The Role for Eltrombopag (Promacta) in the Treatment of HepC-Related Thrombocytopenia

N. Afdhal M.D
Beth Israel Deaconess Liver Center
Harvard Medical School

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Agenda

- Eltrombopag and thrombocytopenia
- Current status of HCV therapy
- The ENABLE 1 and ENABLE 2 P-III Studies
- ELEVATE Study – conclusions on Eltrombopag safety

The Unmet Medical Need for Thrombocytopenia

- Thrombocytopenia is a major factor in patients being unable to achieve a desired clinical outcome in dozens of diseases
- Currently estimated to be nearly two million patients annually in the US who need to be treated for thrombocytopenia
- Current non-drug techniques used to increase platelets (i.e. platelet transfusion, splenectomy) are costly, risky, and inconvenient.
- The need for a more convenient and effective method for combating thrombocytopenia is clear

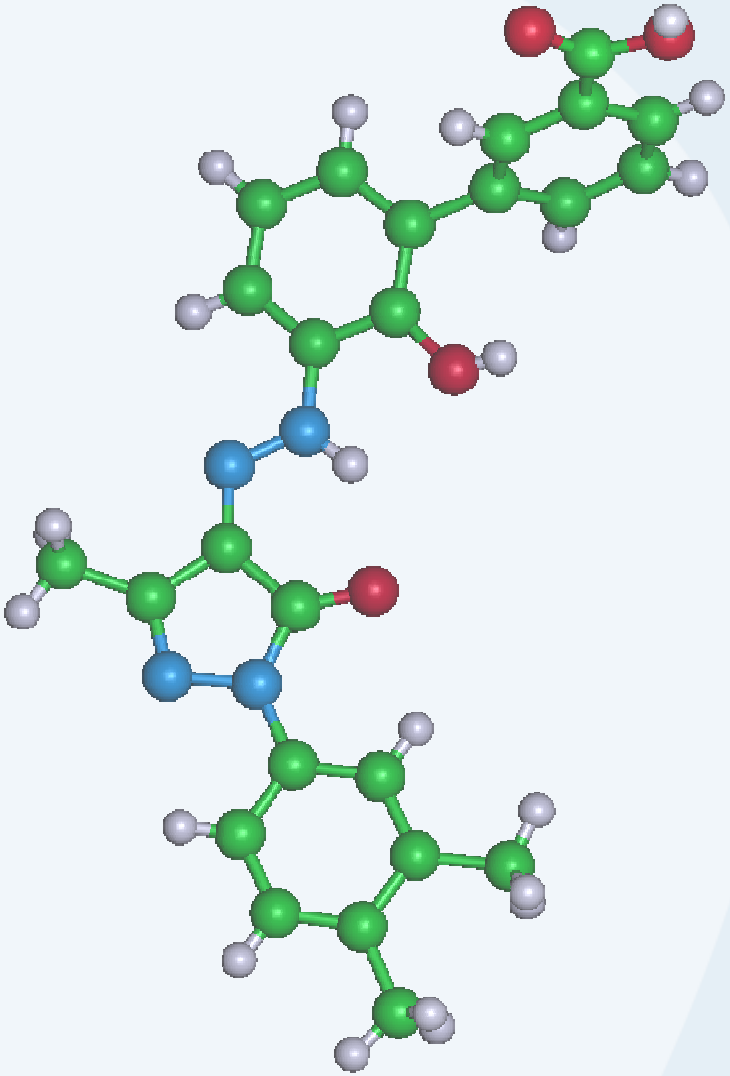
Liver Disease–Associated Thrombocytopenia

- Platelet counts may be as low as 20,000–40,000/μL
- Prevalence of thrombocytopenia increases with severity of liver disease
- Degree of thrombocytopenia correlated with severity of liver disease
- Thrombocytopenia predictive of reduced 5-year survival
- Thrombocytopenia may develop or worsen with interferon-based therapy
  4% in recent DAA trials

Degree of Liver Damage	Thrombocytopenia Prevalence
Normal liver	2.3%
Fatty liver	5.1%
Chronic hepatitis	20.3%
Advanced liver disease	31.8%

Eltrombopag

- Thrombopoietin receptor agonist
- Oral, once-daily tablet
- Induces megakaryocyte proliferation and differentiation
- Increases platelet counts in patients with HCV[1]



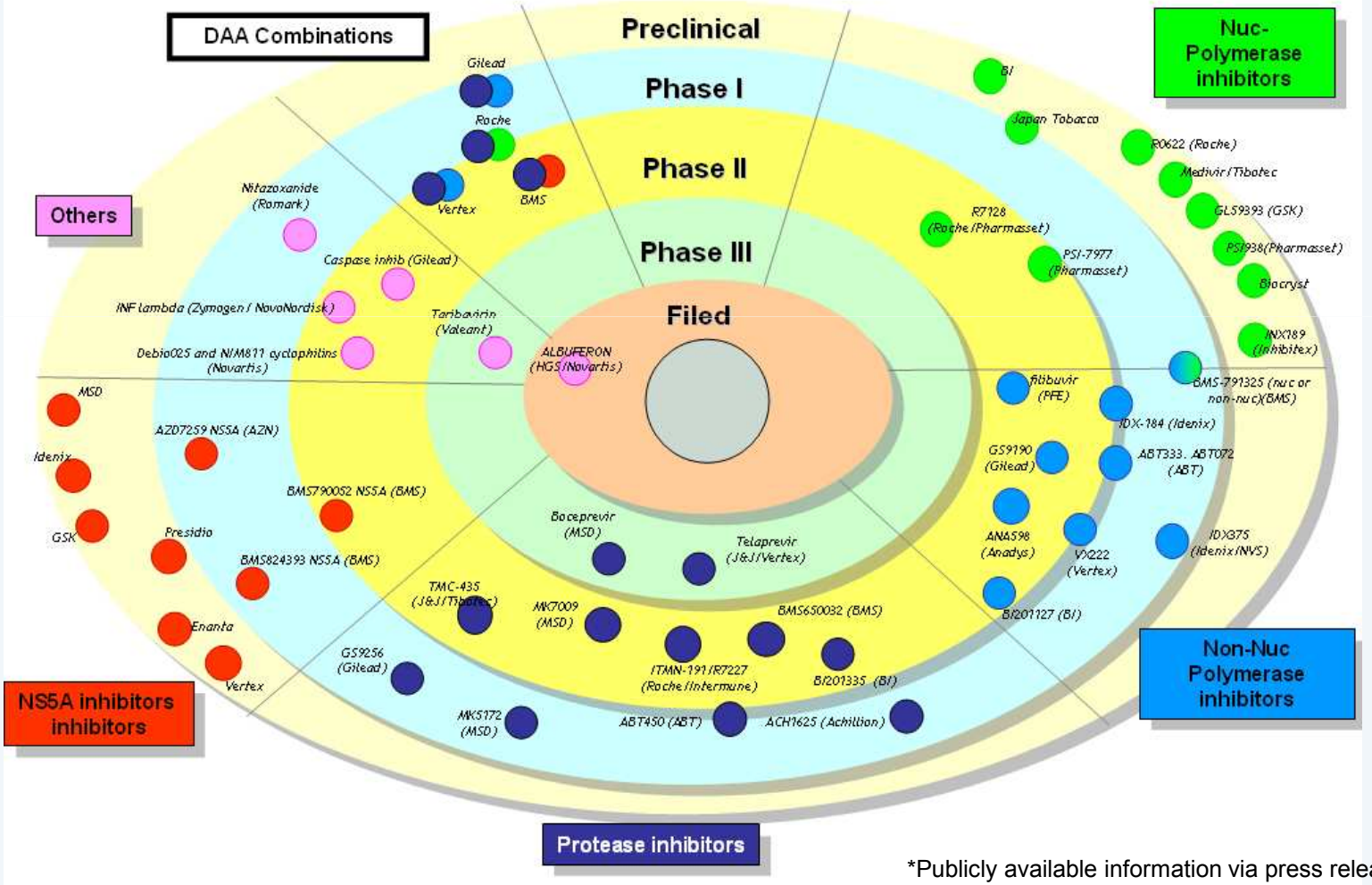
1. McHutchison J, *et al.N Engl J Med.* 2007;357:2227–2236.

Current Status of HCV therapy and the Role for Eltrombopag

Thrombocytopenia, HepC, and Eltrombopag

- Nearly 10% of HepC patients in the US suffer from treatment-limiting thrombocytopenia
- These patients have significantly worse outcomes due to their underlying liver disease and inability to complete antiviral therapies
- Eltrombopag PII data demonstrates that this drug may be useful for these patients to overcome thrombocytopenia limitations and complete antiviral therapy
- Key question arising around the eltrombopag HepC opportunity
  - How will new HepC therapies impact the need for eltrombopag?
  - Is there a long-term safety concern for eltrombopag because of the ELEVATE study results?

HCV Pipeline* by MOA and Stage of Development



3/2/2010 – selected compounds only.

*Publicly available information via press release, corporate presentations, and assumptions based on patent filings.

Target "Regimen" Outcomes

Today's Regimen

IFN + Ribavirin (R)

G1-Naive
- SVR = 40%
- Duration = 48 weeks

G2-3 Naïve
- SVR = 75%
- Duration = 24 weeks

G1-Experienced
- No meaningful option

- Frequent dosing and poor tolerability

1. IFN + R + DAA
2. IFN + DAA + DAA
3. IFN + R + DAA + DAA
4. DAA + DAA (+ DAA)

2015+ Target

New Triple / Quad Combo Regimens

- Highest possible SVR
- No / low resistance
- Better tolerability
- Shorter durations
- Simplified delivery

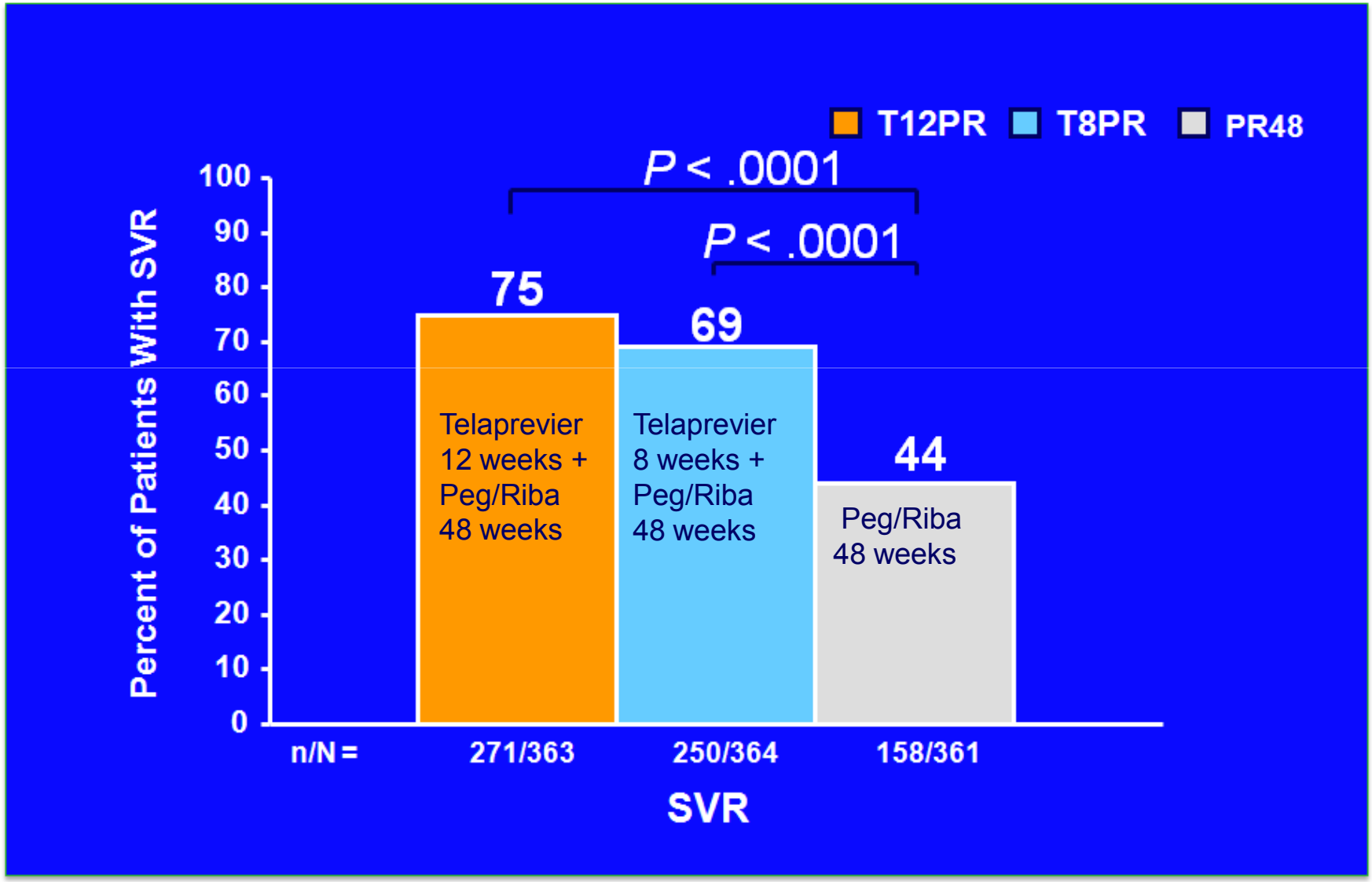
IFN = Interferon

R = Ribavirin

DAA = Novel Direct Acting Antiviral agents

Regimen 4. High risk / low probability / far away / no PoC

SVR Rates in Telaprevir-Treated Patients Compared with Peginterferon/Ribavirin Alone



Jacobson IM et al. *Hepatology.* 2010;52(Suppl 1):Abstract 211.

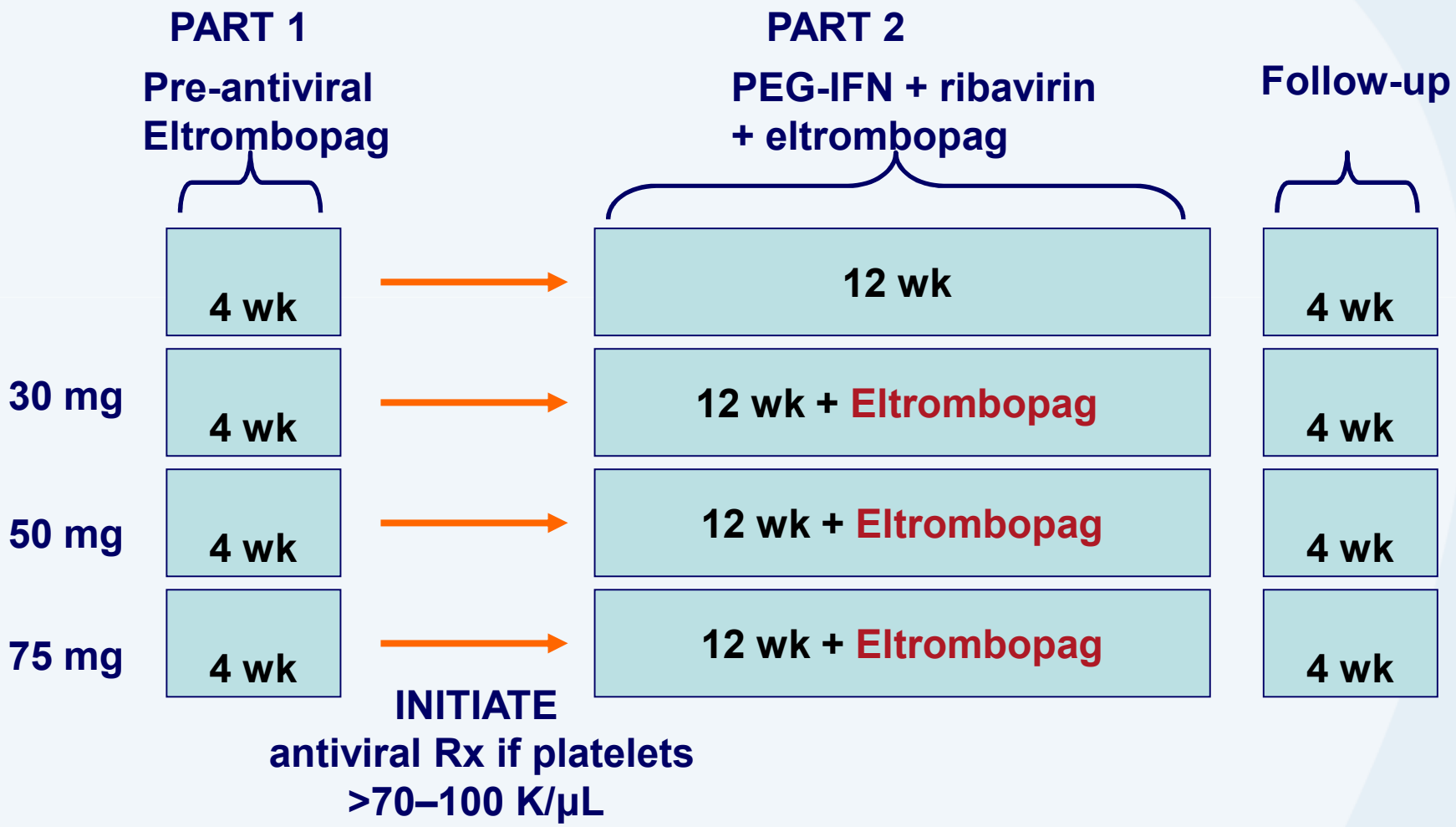
The Impact of New HepC Therapies on the Use of Eltrombopag in HepC

- Underlying thrombocytopenia is still an issue for many HepC patients
- The new protease inhibitors do not change that fact
  - New protease inhibitor therapies slightly increase the rate of thrombocytopenia
- Due to increased SVR seen with new cocktails, the need for eltrombopag should actually increase
  - Higher SVR rates may encourage doctors to treat more aggressively those patients with thrombocytopenia

Eltrombopag Clinical Studies

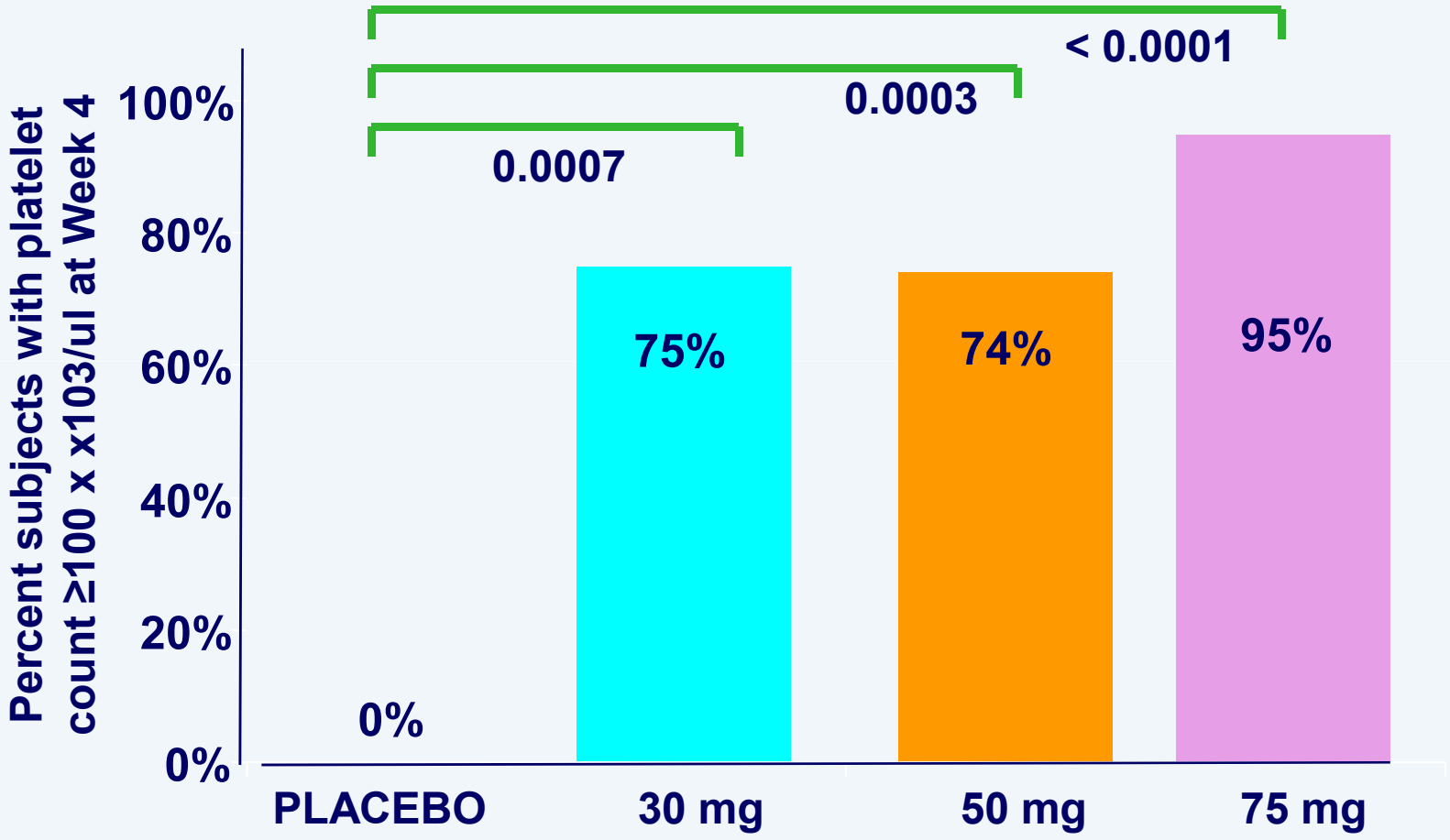
HepC Studies

Eltrombopag PII HepC Study Design



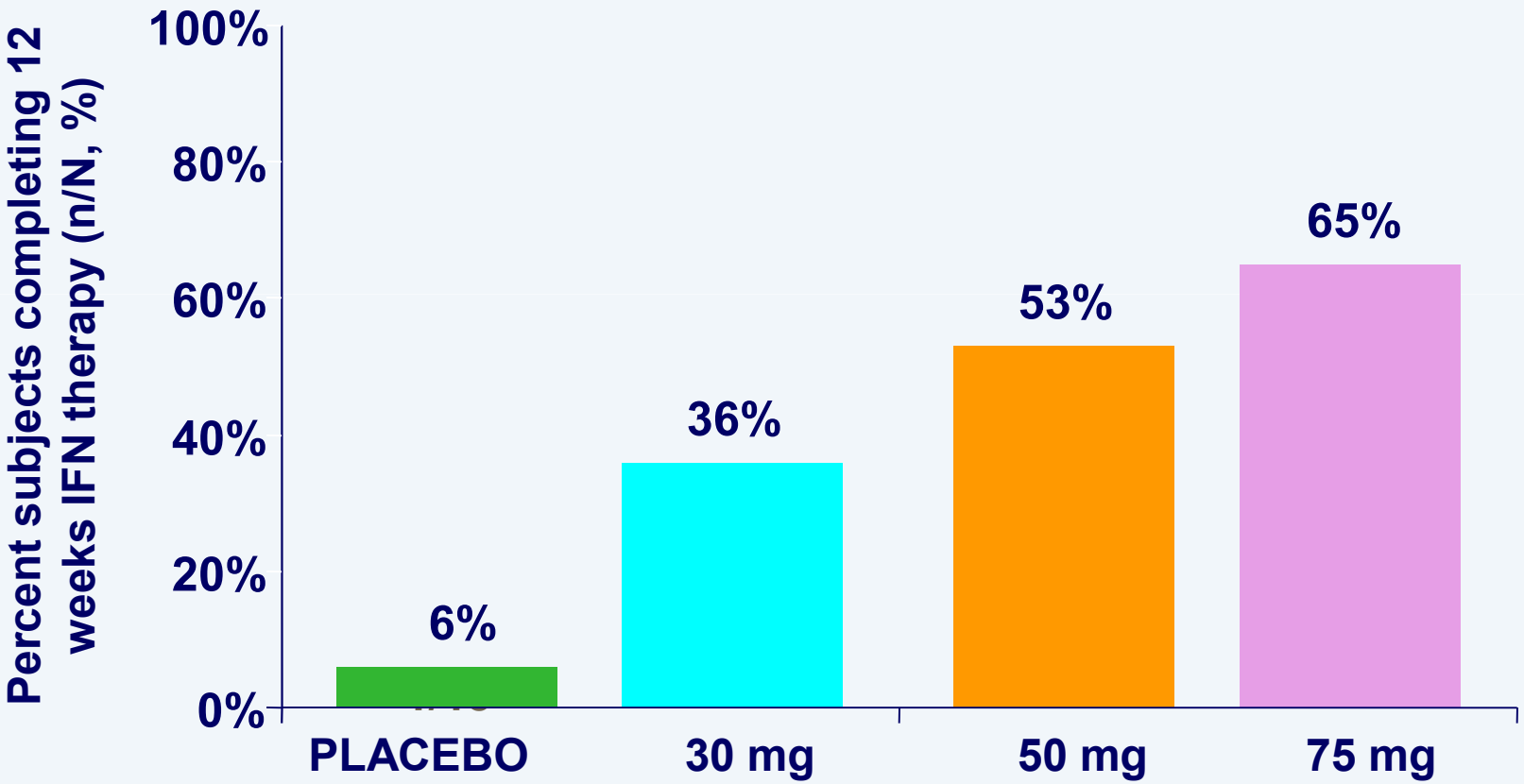
Phase II: Primary Efficacy Endpoint

Platelet count ≥ 100,000/uL at Week 4

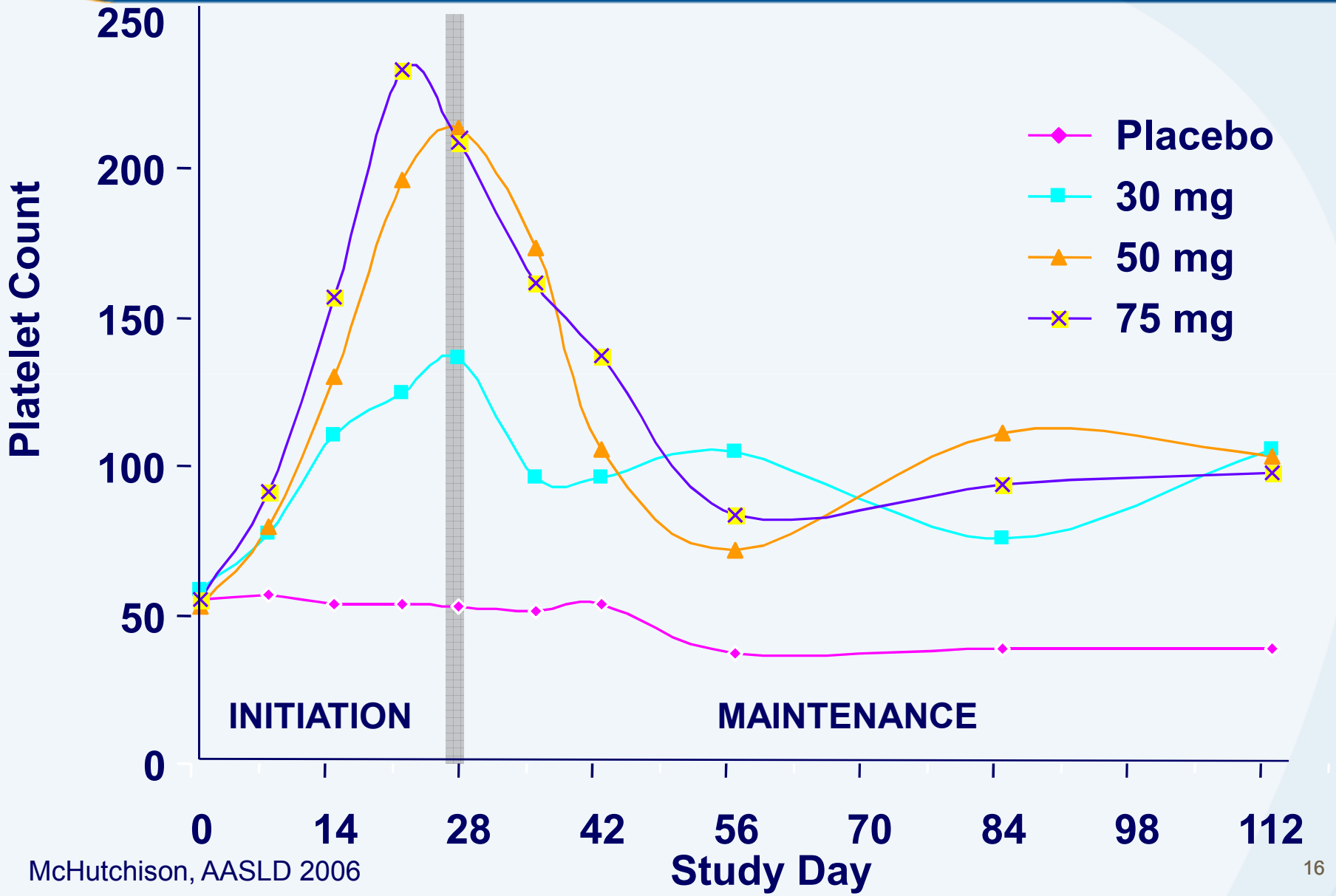


McHutchison, NEJM 2007

Phase II:
Subjects Completing 12 Weeks of PEG-IFN Therapy



Phase II:
Median Platelet Count > 200K without thrombotic events



McHutchison, AASLD 2006

Phase II: Adverse Events – Pre-Antiviral Phase

	Treatment Group, n (%)			
	PBO N=18	30mg N=14	50mg N=19	75mg N=23
Any AE	**10 (56)**	**11 (79)**	**10 (53)**	**13 (57)**
Headache	3 (17)	5 (36)	3 (16)	4 (17)
Dry mouth	1 (6)	2 (14)	2 (11)	2 (9)
Pruritus	0	0	0	2 (9)
Nausea	0	1 (7)	2 (11)	1 (4)
Fatigue	0	0	2 (11)	1 (4)
Upper abdominal pain	0	2 (14)	2 (11)	0
Insomnia	0	0	2 (11)	0
Arthralgia	0	2 (14)	1 (5)	0

No thromboembolic or elevated LFT events of concern

Phase II: Conclusions

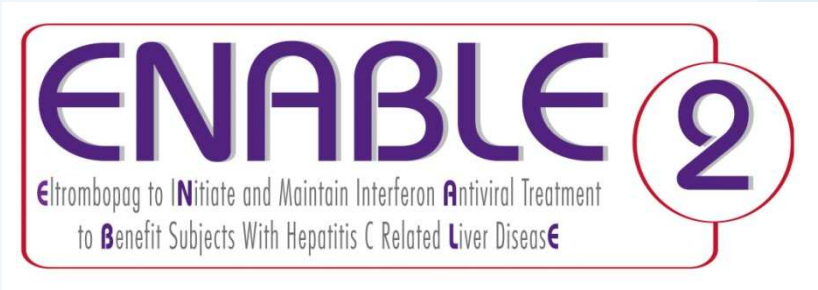
- Eltrombopag increased platelet counts in subjects in all dose groups
- A significant number of subjects achieved the primary endpoint (Week 4) in all dose groups compared to placebo
- Eltrombopag enabled 45/56 subjects to initiate IFN therapy
  - 31 subjects completed 12 weeks of IFN therapy
- Preliminary PK findings in general indicate exposure increases with dose with wide variability
- No safety signals of concern in this initial short term study
- Safety and efficacy data supports further investigation of eltrombopag in this patient population

ENABLE 1 and 2

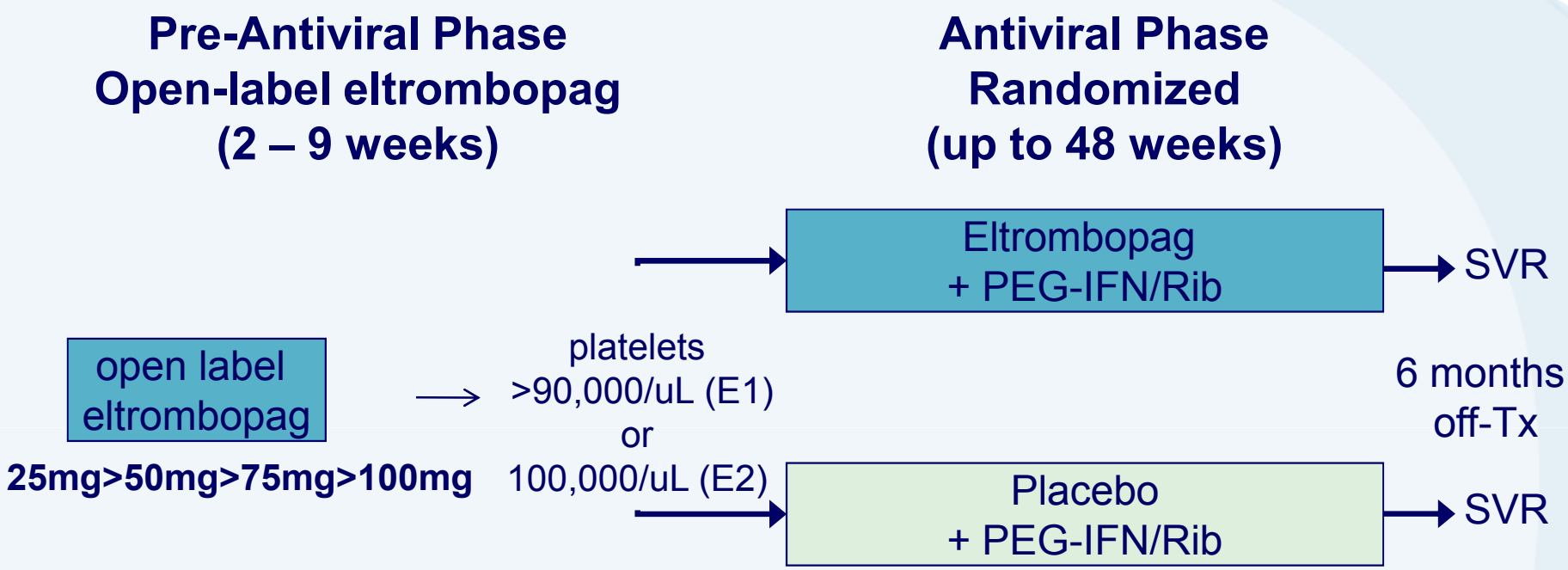
Two parallel global Phase III studies

Eltrombopag to I**N**itiate and Maintain Interferon **A**ntiviral Treatment to **B**enefit Subjects with Hepatitis C related **L**iver Diseas**E**

- peginterferon **alfa-2a (PEGASYS)** plus ribavirin – **ENABLE 1**
- peginterferon **alfa-2b (PEG-Intron)** plus ribavirin – **ENABLE 2**

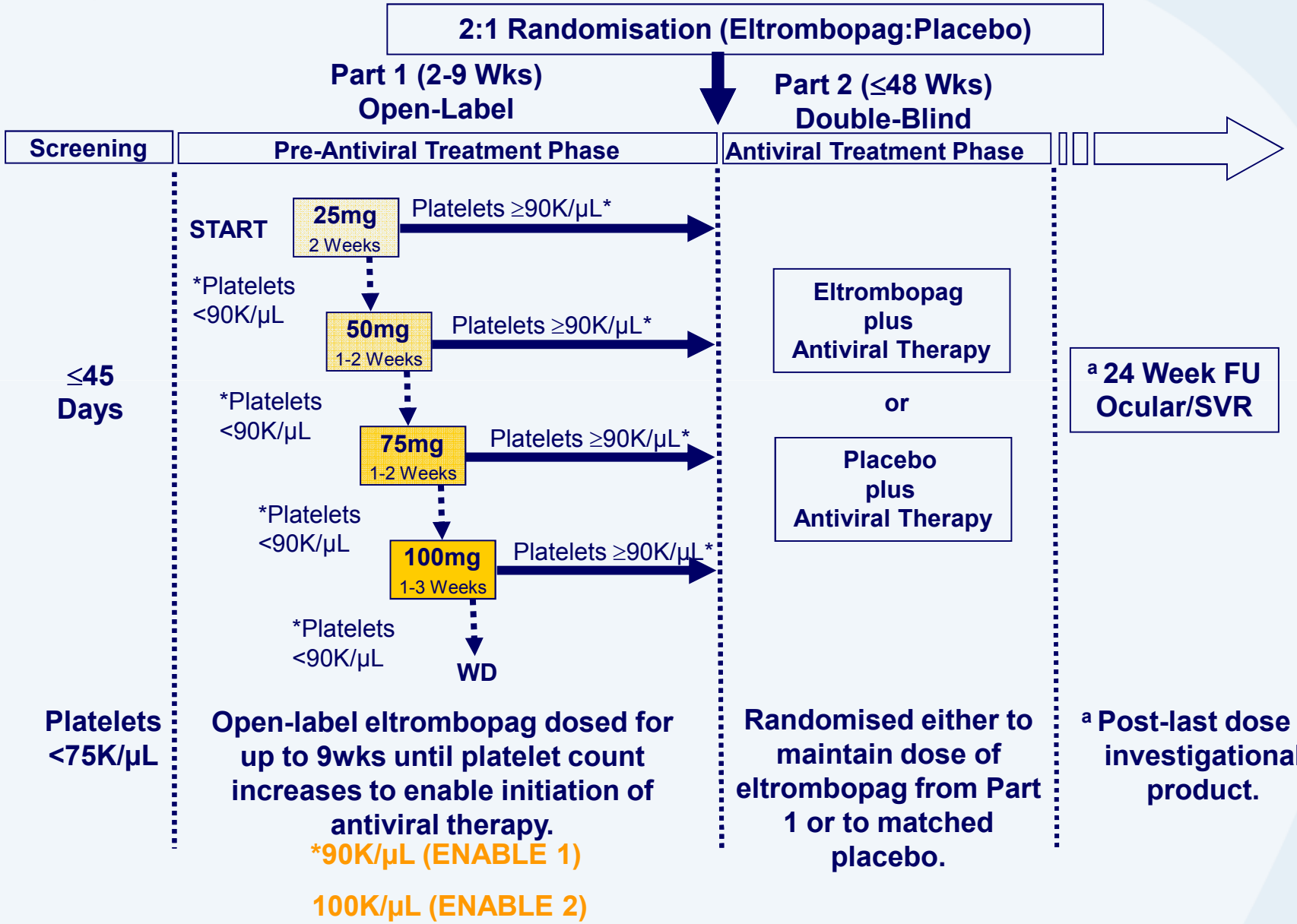


Randomized Withdrawal Design



- 2:1 randomization eltrombopag:placebo
- Dose titration of eltrombopag allowed throughout
- Primary endpoint = proportion of patients achieving SVR (6M off –Tx)
- N=750 dosed/675 randomized study
- 3 regions, 26 countries, >250 centres

ENABLE 1 and 2 Study Design



Endpoints

- **ENABLE 1 study hit primary endpoint of an SVR response**
- **First endpoint met in SVR rate defined as percentage of subjects with non-detectable HCV-RNA at 24 weeks post-completion of the planned treatment period**

- Platelet count ≥90-100,000/μL in Part 1
- Dose modifications
- Safety and tolerability
- Platelet counts
- PK
- RVR, EVR and ETR
- Health-related quality of life
- Safety modified to include risk of thrombotic events – both studies completed without DSMB concerns

Eltrombopag Safety Summary

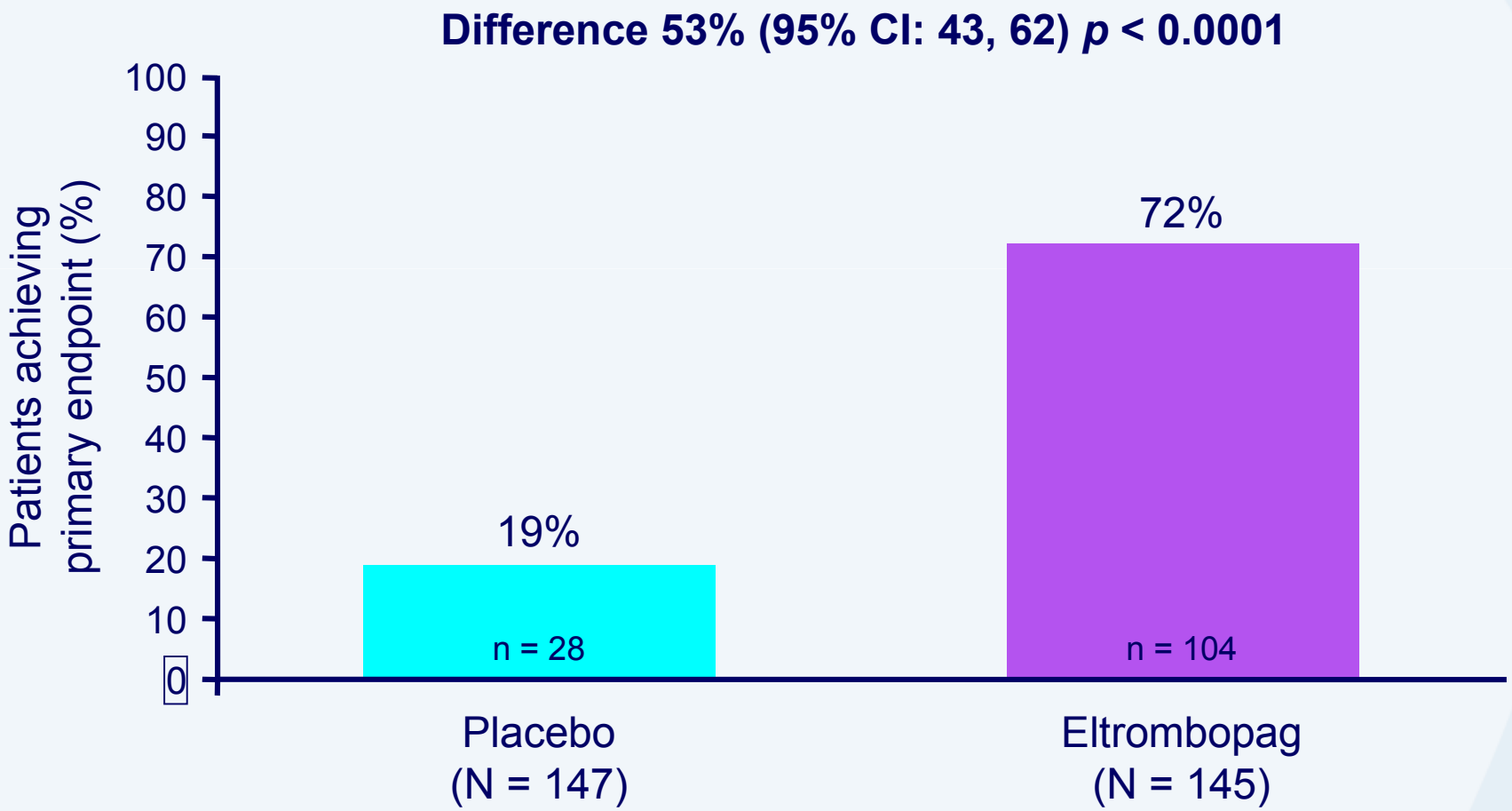
ELEVATE Study and Safety

Eltrombopag in Chronic Liver Disease Patients with Thrombocytopenia Undergoing an Elective Invasive Procedure: Results from ELEVATE, a Randomised Clinical Trial

N. Afdhal,[1] E. Giannini,[2] G.N. Tayyab,[3] A. Mohsin,[4] J-W. Lee,[5] A. Andriulli,[6] L. Jeffers,[7] J. McHutchison,[8] F. Campbell,[9] N. Blackman,[10] D. Hyde,[9] A. Brainsky,[11] D. Theodore[12]

1. Division of Gastroenterology/Liver Center, Beth Israel Deaconess Medical Center, Boston, MA, USA; 2. Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy; 3. Department of Medicine, Gastroenterology and Hepatology, Post Graduate Medical Institute, and Lahore General Hospital, Lahore, Pakistan; 4. Department of Gastroenterology, Services Hospital Lahore, Services Institute of Medical Sciences, Lahore, Pakistan; 5. Department of Internal Medicine, Inha University Hospital and School of Medicine, Incheon, Korea; 6. Department of Internal Medicine, Division of Gastroenterology, Casa Sollievo Sofferenza Hospital, San Giovanni Rotondo, Italy; 7. Center for Liver Diseases, University of Miami, Miller School of Medicine, Miami, FL, USA; 8. Division of Gastroenterology, Duke University Medical Center, Durham, NC, USA; 9. Clinical Development, GlaxoSmithKline, Stockley Park, Uxbridge, UK; 10. Biometrics and Epidemiology, GlaxoSmithKline, Collegeville, PA, USA; 11. Clinical Development, GlaxoSmithKline, Collegeville, PA, USA; 12. Clinical Development, GlaxoSmithKline, Research Triangle Park, NC, USA

Primary Endpoint: Avoiding Platelet Transfusions with Elective Invasive Procedure



Selected Adverse Events

	Placebo (N = 145)	Eltrombopag (N = 143)
	n (%)	n (%)
Bleeding	25 (17)	19 (13)
Thrombotic event	2 (1)	6 (4)
Ocular (focus on cataracts / visual acuity decrease)	6 (4)	6 (4)
Malignancies*	1 (<1)	1 (<1)

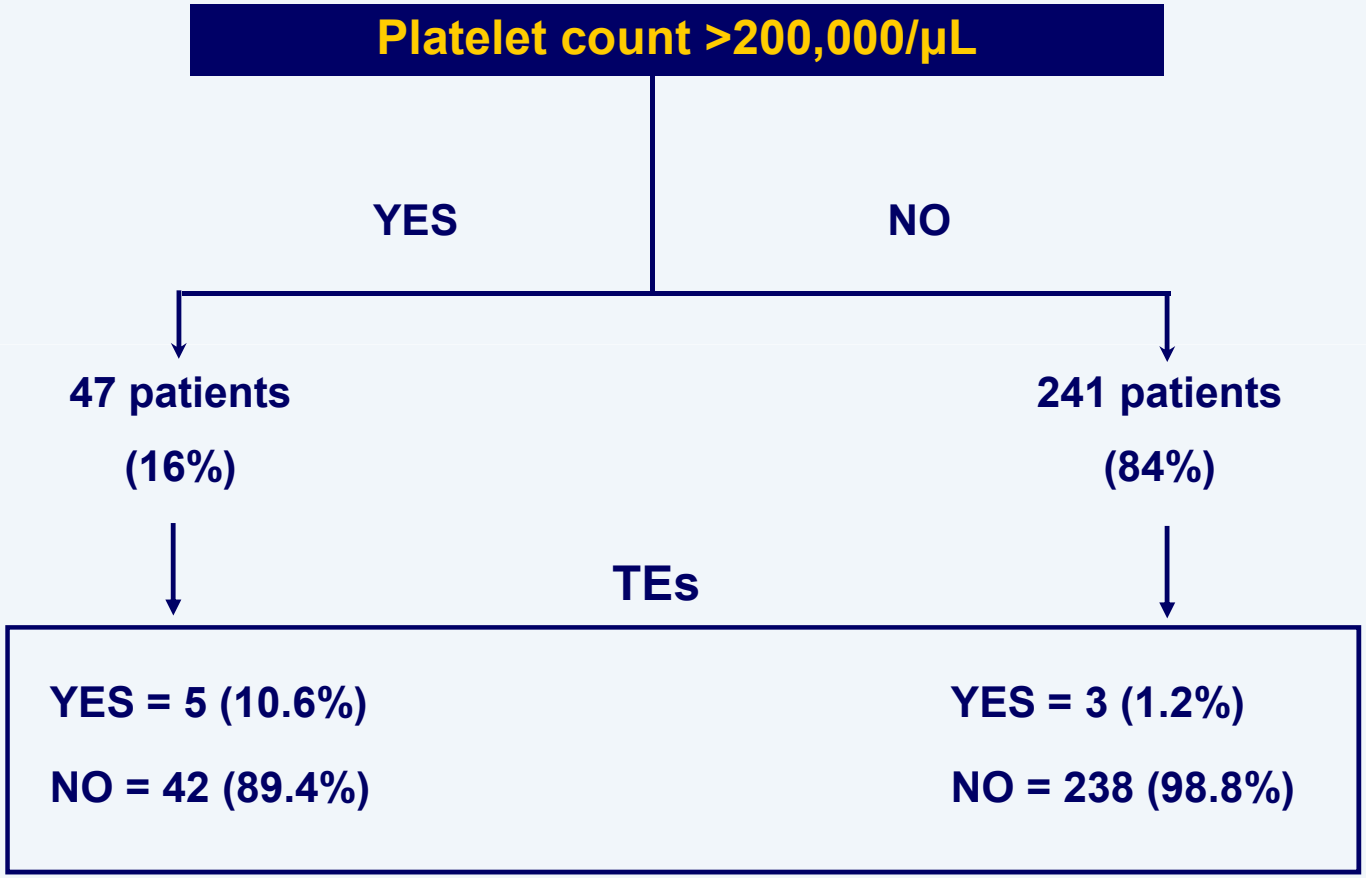
* Basal cell carcinoma (Grade 2) reported for one patient receiving placebo and B cell lymphoma (Grade 4) reported for one patient receiving eltrombopag; neither was considered to be related to treatment by the investigator.

Summary of Thrombotic Events

Thrombotic event	Temporal relationship to last dose	Temporal relationship to procedure	Platelet count at event (Gi/L)	Procedure
Eltrombopag				
PV / SMV thrombosis	+1	–6 days	417	Brain tumour resection
PV thrombosis	+5	+4 days	288	Oesophageal variceal ligation
SMV thrombosis	+8	+7 days	235	Dental extraction
SMV / mesenteric thrombosis	+9	+7 days	289	HCC ablation
SPV thrombosis	+14	+13 days	241	TACE
PV thrombosis	+38	+34 days	33	Oesophageal variceal ligation
Placebo				
Acute MI	+20	+19 days	83	Colon resection
Non-occlusive PV and mesenteric thrombosis	+128	+128 days	Unknown	Oesophagoduo-denoscopy

PV, portal vein; SMV, superior mesenteric vein; SPV, spleno-portal vein; MI, myocardial infarction

Thrombotic Events and Platelet Count



ELEVATE Conclusions

- Eltrombopag 75 mg for 14 days
  - Reduced the need for platelet transfusions in CLD patients with thrombocytopenia undergoing elective invasive procedures
  - Increased platelets during treatment period and up to 2 weeks following treatment
  - Similar incidence of adverse events and serious adverse events
  - More thrombotic events in the eltrombopag group
    - Relationship demonstrated for elevation of platelets
    - Procedure with endovascular inflammation essential feature

Eltrombopag Summary

- GSK announced it received positive data from ENABLE-1 and that full data will be released at an upcoming scientific conference
- ENABLE studies are expected to confirm role of eltrombopag in HCV therapy in 2011
- Eltrombopag is expected to be more widely used in HCV – increased SVR – increased treatment
- Long term safety of eltrombopag continues to be better understood and continued expansion of the eltrombopag franchise is warranted