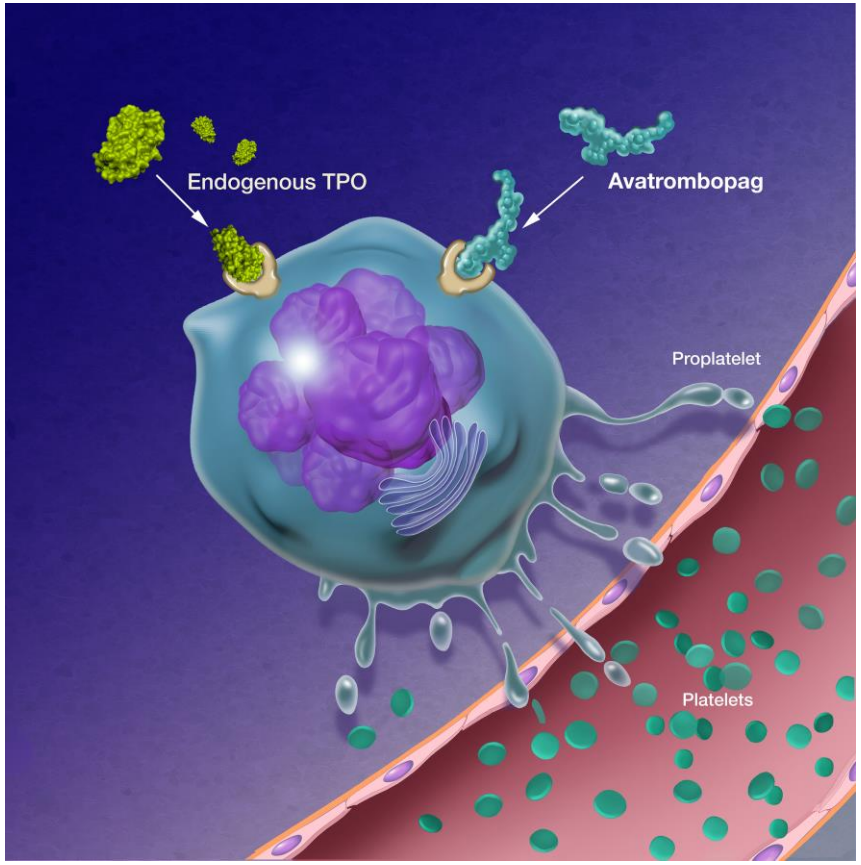
Thrombocytopenia and Chronic Liver Disease

- **Severe thrombocytopenia (platelet count <50 x 10^9/L) common in patients with chronic liver disease and cirrhosis[1]**
- **Platelet transfusions current standard of care to reduce risk of bleeding during invasive procedures in these patients**
  - *associated with risk of transfusion reactions, infections and induction of platelet refractoriness*
- **No pharmacological treatments are currently licensed for this indication**

Avatrombopag- an oral, small molecule TPO receptor agonist being developed to provide a measured increase in platelet count as an alternative to platelet transfusions



The effects of avatrombopag are additive to endogenous TPO

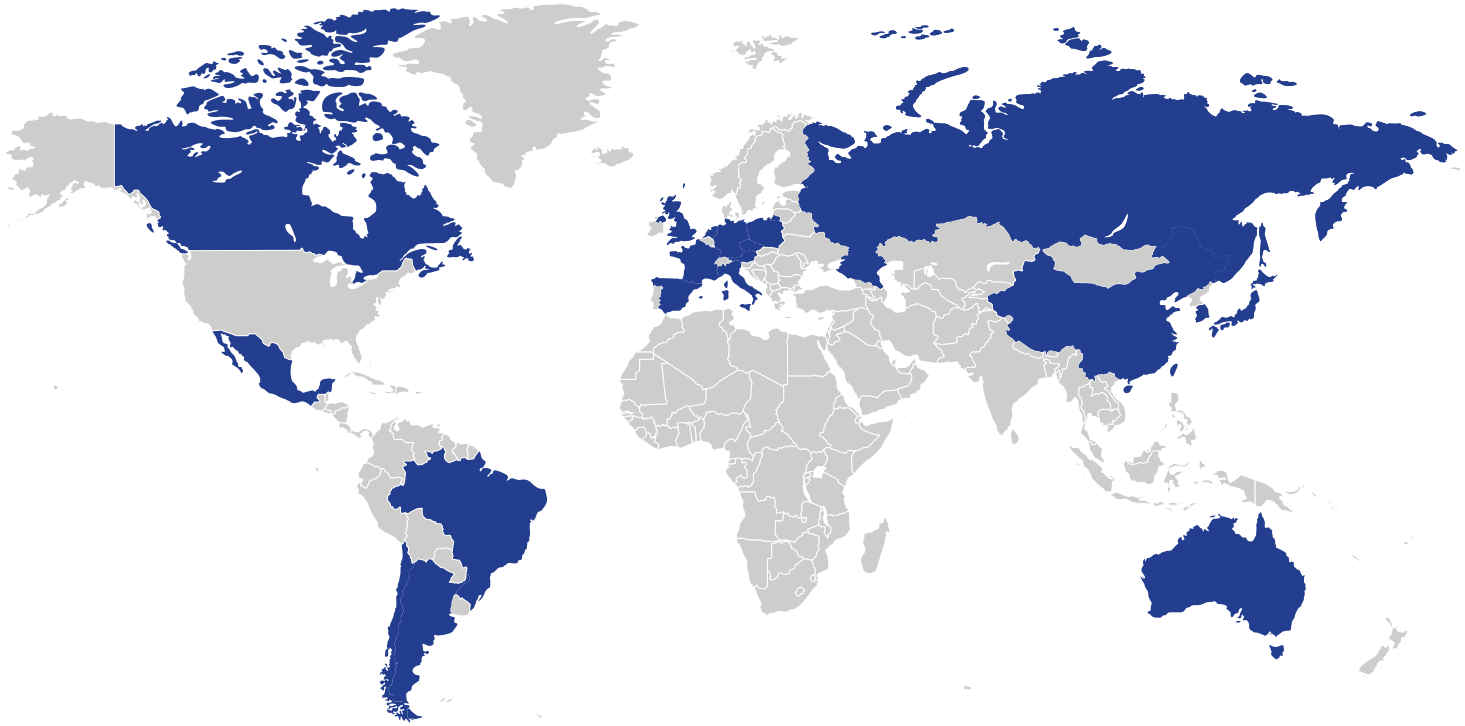
[1]Giannini EG. Aliment Pharmacol Ther. 2006; 23(8): 1055-1065 [2]Afdhal N et al. J Hepatol. 2008; 48(6): 1000-1007 [3]Hod E and Schwartz J. Br J Haematol. 2008; 142(2): 348-360
[4]Meehan KR et al. Am J Hematol. 2000; 64(4): 251-256 [5]Rebulla P. Haematologica. 2005; 90(2): 247-253

Option 1

Avatrombopag Phase 3 Studies- ADAPT-1 & ADAPT-2

Two global Phase III studies of avatrombopag in patients with thrombocytopenia and chronic liver disease undergoing scheduled procedures

- Identically-designed, randomized, double-blind, placebo-controlled, parallel-group studies
- In total, 435 patients recruited from over 20 countries (blue)

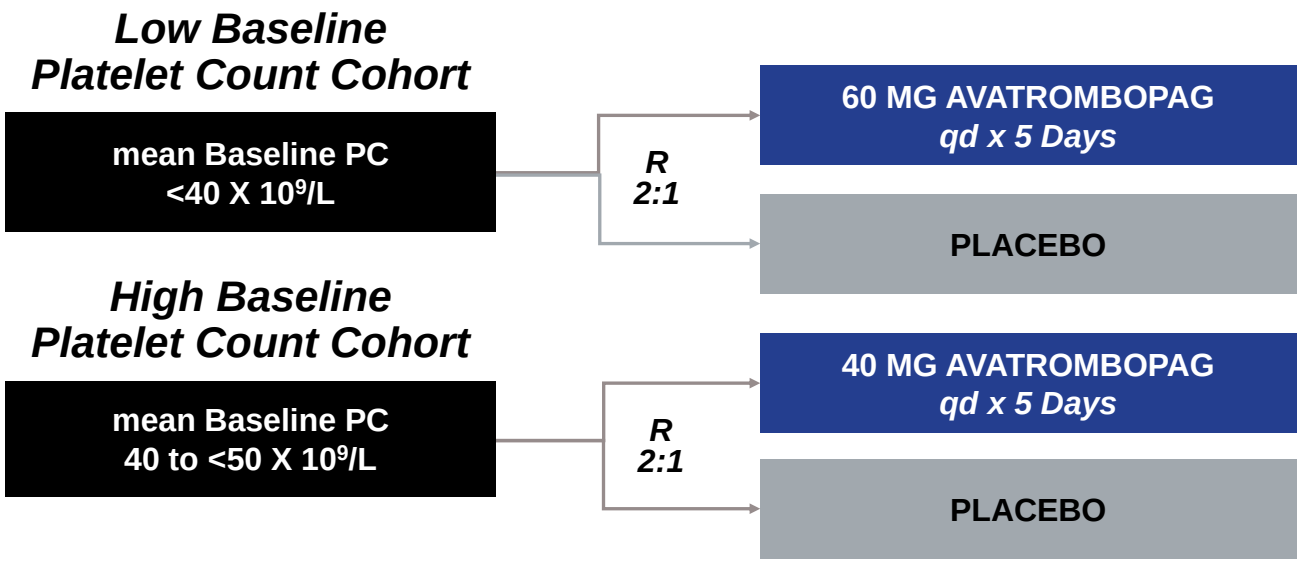


Avatrombopag Phase 3 Study Design

ADAPT-1 & ADAPT-2

PRE-RANDOMIZATION	RANDOMIZATION (*2:1 avatrombopag:placebo*)			FOLLOW-UP	
VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Screening Period Day -14 to -1	**BASELINE** DAY 1	**TREATMENT** DAY 2–5	**PROCEDURE*** DAY 10–13	**7 DAYS POST PROCEDURE**	**DAY 35**
			5–8 days after *last dose of study drug*		***30 days after*** *last dose of study drug*

**Platelet transfusions were not mandatory*



Avatrombopag Phase 3 Study Populations

ADAPT-1 & ADAPT-2

MAIN INCLUSION CRITERIA	MAIN EXCLUSION CRITERIA
Aged ≥18 years	History of arterial or venous thrombosis, hematologic disorders, or cardiovascular disease
Chronic liver disease	Known medical history of genetic pro-thrombotic syndromes
Mean Baseline platelet count <50 x 10^9/L*	Platelet transfusion or use of erythropoietin-stimulating agents within 7 days of screening
MELD score ≤24 at screening	Portal vein flow <10 cm/sec at Screening
Scheduled to undergo an invasive procedure	Hemoglobin ≤8 g/dL or ≥18 g/dL (males) or >15 g/dL (females)
	Hepatocellular carcinoma (HCC) allowed if Barcelona Clinic Liver Cancer Stage A or B

*Platelet counts were measured on 2 separate occasions: During the Screening Period and at Baseline, and performed at least 1 day apart with neither platelet count >60 x 10^9/L

ADAPT-1 & ADAPT-2: Outcome Measures

PRIMARY EFFICACY ENDPOINT:

- **Proportion of patients not requiring platelet transfusion or any bleeding rescue procedure up to 7 days post-procedure**
  - *Rescue procedures included: platelet transfusion, fresh frozen plasma (FFP), cryoprecipitate, vitamin K (phytonadione), desmopression, recombinant activated factor VII, aminocaproic acid, tranexamic acid, whole blood transfusion, packed red cell transfusion, surgical intervention or interventional radiology*

SECONDARY EFFICACY ENDPOINTS:

- **Proportion of patients achieving the target platelet count (≥50 x 10^9/L)**
- **Magnitude of change in platelet count from Baseline to Procedure Day**

SAFETY ENDPOINTS:

- **Adverse events, serious adverse events, Adverse Events of Special Interest (AESI)**

APAPT-1 & ADAPT-2: Disease Characteristics

	ADAPT-1				ADAPT-2			
	Low Baseline Platelet Count Cohort <40 x 10^9/L		High Baseline Platelet Count Cohort 40 to <50 x 10^9/L		Low Baseline Platelet Count Cohort <40 x 10^9/L		High Baseline Platelet Count Cohort 40 to <50 x 10^9/L	
	Placebo (n=48)	Avatrombopag 60 mg (n=90)	Placebo (n=34)	Avatrombopag 40 mg (n=59)	Placebo (n=43)	Avatrombopag 60 mg (n=70)	Placebo (n=33)	Avatrombopag 40 mg (n=58)
Baseline Platelet Count Cohort								
Mean (± SD)	31 ± 7	31 ± 7	45 ± 3	44 ± 3	33 ± 6	33 ± 5	45 ± 3	44 ± 4
Disease Etiology, %								
Alcoholic Liver Disease	15	14	6	19	16	17	15	10
Chronic Viral Hepatitis	63	56	79	63	61	49	55	50
Nonalcoholic Steatohepatitis	8	7	0	7	12	14	15	10
Other	15	22	15	11	12	20	15	29
Hepatocellular Carcinoma, %	23	24	21	9	33	30	33	26
MELD Score								
Mean (SD)	11.1 (3.37)	11.1 (3.33)	10.4 (2.74)	11.5 (3.75)	11.4 (3.08)	11.1 (3.25)	10.5 (3.61)	11.0 (4.07)
Child-Turcotte-Pugh Grade, %								
Grade A	63	55	61	53	49	64	49	55
Grade B	35	43	36	38	49	29	36	38
Grade C	2	2	3	9	2	7	15	7

ADAPT-1 & ADAPT-2: Scheduled Procedures by Bleeding Risk

Bleeding Risk	ADAPT-1				ADAPT-2			
	Low Baseline Platelet Count Cohort <40 x 10^9/L		High Baseline Platelet Count Cohort 40–50 x 10^9/L		Low Baseline Platelet Count Cohort <40 x 10^9/L		High Baseline Platelet Count Cohort 40–50 x 10^9/L	
	Placebo (n=48)	Avatrombopag 60 mg (n=90)	Placebo (n=34)	Avatrombopag 40 mg (n=59)	Placebo (n=43)	Avatrombopag 60 mg (n=70)	Placebo (n=33)	Avatrombopag 40 mg (n=58)
Low %	68	67	66	59	53	60	53	58
Moderate %	20	12	9	20	23	16	28	16
High %	13	21	25	21	25	24	19	7

Low Bleeding Risk Procedures

Thoracentesis
Paracentesis
Endoscopy
Upper GI endoscopy +/- biopsy
Upper GI endoscopy +/- variceal banding, +/- sclerotherapy
Colonoscopy +/- polypectomy/biopsy

Moderate Bleeding Risk Procedures

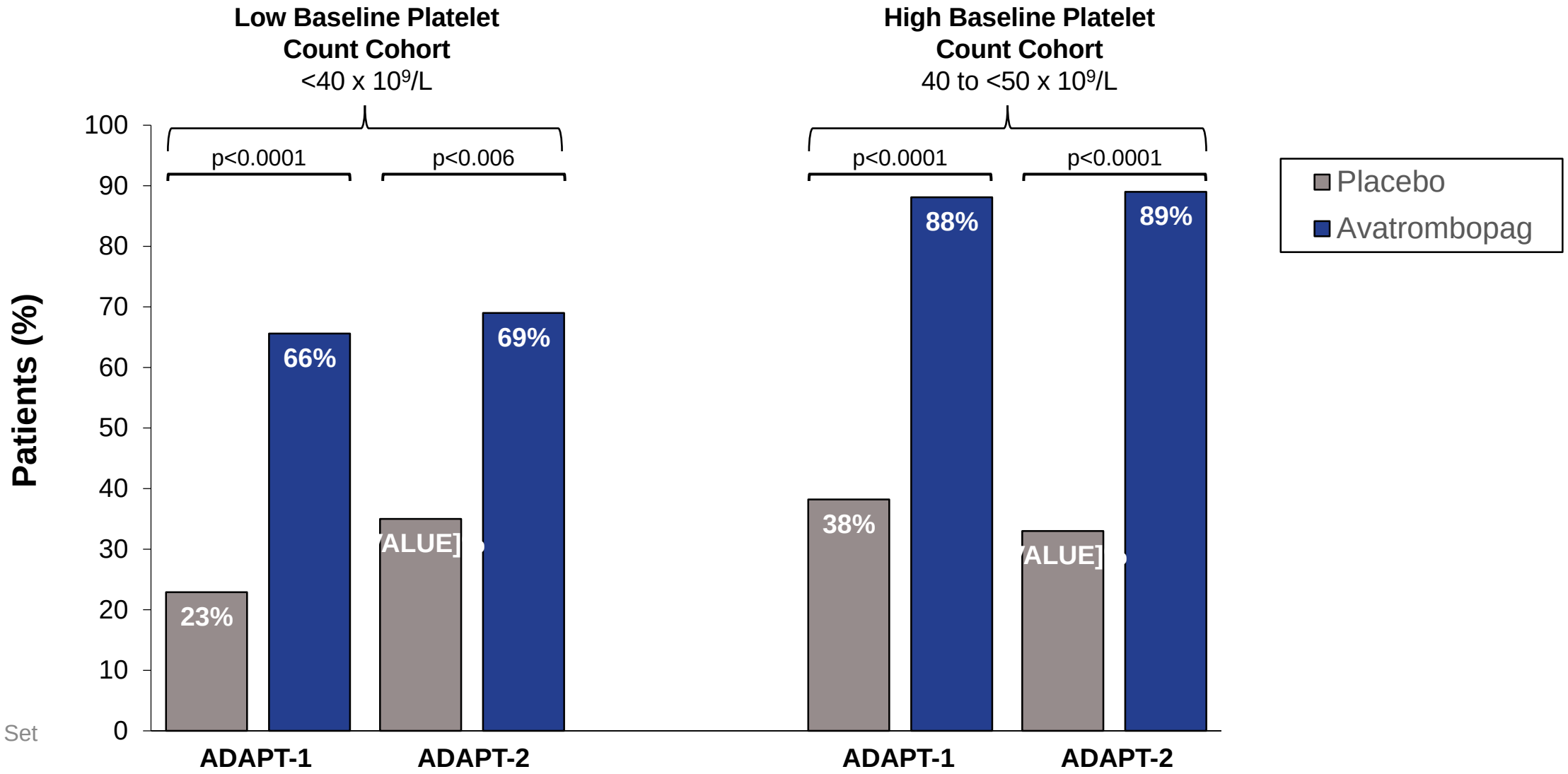
Liver biopsy
Bronchoscopy +/- biopsy
Ethanol ablation
Chemoembolization for HCC

High Bleeding Risk Procedures

Biliary Interventions
Dental procedures
Transjugular intrahepatic portosystemic shunt
Laparoscopic Interventions
Nephrostomy Tube placement
Radiofrequency ablation
Renal Biopsy
Vascular catheterization

ADAPT-1 & ADAPT-2: Primary Endpoint

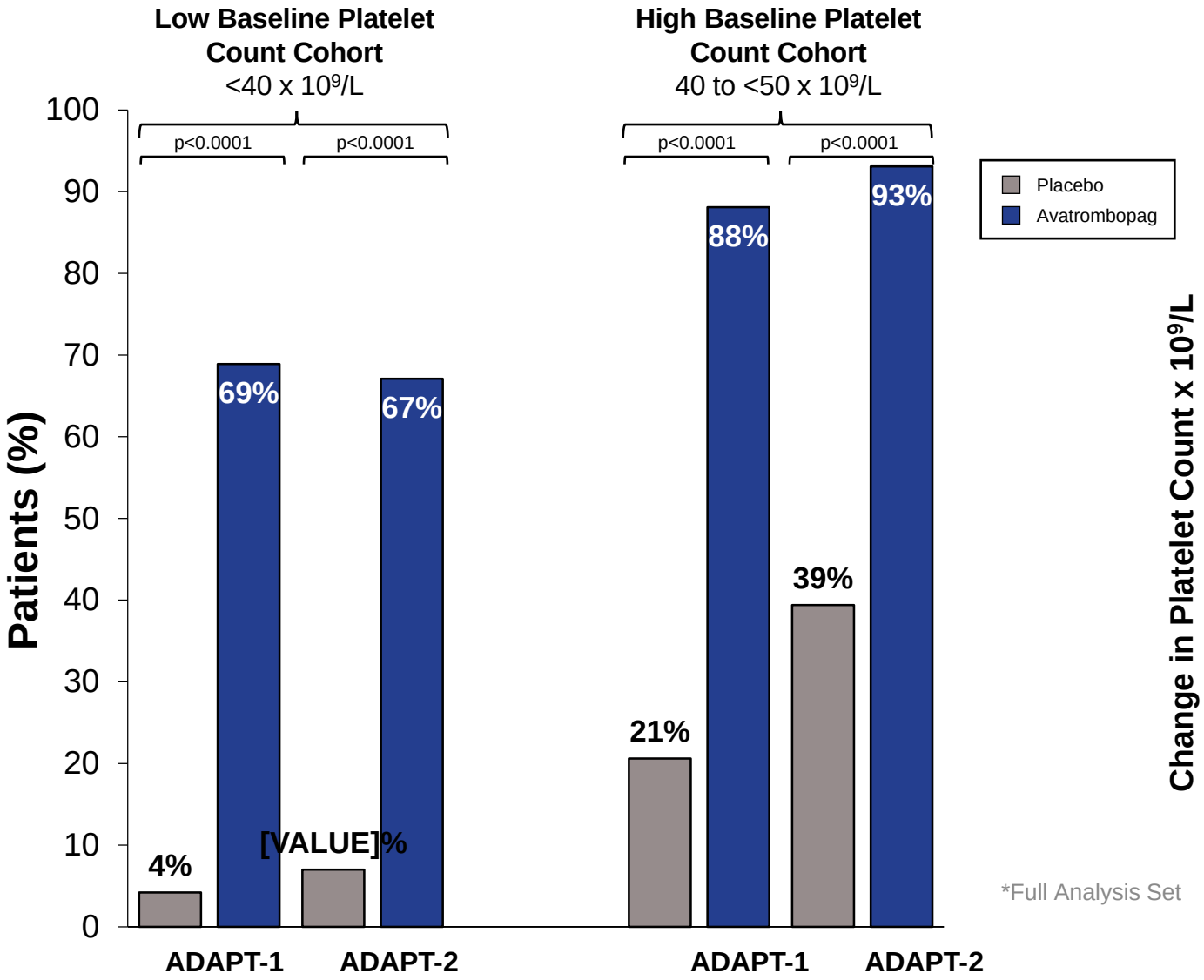
Proportion of Patients Who did NOT Require Platelet Transfusion or Any Rescue Procedure for Bleeding*



*Full Analysis Set

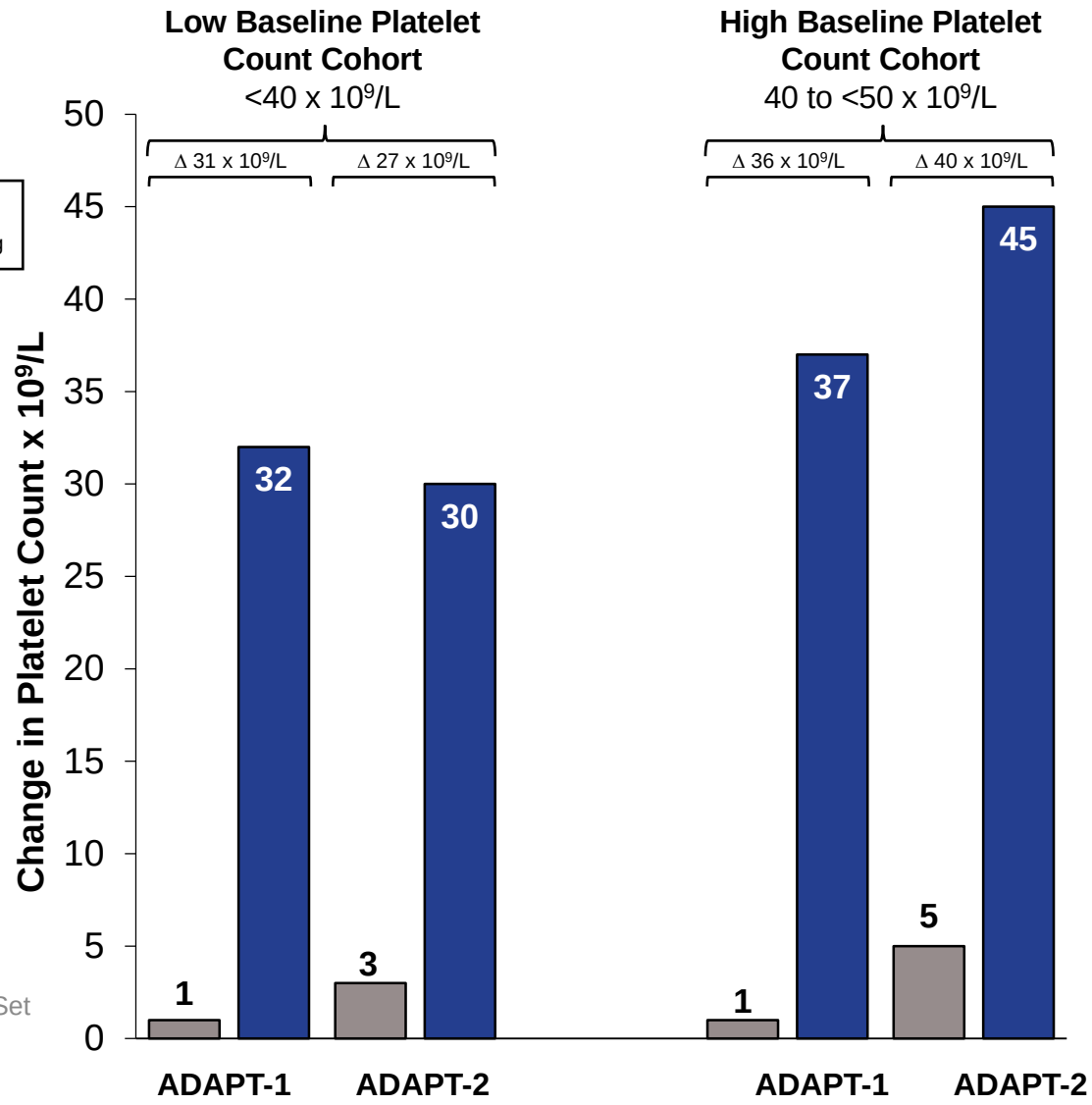
ADAPT-1 & ADAPT-2: Option 2 Secondary Endpoints

Proportion of Patients Who Achieved Platelet Counts ≥ 50 x 10^9/L on Procedure Day*



*Full Analysis Set

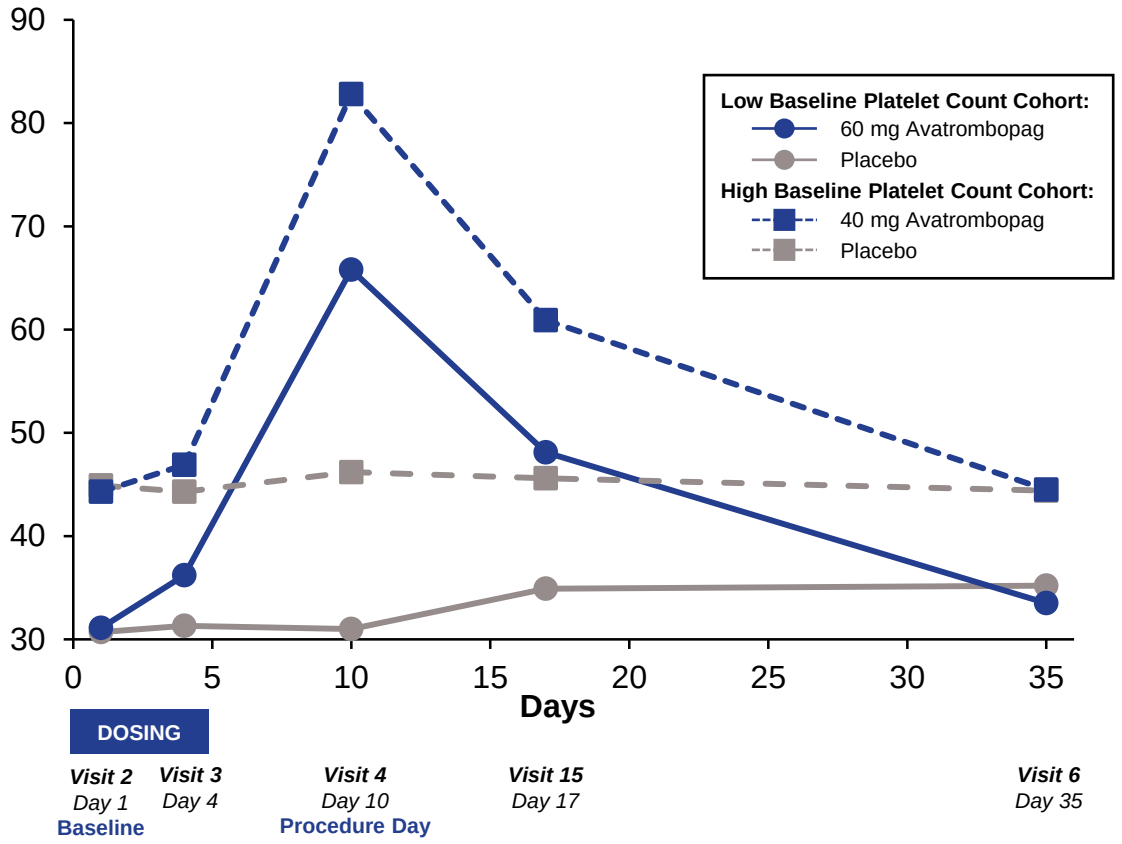
Magnitude of Change in Platelet Count from Baseline to Procedure Day*



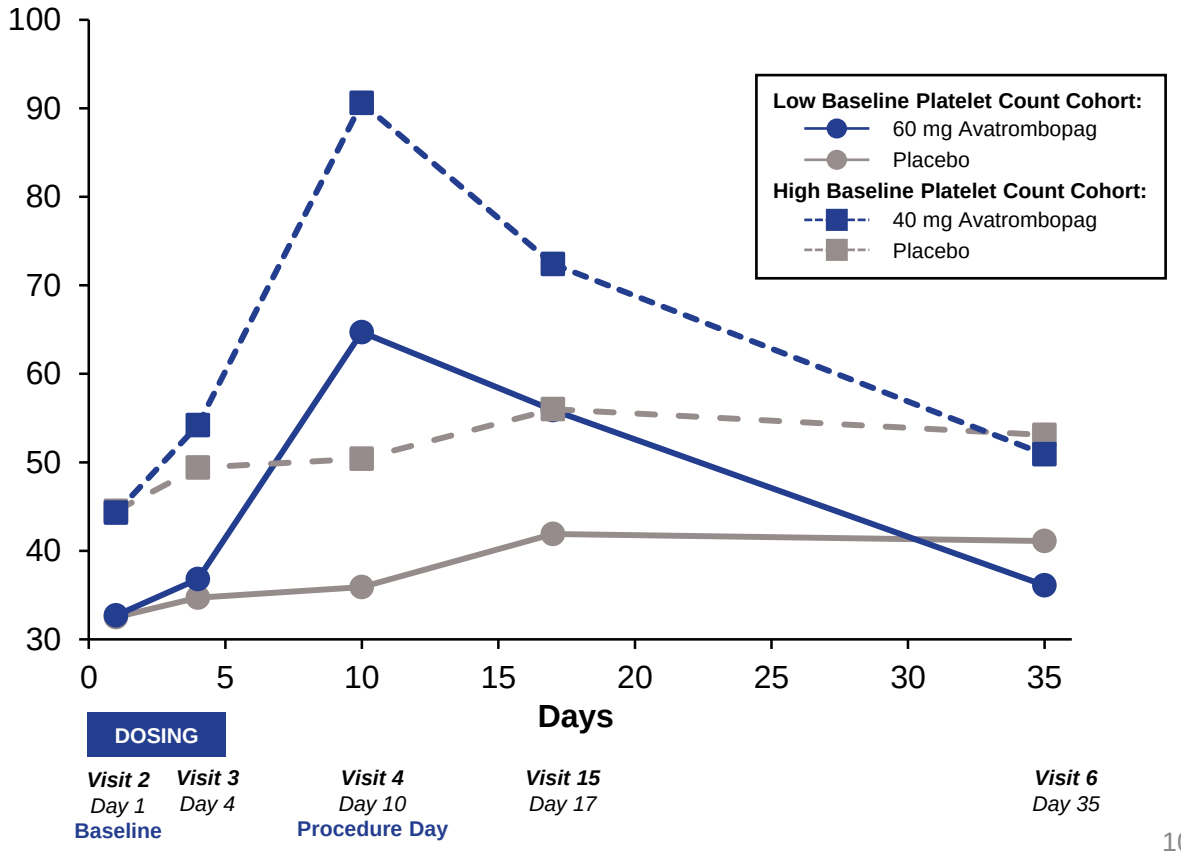
ADAPT-1 & ADAPT-2: Change in Platelet Count Over Time

- **Platelet counts reproducibly increased from Day 4, peaked at Day 10-13, and returned to Baseline levels by Day 35**
- **Only 3 (1.1%) patients had a platelet counts >200 x10^9/L at any time during the study; all were asymptomatic**

ADAPT-1



ADAPT-2



ADAPT-1 & ADAPT-2: Treatment Emergent Adverse Events

	ADAPT-1				ADAPT-2			
	Low Baseline Platelet Count Cohort <40 x 10^9/L		High Baseline Platelet Count Cohort 40 to <50 x 10^9/L		Low Baseline Platelet Count Cohort <40 x 10^9/L		High Baseline Platelet Count Cohort 40 to <50 x 10^9/L	
	Placebo (n=48) %	**Avatrombopag 60 mg** (n=89) %	**Placebo** (n=32) %	**Avatrombopag 40 mg** (n=58) %	**Placebo** (n=43) %	**Avatrombopag 60 mg** (n=70) %	**Placebo** (n=33) %	**Avatrombopag 40 mg** (n=57) %
TEAEs	65	60	56	53	51	51	46	49
Treatment-related TEAEs	15	14	6	7	21	9	6	7
TEAE with CTCAE Grade 3 or Above	17	8	0	17	9	9	12	12
Serious TEAEs	23	11	3	14	2	1	3	2
Deaths	0	0	0	3	0	0	3	0
Other SAEs	23	11	3	10	2	1	0	2
Life threatening	0	1	0	0	0	0	0	0
Hospitalization	19	11	3	10	2	1	0	2
Important Medical Events	6	0	0	4	0	0	0	0
TEAEs leading to study drug dose adjustment	0	2	0	0	0	0	0	0
TEAEs leading to study drug withdrawal	0	2	0	0	0	0	0	0

Full Analysis Set (FAS) all randomized subjects; Treatment-emergent Adverse Event (TEAE) an adverse event that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug. For each row category, a subject with two or more adverse events in that category is counted only once.

ADAPT-1 & ADAPT-2:
Deaths & Adverse Events of Special Interest

Deaths:

- N=2 in ADAPT-1 → Both in the 40 mg avatrombopag group; not considered to be study drug-related
- N=1 in ADAPT-2 → In the placebo group; not considered to be study drug-related

AEs Leading to Study Drug Discontinuation:

- N=2 in ADAPT-1 → Both occurred in the 60 mg avatrombopag group
- Only one subject discontinued due to study drug-related TEAEs of myalgia and anemia

Medically Significant Events:

- N=1 in ADAPT-2 TEAE of portal vein thrombosis in a 71 yo male in the 40 mg avatrombopag group
  - *Platelet count 45 x10^9/L at Baseline that increased to 77 x 10^9/L on Procedure Day, and then decreased to 61 x 10^9/L at Visit 5 and 45 x10^9/L at Visit 6*
  - *Scheduled procedure: upper gastrointestinal endoscopy with variceal banding*
  - *Partial portal vein thrombosis identified 14 days after the last dose of avatrombopag*
  - *Event was judged as non-serious and potentially drug-related, although causality assessment confounded by concomitant medication (ie, bisoprolol- associated with mesenteric thrombosis)*

Summary and Conclusions

- **Avatrombopag was superior to placebo in:**
  - Reducing the need for platelet transfusion or any rescue procedure for bleeding following a scheduled procedure
  - Increasing the proportion of patients achieving the target platelet count (≥50 x 10^9/L)
  - The magnitude of change in platelet count from Baseline to Procedure Day
- **Pharmacodynamics were predictable & durable**
  - Platelet counts reproducibly increased after 4 days, peaked after 10-13 days, and returned to Baseline by Day 35
- **The safety profile of avatrombopag was similar to placebo**
- **No hepatotoxicity or increase in thromboembolic or bleeding events, no rebound thrombocytopenia**

Avatrombopag offers an effective and safe alternative to platelet transfusion for patients with thrombocytopenia and chronic liver disease undergoing scheduled procedures