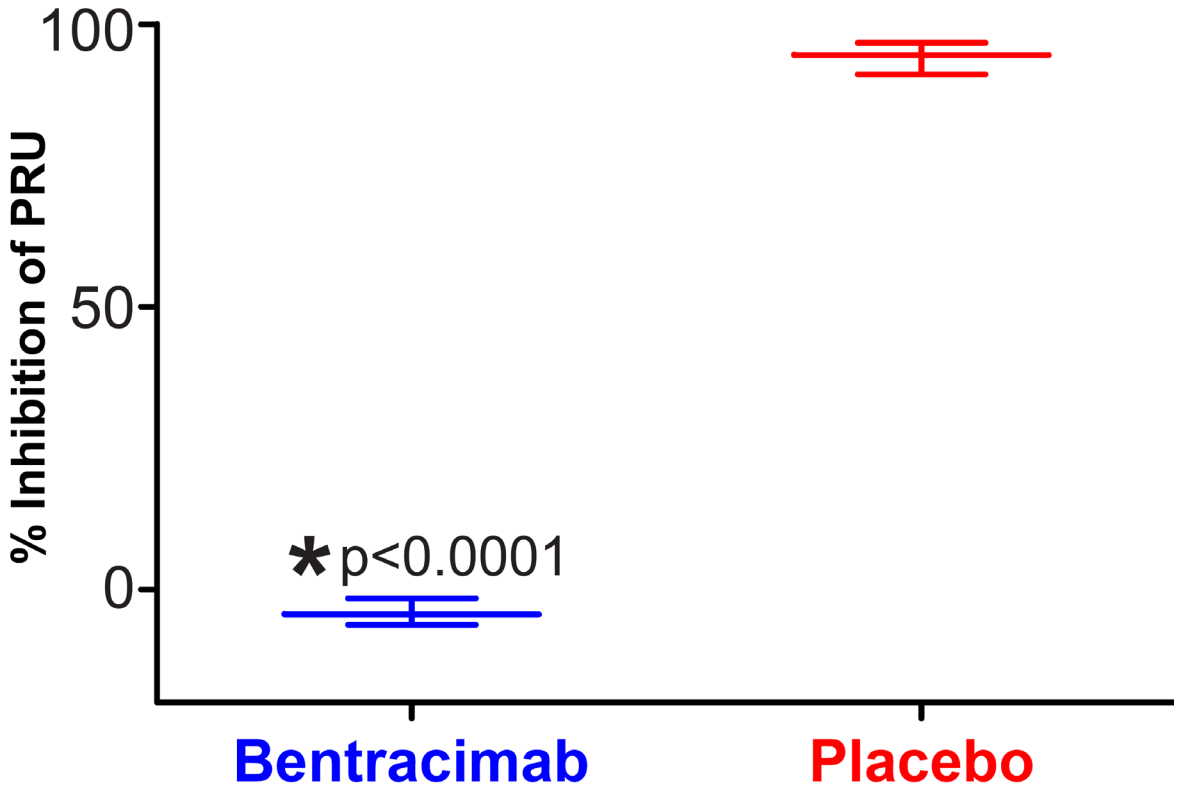


Timepoint	5 min	10 min	30 min	1 hr	4 hr	12 hr	20 hr	24 hr	36 hr	48 hr
P value	0.0572	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.2802	0.4562

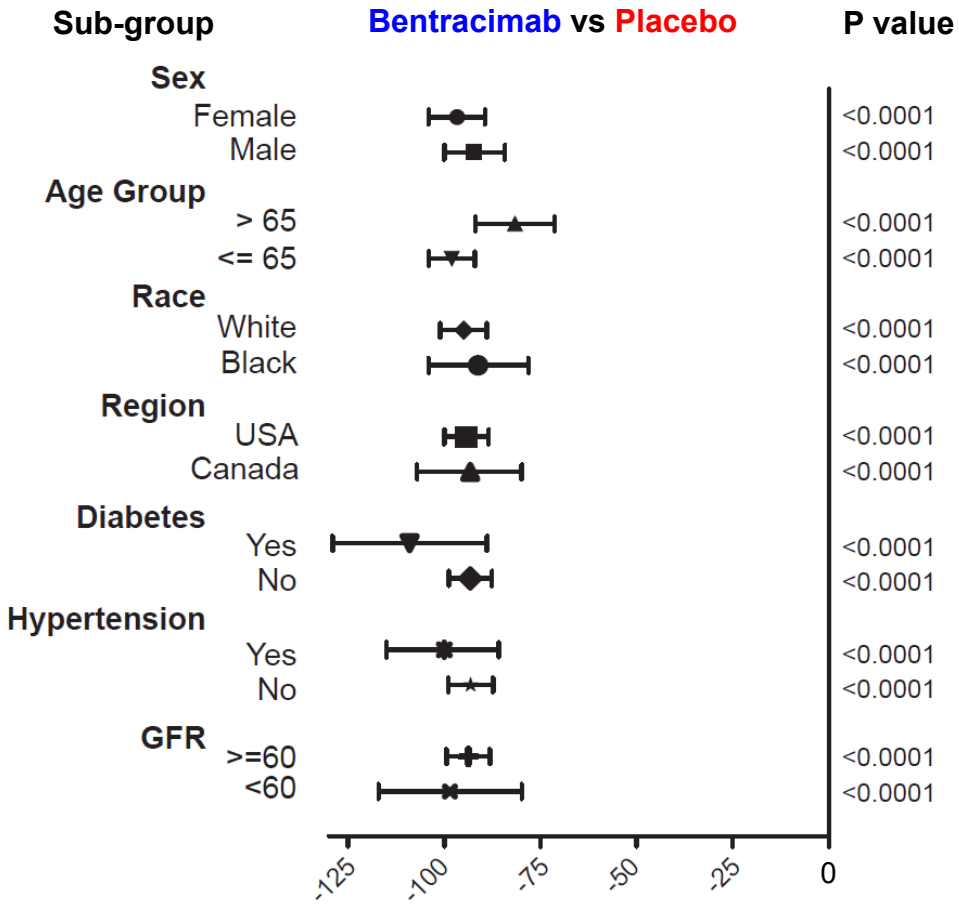
Bentracimab achieved immediate and sustained reversal in 50-80 year-olds pretreated with DAPT

Primary Endpoint and Subgroup Analysis

Primary Endpoint Analysis
(Minimum % inhibition of PRU within 4 hrs)

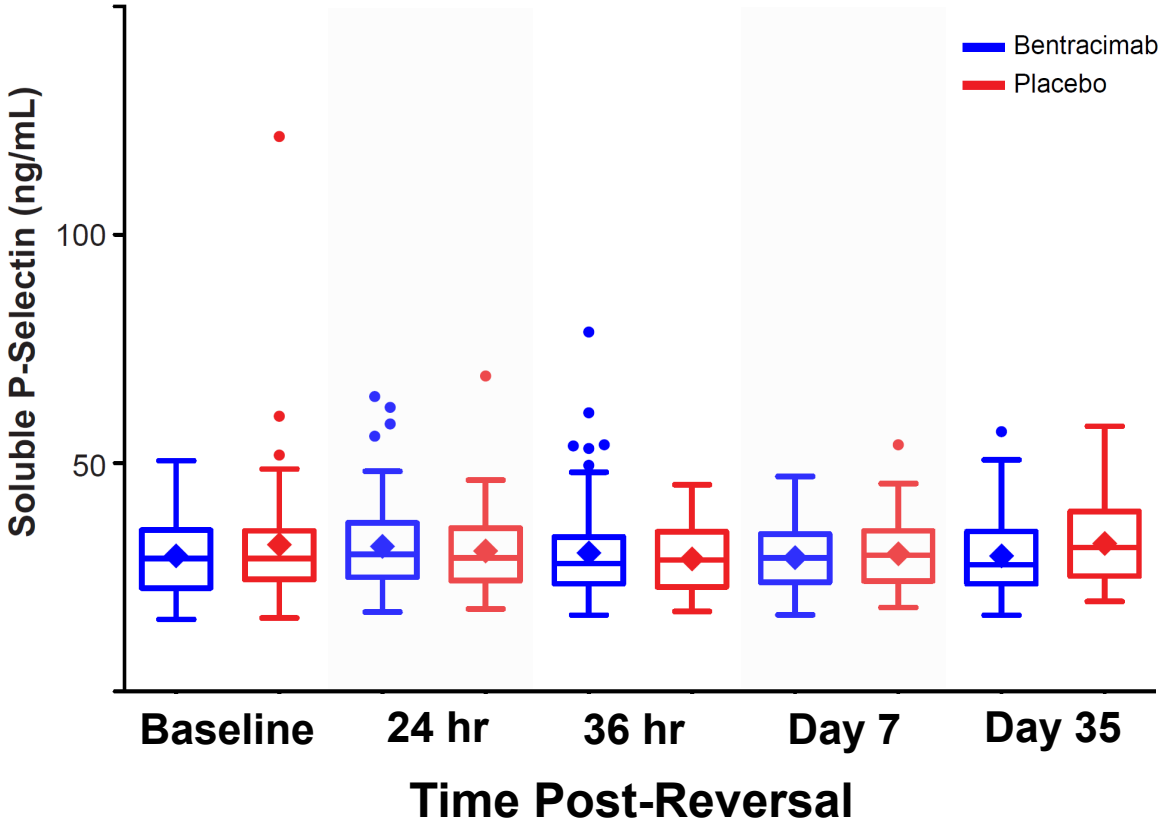


Forest Plot of Treatment Difference
(Mean change in minimum % inhibition of PRU)

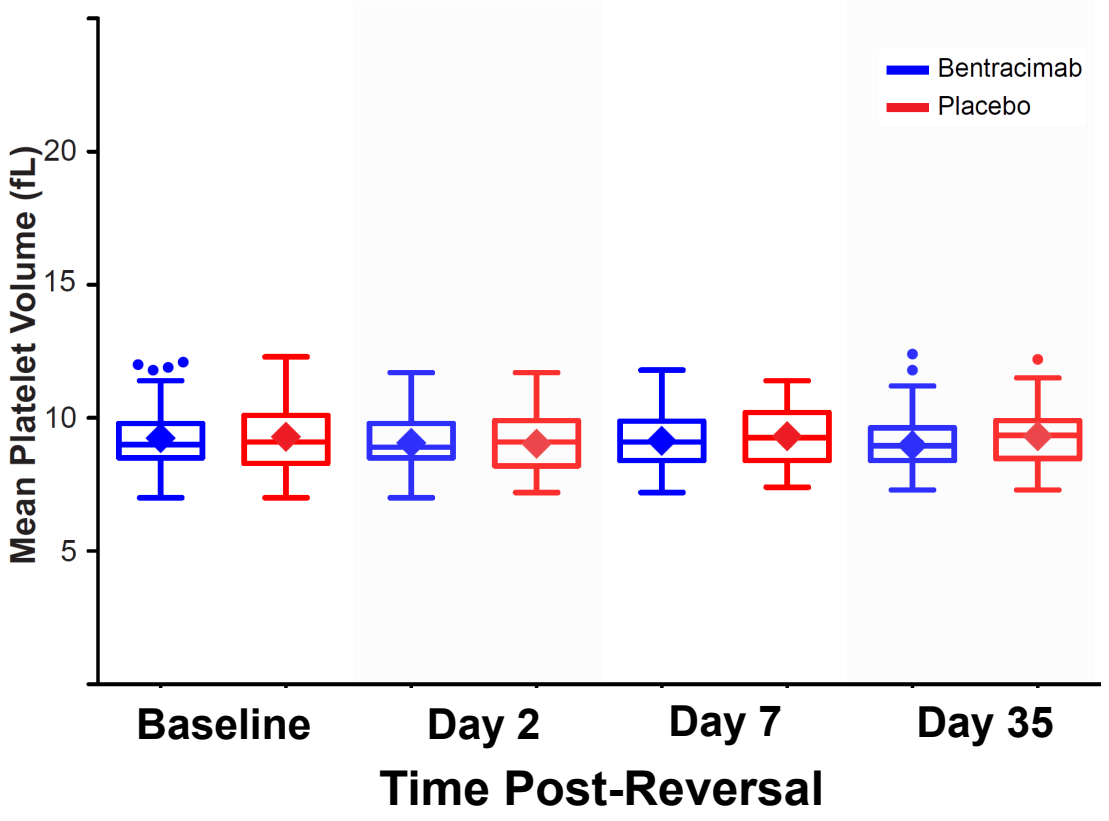


Markers of Platelet Activation

P-Selectin Analysis



Mean Platelet Volume Analysis



No evidence of elevated platelet activation post-reversal in Bentracimab or Placebo groups

Bentracimab Safety Profile

Treatment Emergent Adverse Events in >1 Subject

TEAEs	Placebo N = 51 n (%)	Bentracimab* N = 154 n (%)
Headache	4 (7.84)	6 (3.90)
Ecchymosis	2 (3.92)	6 (3.90)
Contusion	2 (3.92)	5 (3.25)
Vessel puncture bruise	1 (1.96)	4 (2.60)
Nausea	2 (3.92)	3 (1.95)
Diarrhea	1 (1.96)	3 (1.95)
Edema	1 (1.96)	2 (1.30)
Dizziness	1 (1.96)	2 (1.30)
Infusion site extravasation	0	2 (1.30)
Pain in extremity	0	2 (1.30)
Asymptomatic COVID-19	0	2 (1.30)
Catheter site bruise	1 (1.96)	1 (0.65)
Constipation	1 (1.96)	1 (0.65)
Occult blood	1 (1.96)	1 (0.65)
Hematochezia	2 (3.92)	0
Hyperglycemia	2 (3.92)	0

*There was no significant difference between Bentracimab and Placebo for any TEAE, P=0.52

All Serious Adverse Events

Preferred Term	Placebo (N=51) n (%)	Bentracimab (N=153) n (%)
Total SAEs	1	0
Drug-related SAEs	0	0
Unrelated SAEs	1	0
Car accident	1	0

- **No drug-related SAE's**
- **No thrombotic events**

Limitations

- We studied 50-80 year-old volunteers and not patients with known coronary artery disease, although no reason to believe **bentracimab** would behave differently.
- The sample size was modest, although it was well-powered for pharmacodynamic endpoints, and all platelet assay results were consistent and highly statistically significant.
- This study was not designed to evaluate the impact of **bentracimab** on clinical bleeding events.

Conclusions

- Compared with placebo, **bentracimab** **significantly restored platelet function as measured** by multiple assays by binding and eliminating free ticagrelor and ticagrelor active metabolite.
- **No thrombotic events and no SAEs** reported in volunteers randomized to **bentracimab**, confirming the safety profile.
- Based on these data, **bentracimab** **appears to be a very promising option for ticagrelor reversal**.
- Assessment of **bentracimab's** clinical effect on patients with bleeding awaits completion of the **REVERSE-IT** study.

BRIGHAM AND WOMEN'S HOSPITAL

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Thank You!

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