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End of Phase 1 Meeting Update

August 14, 2019

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PB2452 Highlights

- PB2452, a novel reversal agent for Brilinta® (ticagrelor), provided immediate and sustained reversal of ticagrelor's antiplatelet effects in a Phase 1 trial
- PB2452 received ***Breakthrough Therapy*** designation from FDA (May 2019)
- Reversal agent availability would further differentiate ticagrelor from other antiplatelet drugs
- PB2452 has the potential to transform treatment of ticagrelor patients by mitigating concerns regarding bleeding risks

Bhatt DL, Pollack CV, Weitz JI, et al. Antibody-Based Ticagrelor Reversal Agent in Healthy Volunteers. *N Engl J Med* 2019;Mar 17:[Epub ahead of print].
Presented by Dr. Deepak L. Bhatt at the American College of Cardiology Annual Scientific Session (ACC 2019), New Orleans, LA, March 17, 2019. Slides available at: https://www.acc.org/~/media/Clinical/PDF-Files/Approved-PDFs/2019/03/15/ACC19_Slides/Mar17_Sun/3pmET_Ticagrelor-Reversal-Agent-acc-2019.pdf

PB2452 End of Phase 1 Meeting
Meeting Results and Next Steps

- FDA has agreed that Accelerated Approval pathway is the appropriate regulatory pathway for PB2452
- Single, non-randomized, open label Phase 3 trial in both surgical and major bleeding populations planned to support a Biologics License Application (BLA)
  - BLA submission for Accelerated Approval to include data from interim analysis of first 100 subjects in the Phase 3 trial, targeting ~50 subjects in each of the major bleeding and surgical populations
  - VerifyNow® PRUTest® biomarker confirmed as the primary efficacy endpoint; has demonstrated high degree of correlation with other platelet function assays in Phase 1 and Phase 2a trials of PB2452
  - FDA recommended enrollment of 200 total patients in the Phase 3 trial to support full approval for surgical and major bleeding populations
- Ongoing Phase 2a trial will explore PB2452 reversal of supratherapeutic blood levels of ticagrelor that could result from ticagrelor overdosage or drug-drug interactions; dosing of these subjects to begin this quarter (Q3 2019)
- Phase 2b trial expected to begin in Q4 2019; will run in parallel with Phase 3 trial and complete in time for BLA filing
- Phase 3 trial is expected to begin in Q1 2020; based on an 18-month estimated enrollment timeline to reach interim analysis, a potential BLA submission in 2H 2022
- FDA recommended post-approval commitments include completion of the Phase 3 trial and the establishment of a patient registry

PB2452 - Novel reversal agent for ticagrelor

- Human monoclonal antibody fragment (Fab), delivered intravenously in the hospital
- Phase 1 Proof of Concept Trial completed
  - Selected for late-breaking oral presentation American College of Cardiology's Annual Scientific Session (March 17, 2019)
  - Simultaneously published in the *New England Journal of Medicine*
- Immediate and sustained reversal of ticagrelor antiplatelet effects
  - $P2Y_{12}$ receptor antagonist with demonstrated superior efficacy to clopidogrel
- Reversal agent availability would differentiate ticagrelor on safety vs. other oral antiplatelet agents
  - Growth in ticagrelor share of $P2Y_{12}$ market would increase need for reversal agent

Significant unmet need for antiplatelet agent reversal

Major Bleeding

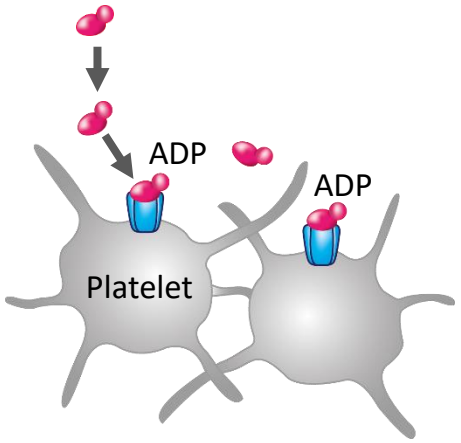
- All oral antiplatelet agents have the potential to cause major bleeding, which can be severe or even fatal
- PB2452 immediately and sustainably reverses the antiplatelet effects of ticagrelor

Urgent Surgery or Intervention

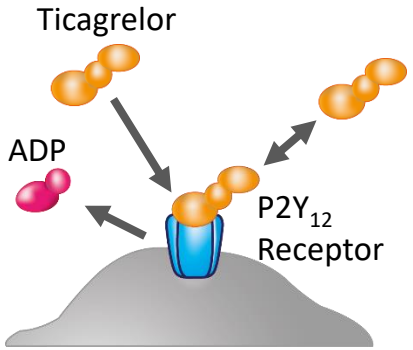
- Currently oral $P2Y_{12}$ agents, including ticagrelor, require a ≥5 day washout prior to surgery[1,2]
  - Urgent surgery cannot wait 5 days
  - High thrombotic risk during washout
- In the Phase 1 trial, PB2452 immediately and sustainably reversed ticagrelor inhibition of platelet activation
  - Enables immediate surgery

1. Plavix/clopidogrel Prescribing Information: https://packageinserts.bms.com/pi/pi_plavix.pdf, https://www.ema.europa.eu/en/documents/product-information/plavix-epar-product-information_en.pdf
2. Brilinta/Brilique/ticagrelor Prescribing Information: https://www.azpicentral.com/brilinta/brilinta.pdf#page=1, https://www.ema.europa.eu/en/documents/product-information/brilique-epar-product-information_en.pdf

PB2452: Well-Characterized Mechanism of Reversal of Ticagrelor

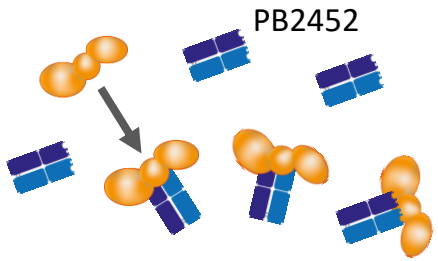


1. ADP binds to $P2Y_{12}$ receptor causing platelet aggregation

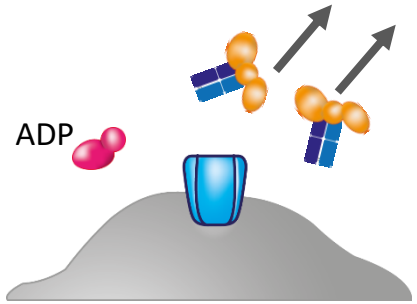


This is a reversible process with ticagrelor cycling on/off the $P2Y_{12}$ receptors

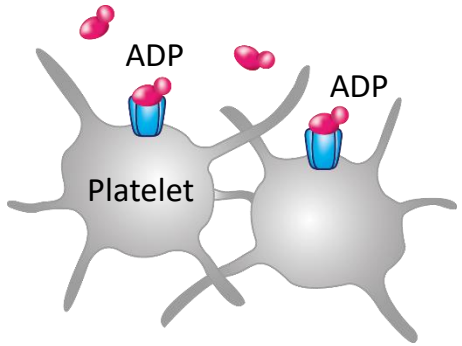
2. Ticagrelor binds to $P2Y_{12}$, inhibiting ADP-induced platelet aggregation



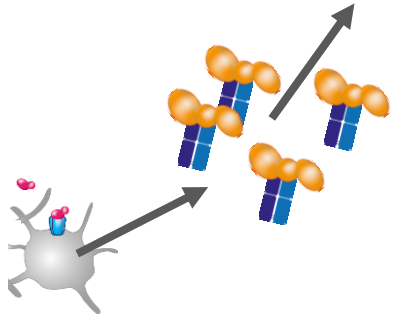
3. PB2452 binds to free ticagrelor with very high affinity



4. PB2452:ticagrelor binding is preferential to ticagrelor:$P2Y_{12}$ binding



5. As free ticagrelor is eliminated, ADP can again activate the $P2Y_{12}$ receptor, restoring platelet activity



6. PB2452:ticagrelor is eliminated from the bloodstream

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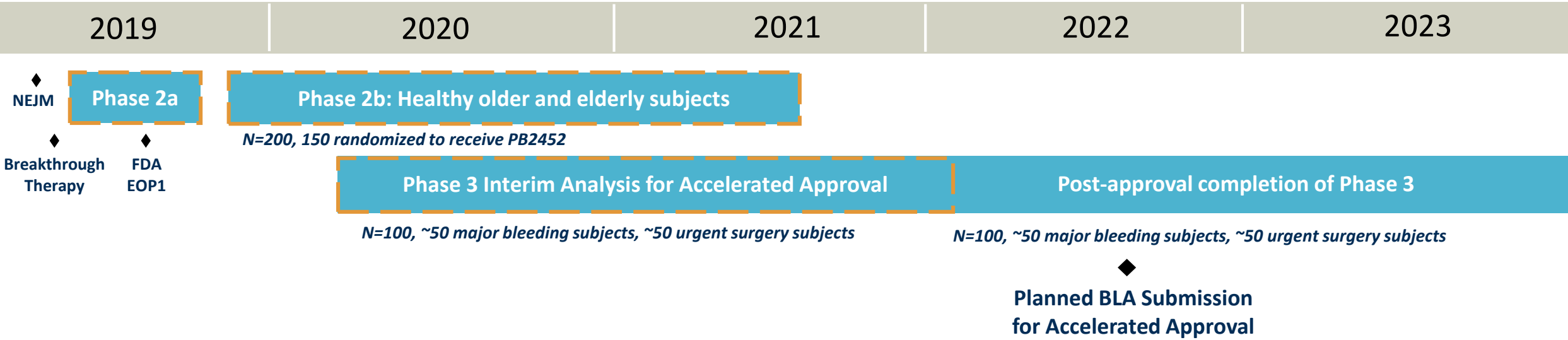
Development and Regulatory Timelines

Clinical Studies

BLA enabling data



Clinical Trial Timelines

- Phase 2a testing additional reversal regimen to cover 180 mg BID (2x recommended dose) in healthy subjects
  - Trial will be completed Q4 2019, not required to finish prior to Phase 2b
- Phase 2b expected to start Q4 2019, N=200 total, evaluation of dosing regimen and overall safety of PB2452 in healthy older and elderly subjects on DAPT
- Phase 3 initiation expected Q1 2020, N=200 total, evaluation of efficacy in ticagrelor-treated subjects with major bleeding events or requiring urgent surgery
  - Interim analysis of first 100 patients recommended by FDA for Accelerated Approval submission, with approximately 50 in each of the major bleeding and surgery populations

NEJM= New England Journal of Medicine, EOP1=End of Phase 1 Meeting, BID=twice per day, DAPT=Dual antiplatelet therapy (ticagrelor + aspirin), BLA=Biologics License Application

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PB2452 Phase 1 Proof-of-Concept Trial in Healthy Subjects

Cohort	Ticagrelor Pretreatment	PB2452 IV regimen	Volunteers Active:Placebo
1	None	0.1 g 30 min	3A:1P
2	None	0.3 g 30 min	3A:1P
3	None	1 g 30 min	3A:1P
4	180 mg PO + 90 mg BID x 2 days	1 g 30 min	6A:2P
5	180 mg PO + 90 mg BID x 2 days	3 g 30 min	6A:2P
6	180 mg PO + 90 mg BID x 2 days	9 g 30 min	6A:2P
7	180 mg PO + 90 mg BID x 2 days	18 g (3 g 5 min + 15 g 7 hr 55 min)	6A:2P
8	180 mg PO + 90 mg BID x 2 days	18 g (6 g 15 min + 6 g 3 hr + 6 g 8hr 45 min)	6A:2P
9	180 mg PO + 90 mg BID x 2 days	18 g (6 g 15 min + 6 g 4 hr + 6 g 12 hr)	3A:1P
10	180 mg PO + 90 mg BID x 2 days	18 g (6 g 10 min + 6 g 3 hr + 6 g 13 hr)	6A:2P

- Randomized, double-blind, placebo-controlled, single ascending dose trial (n=64)
  - 0.1 – 18 g of PB2452 infused intravenously over 0.5 – 16 hours
- Platelet function evaluated using three well established and commonly used assays; LTA, VerifyNow PRUTest and VASP
- Cohorts 9 and 10 achieved trial objectives, forming the basis for dosing in the Phase 2a trial in healthy older and elderly subjects

g = grams, min= minutes, A = active, P = placebo, mg=milligrams, hr=hours, PO=orally, BID= twice per day, LTA = light transmittance aggregometry, VASP = vasodilator stimulated phosphoprotein phosphorylation immunoassay

Bhatt DL, Pollack CV, Weitz JI, et al. Antibody-Based Ticagrelor Reversal Agent in Healthy Volunteers. *N Engl J Med* 2019;Mar 17:[Epub ahead of print].
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Treatment-Emergent Serious Adverse Events in Phase 1 Trial

None were drug-related per blinded investigator

Preferred Term	All Placebo (N=16) n (%)	All PB2452 (N=48) n (%)
Total Number of SAEs	0	2
PB2452-related SAEs	0	0
Unrelated SAEs*	0	2 (4.2)
Alcohol intoxication	0	1 (2.1)
Acute Respiratory Failure	0	1 (2.1)

*Both SAEs occurred in the same individual 4 days after discharge from the clinical site

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Treatment-Emergent Adverse Events

Preferred Term	All Placebo (N=16) n (%)	All PB2452 (N=48) n (%)
Total Number of TEAEs	3	27
Number of volunteers with at Least 1 TEAE	2 (12.5)	17 (35.4)
Infusion site bruising	0	4 (8.3)
Medical device site reaction	0	3 (6.3)
Infusion site extravasation	0	2 (4.2)
Vessel puncture site bruise	0	2 (4.2)
Abdominal pain	0	1 (2.1)
Acute respiratory failure	0	1 (2.1)
Alcohol poisoning	0	1 (2.1)
Blood urine present	0	1 (2.1)
Conjunctivitis	0	1 (2.1)
Contusion	1 (6.3)	0
Dizziness	0	1 (2.1)
Eyelid irritation	1 (6.3)	0
Gastroenteritis	0	1 (2.1)
Hematuria	0	1 (2.1)
Infusion site reaction	0	1 (2.1)
Musculoskeletal chest pain	1 (6.3)	0
Nasopharyngitis	0	1 (2.1)
Oropharyngeal pain	0	1 (2.1)
Pharyngitis streptococcal	0	1 (2.1)
Pneumonia aspiration	0	1 (2.1)
Skin abrasion	0	1 (2.1)
Upper limb fracture	0	1 (2.1)

- Treatment-emergent adverse events were limited mostly to mild injection site issues

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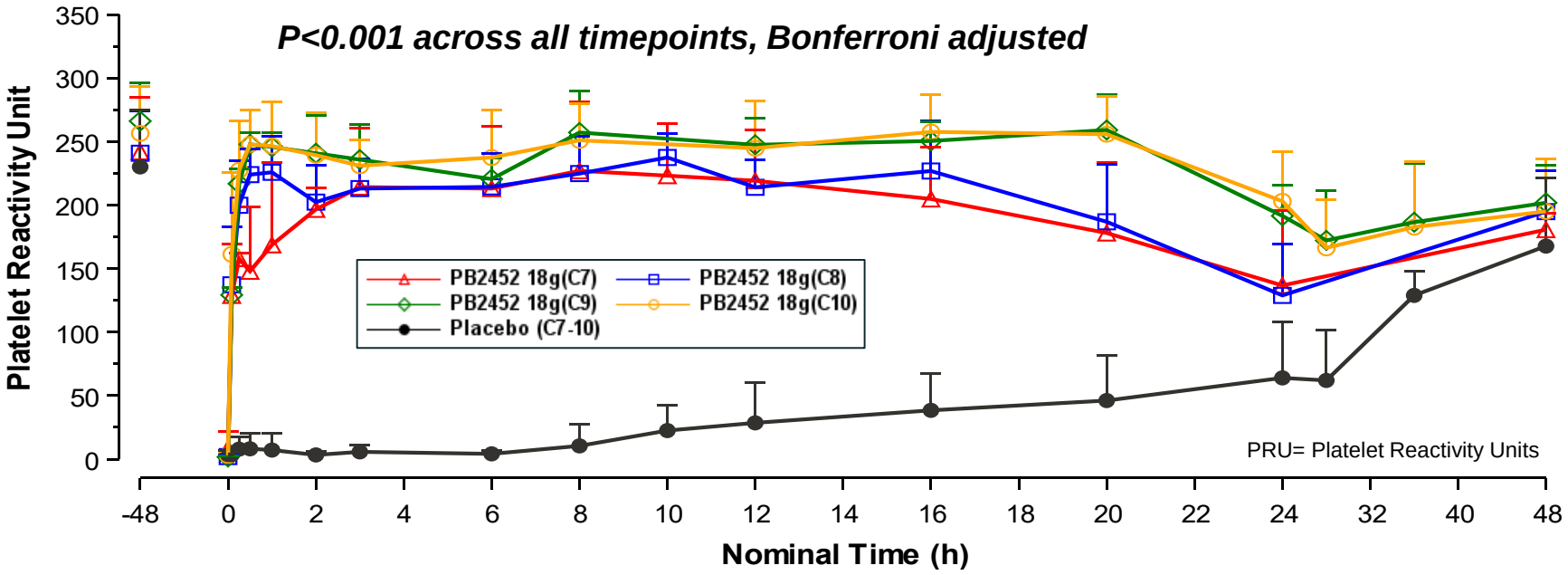
Onset and Duration of Ticagrelor Reversal – VerifyNow PRUTest

Platelet aggregation as observed in the PB2452 and placebo groups (Cohorts 7-10)



Key Trial Results

1. Immediate and sustained reversal with bolus + prolonged infusion of 18 g PB2452
2. Complete reversal was observed 5 min after initiation of infusion
3. Duration was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion

No platelet rebound effect observed

- Absence of platelet hyper-reactivity, or rebound effect with arachidonic acid and thrombin receptor activating peptide between 5 minutes and 48 hours*
- Platelet rebound between 5 minutes and 48 hours was also ruled out by the response to low-dose ADP versus high-dose ADP*

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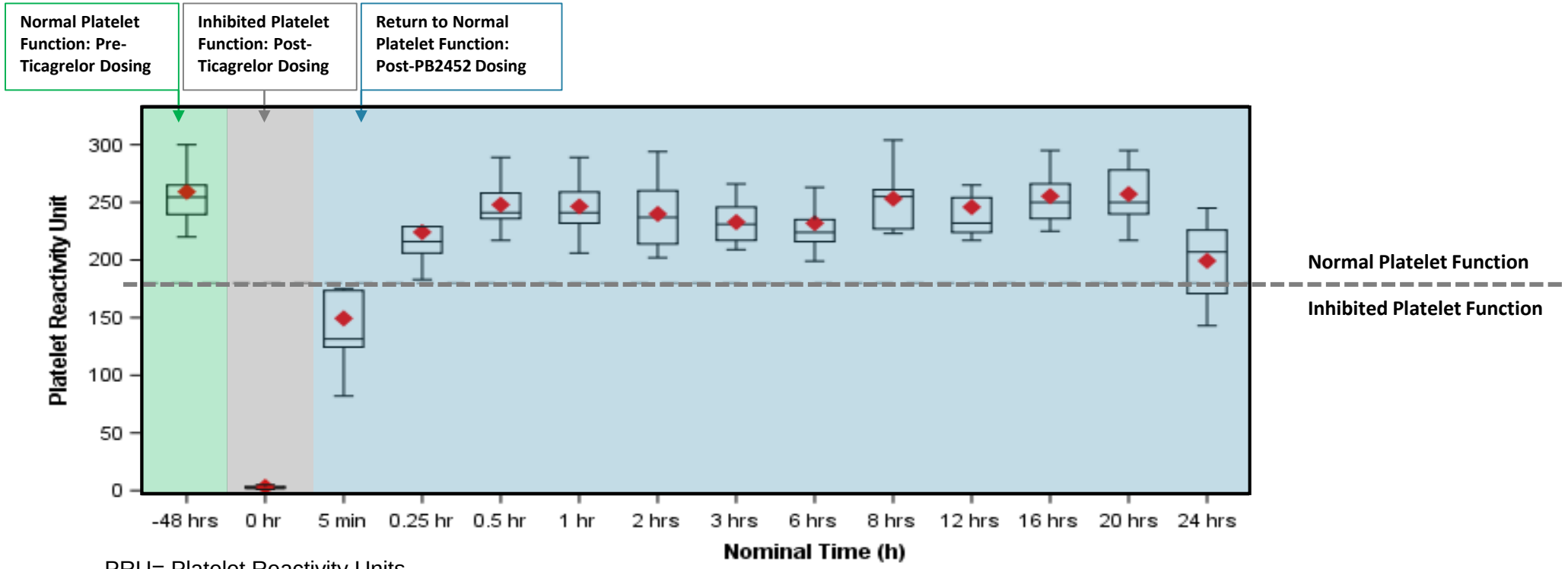
*Data presented by Dr. Deepak L. Bhatt at the American College of Cardiology Annual Scientific Session (ACC 2019), New Orleans, LA, March 17, 2019. Slides available at: https://www.acc.org/~/media/Clinical/PDF-Files/Approved-PDFs/2019/03/15/ACC19_Slides/Mar17_Sun/3pmET_Ticagrelor-Reversal-Agent-acc-2019.pdf

Normalized Platelet Function After Ticagrelor Reversal

VerifyNow PRUTest



PRU= Platelet Reactivity Units

Cohorts 9 and 10 achieved study objectives and will be the basis for dosing in the Phase 2a study in generally healthy older volunteers

- ✓ Dose-dependent response across all cohorts tested
- ✓ Immediate reversal within 5 minutes of start of infusion
- ✓ Sustained duration of reversal extended to 20+ hours
- ✓ Rapid resumption of ticagrelor dosing post infusion
- ✓ Well tolerated across all cohorts
- ✓ No drug-related SAEs

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Phase 2a Trial Preliminary Results (First 2 Cohorts)

PB2452 exhibited immediate and sustained reversal in healthy older (50-64) and elderly (65-80) subjects on DAPT

- Statistically significant reversal at 5 minutes, sustained for over 20 hours, in total population and subgroups by age
- Complete reversal achieved by 15 minutes
- Results from all 3 platelet function tests highly correlated

PB2452 generally well-tolerated, with only minor AEs and no drug-related SAEs

- Cohort 1: no PB2452-related AEs, no SAEs, no infusion-related reactions, no dose-limiting toxicity
- Cohort 2: one “possibly related” AE of light headedness in 72-year-old female in response to multiple blood draws
  - One unrelated SAE, no infusion-related reactions, no dose limiting toxicity
- Consistent with Phase 1 trial

https://investors.phasebio.com/news-releases/news-release-details/phasebio-announces-positive-preliminary-results-phase-2a

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PB2452 Program Summary and Next Steps

- Product profile: Immediate and sustained reversal of ticagrelor antiplatelet effects
  - Major bleeding and urgent surgical scenarios require immediate and sustained reversal
  - Duration of reversal dependent on infusion length
- Clinically important immediate and sustained reversal of ticagrelor observed in Phase 1 and Phase 2a trials
  - Well tolerated and no PB2452-related SAEs
- Announced receipt of meeting minutes from PB2452 End of Phase 1 meeting with FDA
  - FDA agreement on development plan and Accelerated Approval regulatory path
  - Single, non-randomized, open label Phase 3 trial in both surgical and major bleeding populations planned to support a Biologics License Application
- Next steps for program
  - Preliminary results from Phase 2a trial demonstrated immediate and sustained reversal in healthy older and elderly subjects on DAPT
  - Phase 2a trial to confirm regimen for reversal of supratherapeutic blood levels of ticagrelor
  - Initiation of large Phase 2b trial in healthy older and elderly subjects: Q4 2019
  - Non-randomized Phase 3 trial to start in Q1 2020

SAEs=Serious adverse events, DAPT=Dual antiplatelet therapy (ticagrelor + aspirin)

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