

**NDA 22-291**  
**PROMACTA<sup>®</sup> (eltrombopag)**

**GlaxoSmithKline Presentation to the  
Oncologic Drugs Advisory Committee**

**30 May 2008**

# Presentation Overview

**Introduction**

**Debasish Roychowdhury, MD**

**Idiopathic**

**James Bussel, MD**

**Thrombocytopenic Purpura**

**Clinical Overview**

**Michael Arning, MD, PhD**

**Concluding Remarks**

**Debasish Roychowdhury, MD**

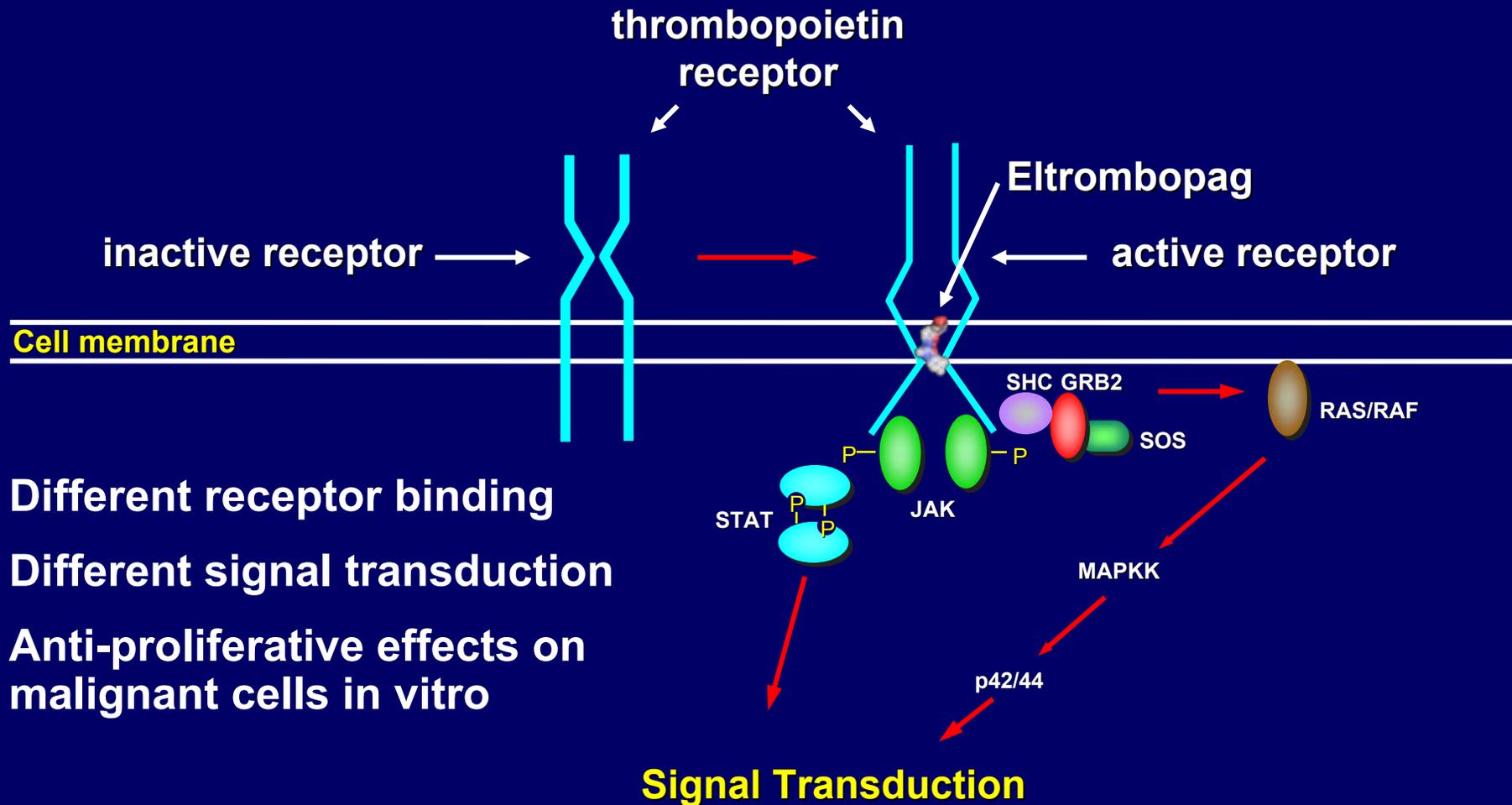
# External Participants

- **James Bussel, MD**
  - Prof. of Medicine, Pediatrics and Ob/Gyn, Cornell Medical Center
- **Gregory Cheng, MD, PhD**
  - Prof. of Medicine and Therap., Chinese University of Hong Kong
- **Douglas Cines, MD**
  - Prof. of Path. and Lab Medicine, Univ. of Pennsylvania
- **Gary Koch, PhD**
  - Prof. of Biostatistics, University of North Carolina-Chapel Hill
- **Willis Maddrey, MD**
  - Prof. of Medicine, UT Southwestern Medical Center
- **Andrew McAfee, MD, MSc**
  - Executive Director, Epidemiology, i3 Drug Safety
- **Mansoor Saleh, MD**
  - Prof. of Medicine, University of Alabama

# ITP - Unmet Medical Need

- **Treatment paradigm -**
  - Elevate and maintain platelets in “safe zone” for necessary time period**
- **Current treatments**
  - Not tested in randomized placebo controlled studies, benefit risk unclear, most are not approved**
    - Corticosteroids, high dose IVIg, Anti-D
    - Splenectomy
    - Danazol, cyclosporine, chemotherapy, rituximab
- **Short-term use**
- **Intermittent short-term use**
- **Long-term use**

# Eltrombopag – Thrombopoiesis Mechanism of Action



Different receptor binding  
Different signal transduction  
Anti-proliferative effects on malignant cells in vitro

# **Promacta Clinical Development Plan**

- **Idiopathic Thrombocytopenic Purpura**
  - Phase II and III Short-term Dosing – TRA100773A\* and B\*
  - Phase II Intermittent Dosing: REPEAT
  - Phase III Long-term Dosing: EXTEND and RAISE\*
- **Hepatitis C associated Thrombocytopenia**
- **Chronic Liver Disease**
- **Chemotherapy Induced Thrombocytopenia (CIT)**

\* Placebo controlled studies

# Key Regulatory Milestones

<b>Date</b>	<b>Activity</b>
<b>September 2004</b>	<b>IND opened</b>
<b>December 2006</b>	<b>EOP2 meeting</b> <ul style="list-style-type: none"><li>● <b>Agreement on NDA data package for submission and review of short term ITP</b></li></ul>
<b>August 2007</b>	<b>pre-NDA meeting</b>
<b>December 2007</b>	<b>NDA submitted</b>
<b>March and April 2008</b>	<b>Discussion on RMP and possible indication for long term use</b>
<b>April 2008</b>	<b>Safety Update submitted</b>
<b>May 2008</b>	<b>Granted Orphan Drug Designation</b>

## Proposed Indication in NDA

- ***Promacta*** is indicated for the short-term treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding

# James Busse: Disclosures

- Professor of Pediatrics, Medicine and OB-GYN at Weill Medical College of Cornell University---New York Presbyterian Hospital
- My family owns stock in Amgen and GlaxoSmithKline (in trusts or IRA's not directly under my control)
- I receive support as a clinical investigator and have been on advisory boards for Amgen, GlaxoSmithKline, MGI Pharma, Ligand, and several other members of the pharmaceutical industry

# **Idiopathic Thrombocytopenic Purpura: ITP**

**James Busse MD**

**Director, Platelet Disorders Center,**

**Departments of Medicine and Pediatrics**

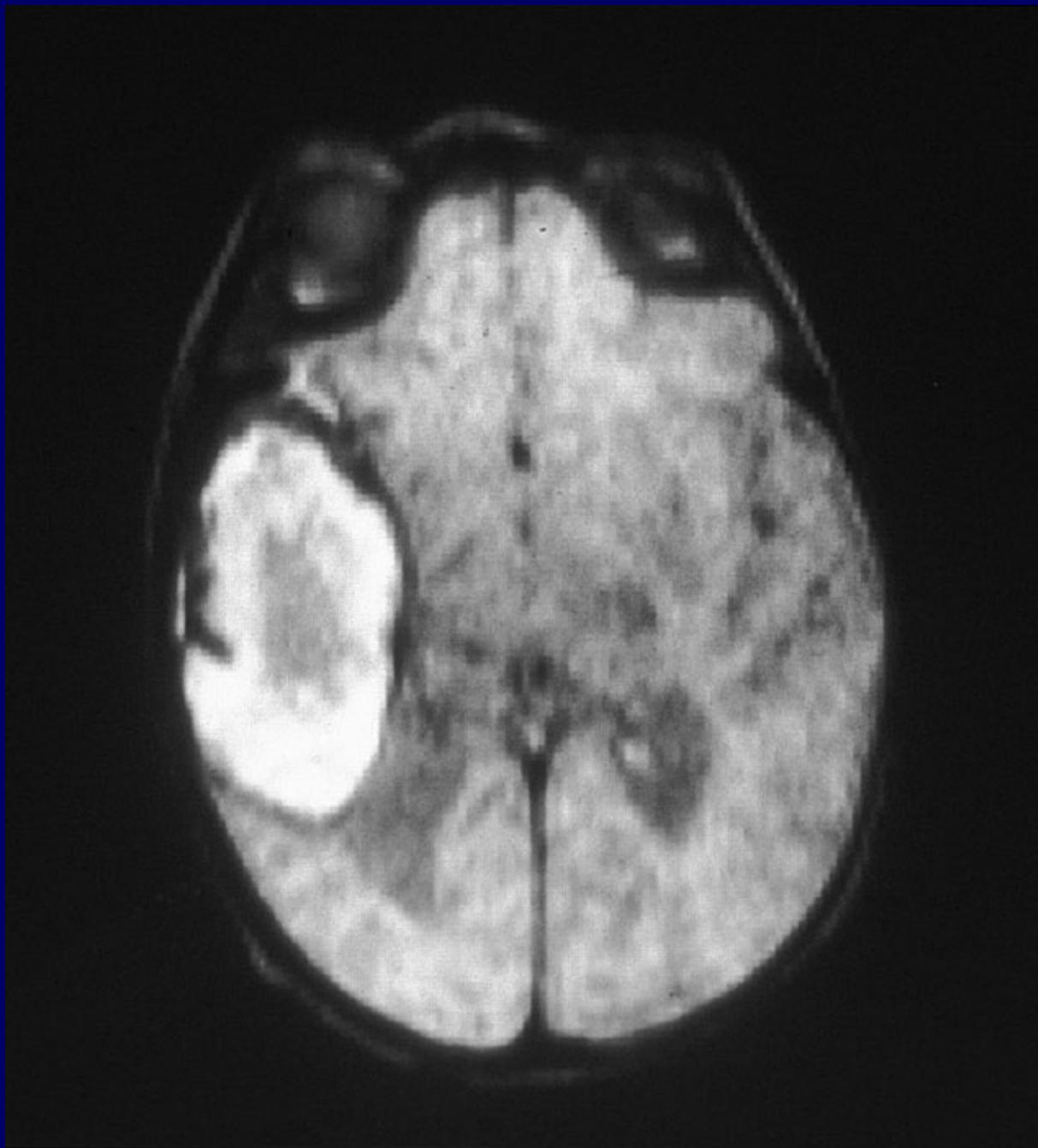
**Weill Medical College of Cornell University---  
New York Presbyterian**

# Petechiae



# “Wet” Purpura

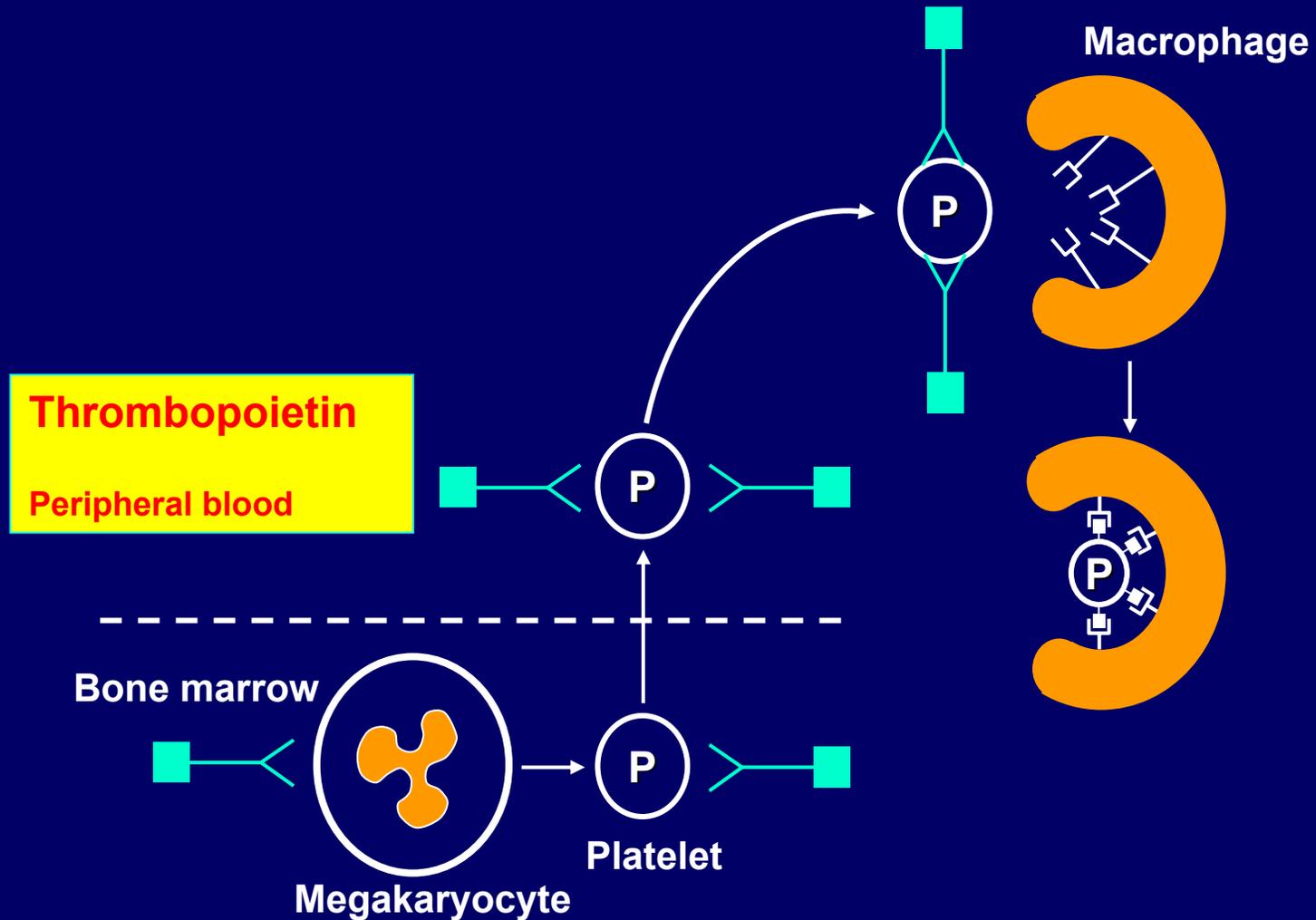




# **ITP: New Issues and Unmet Needs**

- A. Thrombocytopenia in ITP is a result of both platelet destruction and sub-optimal platelet production**
- B. ITP has significant clinical manifestations and negative impact on HRQOL**
- C. ITP is often difficult to treat**
- D. Patients with ITP need more effective and better tolerated therapies**

# Pathophysiology of ITP



# Chronic ITP: Adverse Effects on Patients

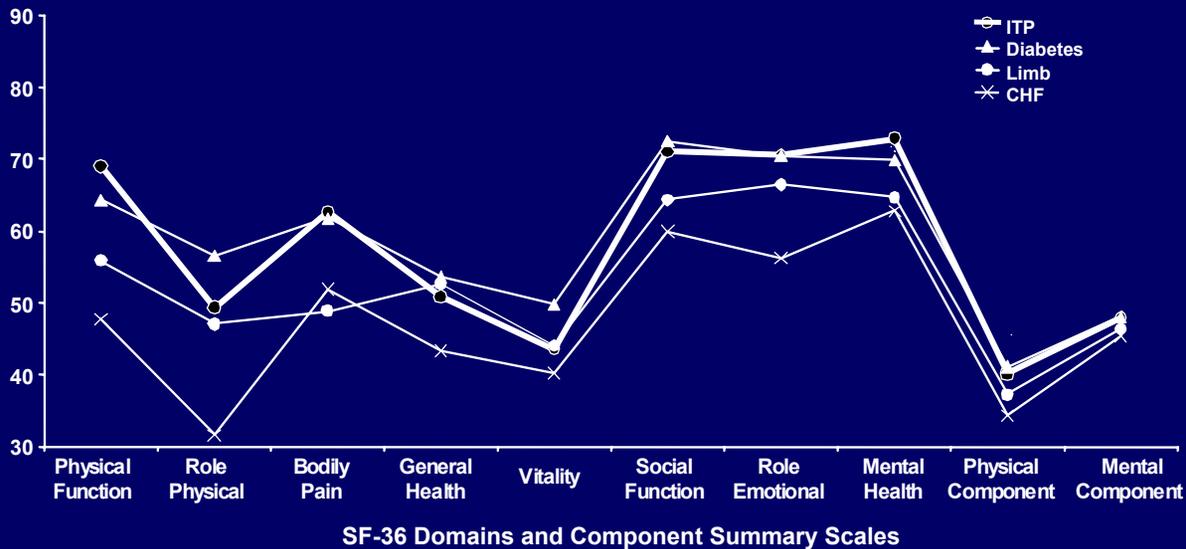
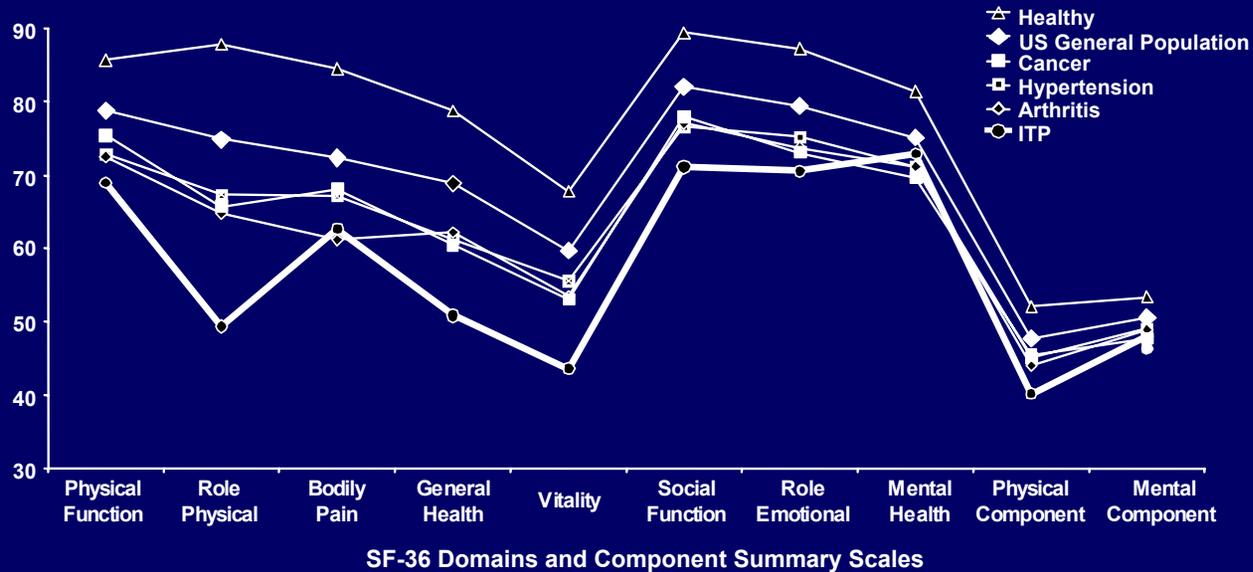
## Psychologic effects:

- 1) Dealing with bleeding symptoms
- 2) Anxiety - fear driven by thrombocytopenia

## Organic Effects:

- 3) Side effects of treatments, eg pred
- 4) Poorly understood effects of ITP itself on HRQOL, e.g. energy

# ITP adversely affects patients' quality of life



# Challenges of ITP Treatment

- **Current treatments work in a variable fraction of patients**
- **Prediction of efficacy is impossible: trial and error rules the day**
- **Current treatments are useful but have serious toxicities:**
  - **IVIg, IV anti-D, steroids, rituximab, splenectomy, immunosuppressives and others**

# Short term treatment in ITP

- **Short term treatment is a typical way to treat patients**
  - **Stop or prevent acute hemorrhage**
  - **Allow surgery or another hemostatic challenge to proceed safely**
  - **Allow work activity at risk of bleeding**
  - **Minimize risk of bleeding while traveling and away from easy access to care**
  - **Allow a short course of NSAID's for arthritis**
  - **Allow short term use of coumadin for treatment of DVT in thrombocytopenic patient**

# **Treatments Effective in the Short Term Are Useful for the Long Term**

**Examples of this in ITP include:**

- 1. Repeated infusions of IVIG**
- 2. Repeated infusions of IV anti-D**
- 3. Cycles of pulse dexamethasone**
- 4. Periodic retreatment with Rituximab**

# **Idiopathic Thrombocytopenic Purpura**

- A. Thrombocytopenia in ITP is a result of both platelet destruction and sub-optimal platelet production**
- B. ITP has significant clinical manifestations and negative impact on HRQOL**
- C. ITP can be difficult to treat**
- D. Patients with ITP need more effective and better tolerated therapies**

# **Clinical Overview**

**Michael Arning, MD, PhD**

# Overview of Studies Contained in NDA

Total exposure > 1000 subjects (ITP Patients = 460)

Exposure	Efficacy	Safety	
Short term	100773A: N=117		Placebo controlled
	100773B: N=114		
Intermittent	REPEAT: N=66		Open label
Long term	EXTEND: N=207		Open label
	RAISE: N=196		Placebo controlled

# Efficacy Endpoints

- **Platelet Count Elevation (assessed weekly)**
- **Bleeding Symptoms (assessed weekly)**

## **WHO Bleeding Scale:**

- Grade 0 no bleeding
  - Grade 1 petechiae (incl. minimal mucosal bleeding)
  - Grade 2 mild blood loss (e.g. macroscopic blood in stool/urine; multiple blood blisters; moderate hemoptysis)
  - Grade 3 gross blood loss (profuse bleeding)
  - Grade 4 debilitating blood loss (life-threatening bleeding)
- **Hemostatic Challenges (observational)**
    - **Diagnostic, surgical procedures, unexpected trauma**

# Short Term Treatment Studies

Largest randomized, double-blind, placebo-controlled ITP studies

## **TRA100773A**

Phase II dose finding study

Placebo + SoC  
N=29

30mg *Promacta* + SoC  
N=30

50mg *Promacta* + SoC  
N=30

75mg *Promacta* + SoC  
N=28

## **TRA100773B**

Phase III confirmatory study

Placebo + SoC  
N=38

50mg *Promacta* + SoC  
N=76

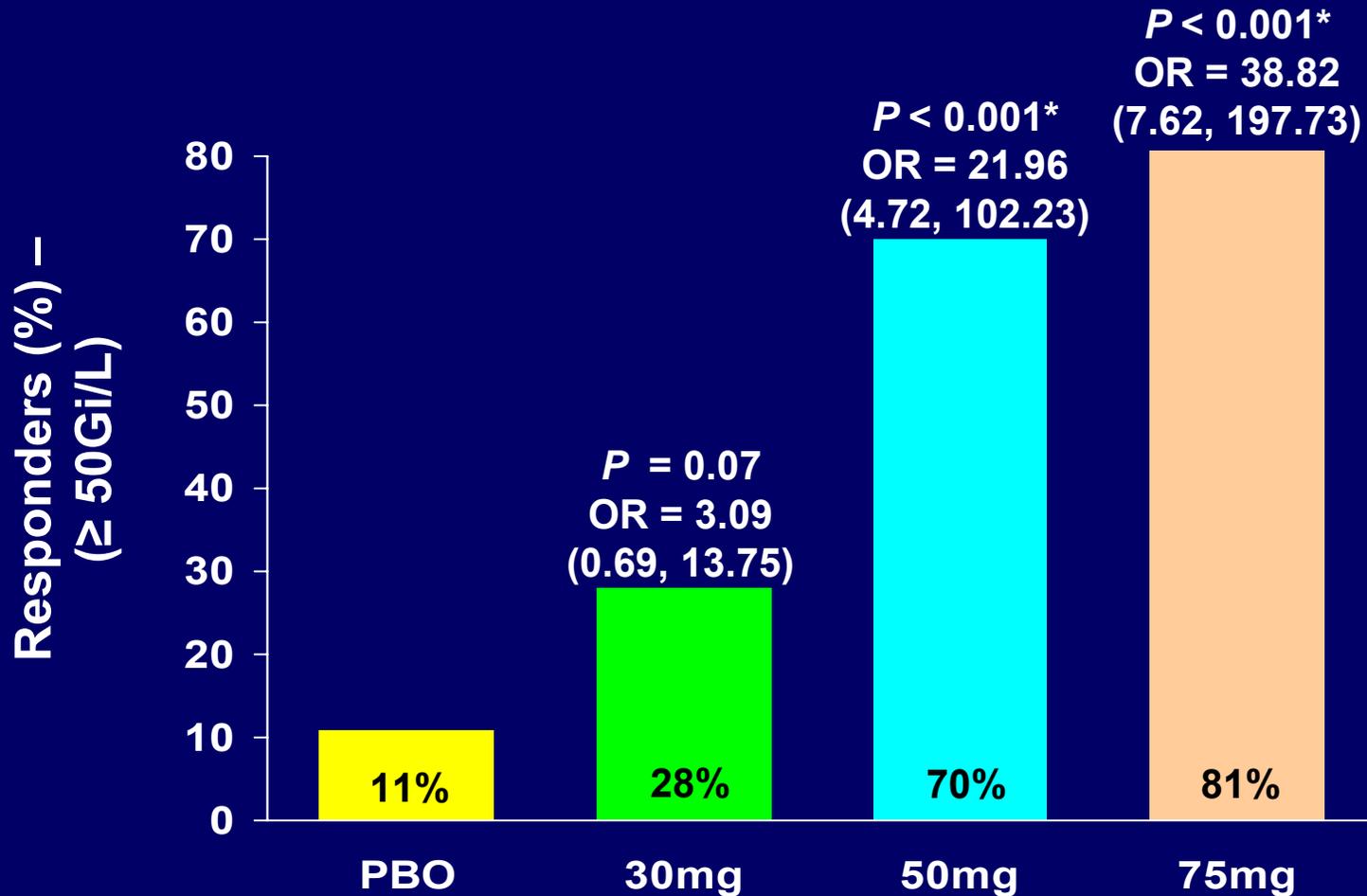
# Short Term Treatment Studies

- 6 week treatment duration, 6 week follow up
- Baseline platelet count:  $< 30\text{Gi/L}$
- Primary endpoint: proportion of subjects with platelet count  $\geq 50\text{Gi/L}$  on day 43
  - Subjects with  $> 200\text{Gi/L}$  stopped therapy early – counted as responders
- Stratification
  - Use of concomitant ITP medication
  - Splenectomy status
  - Baseline platelet count

# Baseline Characteristics

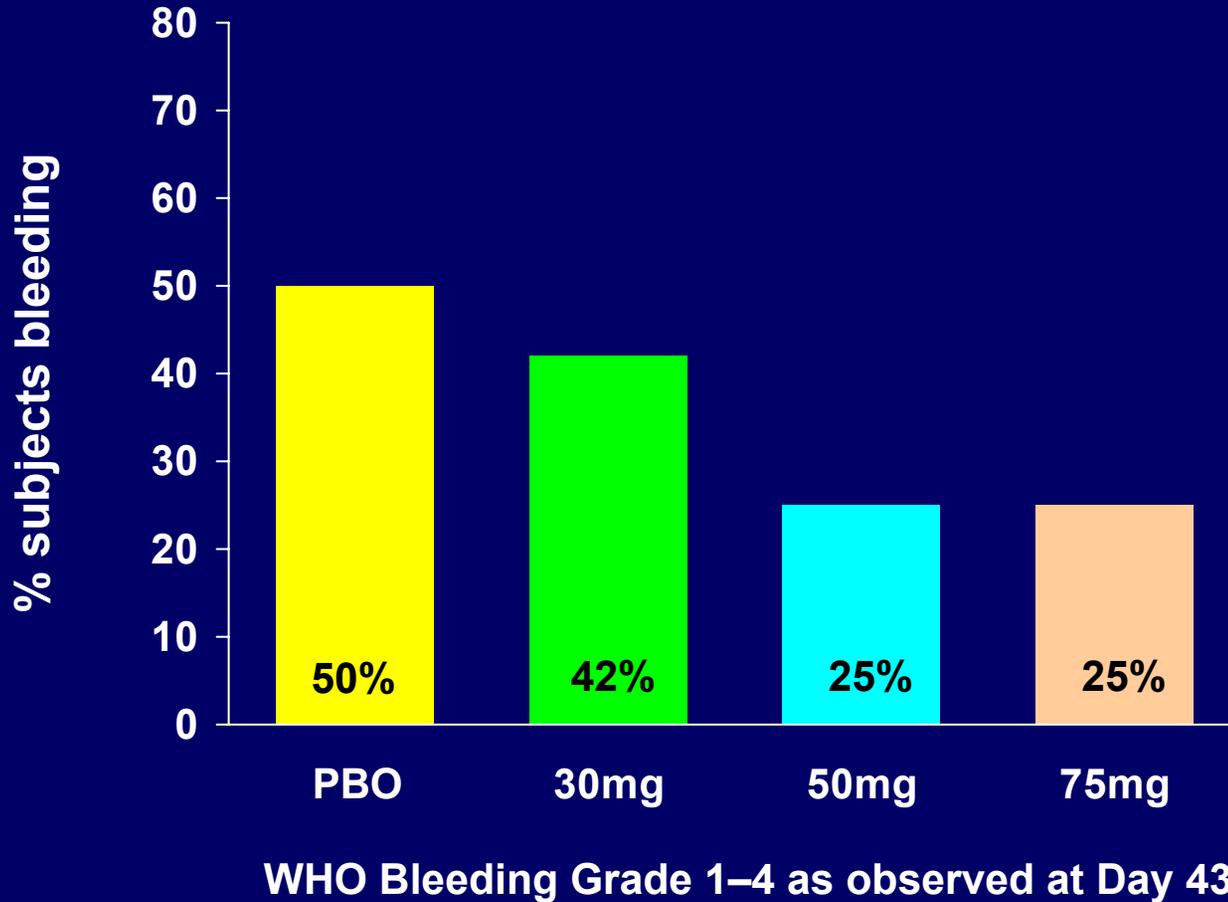
Baseline Characteristics	TRA100773A		TRA100773B	
	PBO N=29 n (%)	<i>Promacta</i> (30, 50, 75 mg) N=88 n (%)	PBO N=38 n (%)	<i>Promacta</i> 50 mg N=76 n (%)
Median age (years)	42	51	51	47
Female	16 (55)	57 (65)	27 (71)	43 (57)
Use of other ITP medication at randomization	6 (21)	32 (36)	17 (45)	32 (42)
Splenectomized	14 (48)	41 (47)	14 (37)	31 (41)
Baseline Platelet Counts $\leq 15 \text{Gi/L}$	14 (48)	42 (48)	17 (45)	38 (50)
Number of prior treatments				
$\geq 3$ prior therapies	14 (48)	46 (52)	16 (42)	42 (55)
$\geq 4$ prior therapies	12 (41)	30 (34)	9 (24)	30 (39)
$\geq 5$ prior therapies	8 (28)	22 (25)	7 (18)	16 (21)

# TRA100773A: Elevation of Platelet count



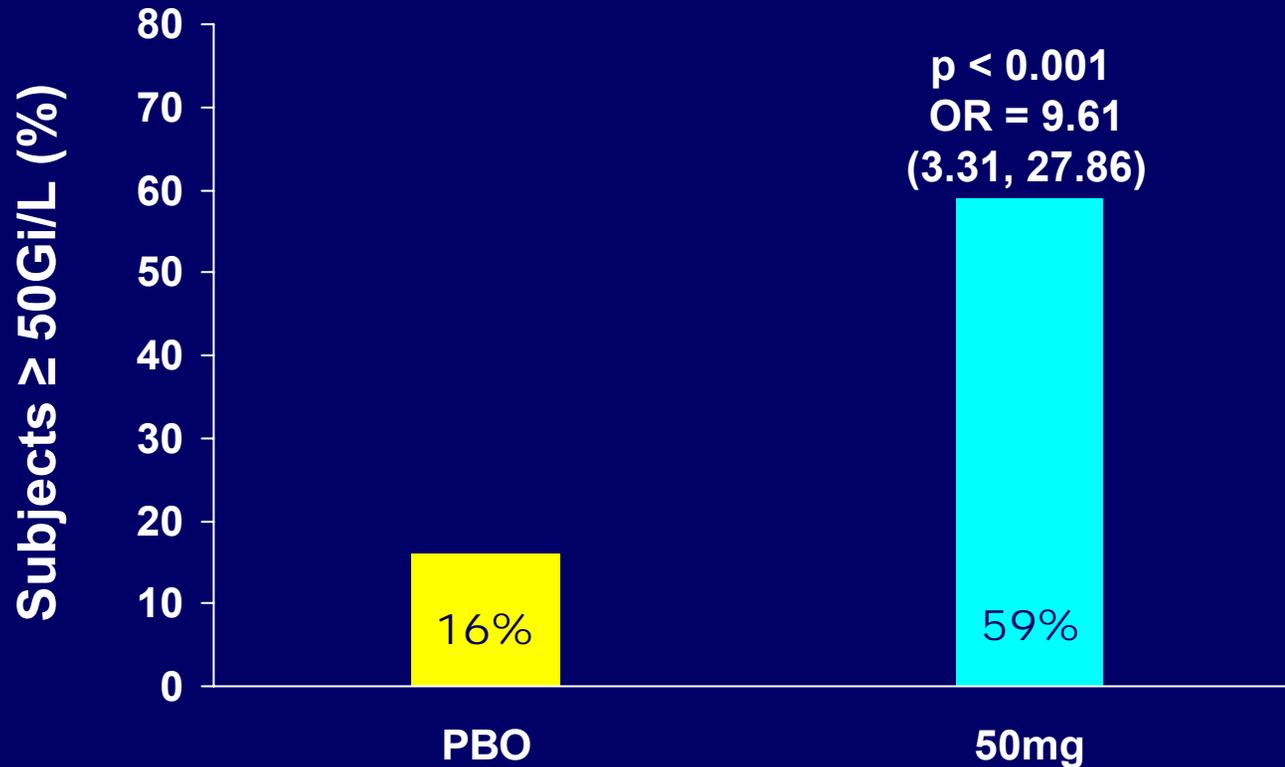
\*1-sided *P* value. odds ratio (OR) ; *Promacta* / placebo

# TRA100773A: Reduction of Bleeding



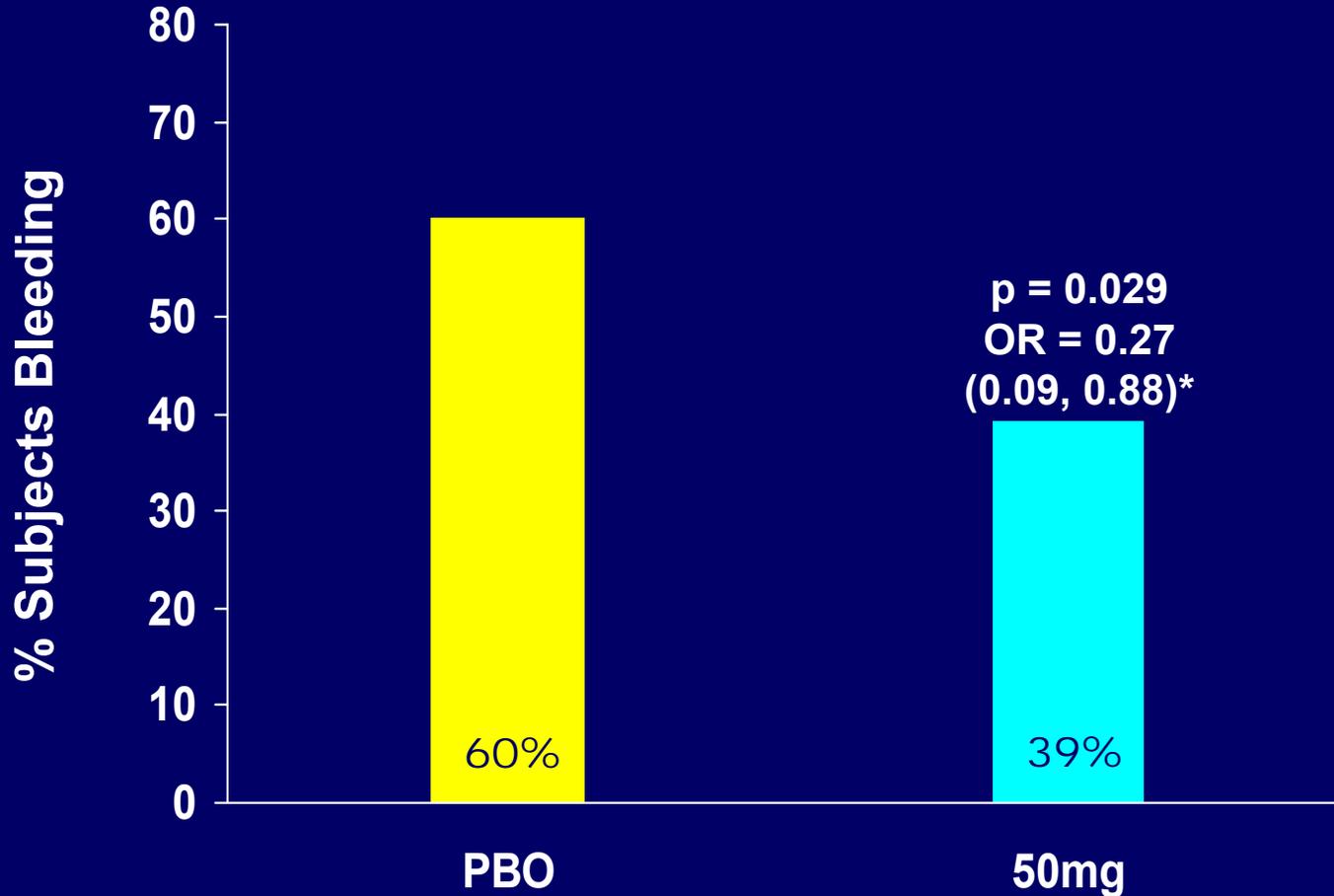
**Reduction in bleeding not statistically significant**

# TRA100773B: Elevation of Platelet Count



\*2-sided  $P$  value, OR, odds ratio; *Promacta* / placebo

# TRA100773B: Reduction of Bleeding



WHO Bleeding Grade 1–4 as observed at Day 43

\*Logistic regression

# Statistically Significant Reduction in Bleeding

## TRA100773B: WHO Bleeding Scale (Grade 1-4)

### Odds Ratios (95% CI)

#### Pre-specified Analyses

Bleeding at D43  
Logistic Regression



Bleeding over time  
Repeated Binary Data (GEE)



Severity of bleeding at D43  
Ordinal Logistic Regression



#### Sensitivity Analyses

Bleeding End of Treatment  
Logistic Regression



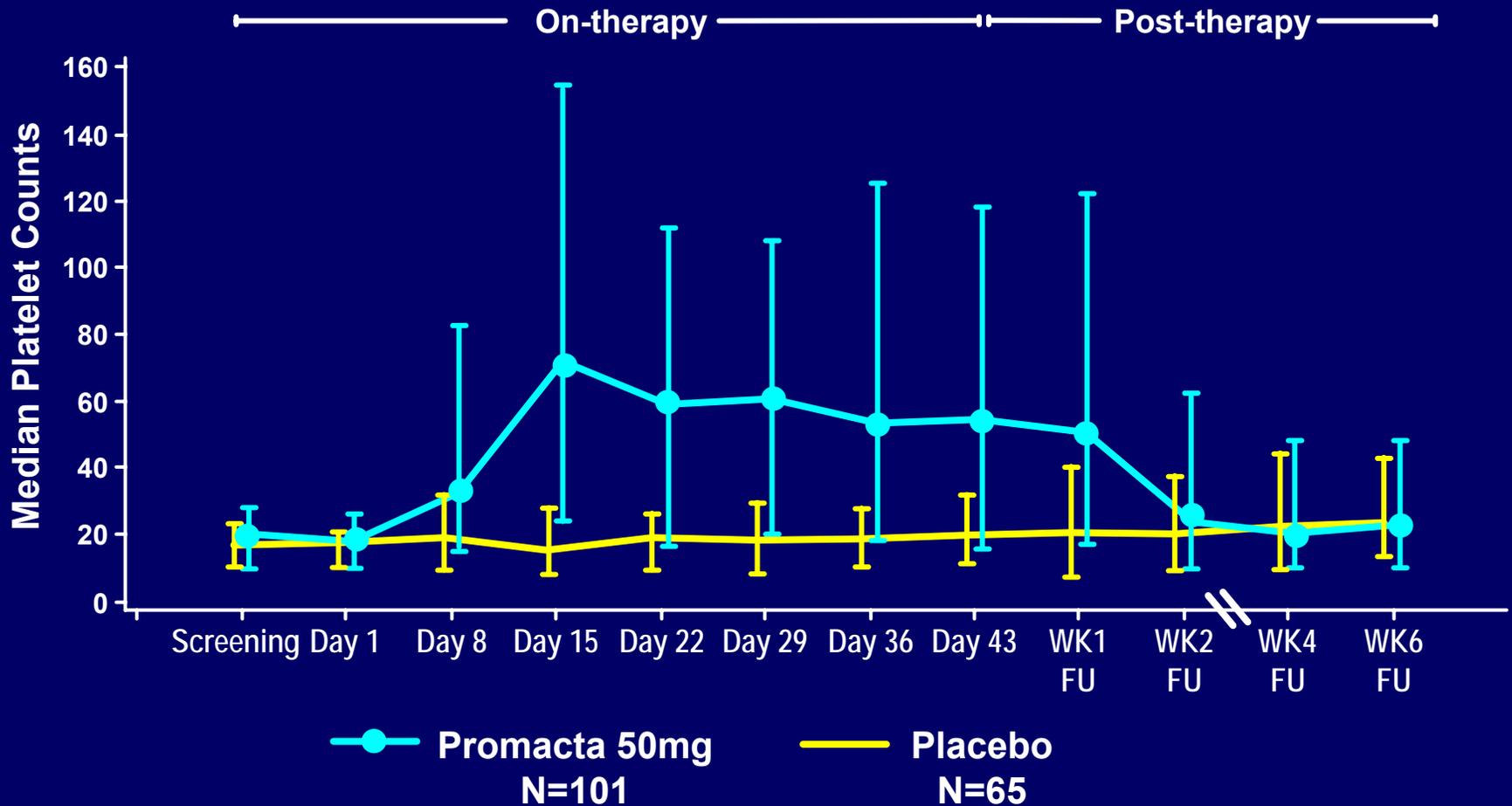
Bleeding over time  
Repeated Binary Data (SS)



0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2

# Platelet Count Dynamics

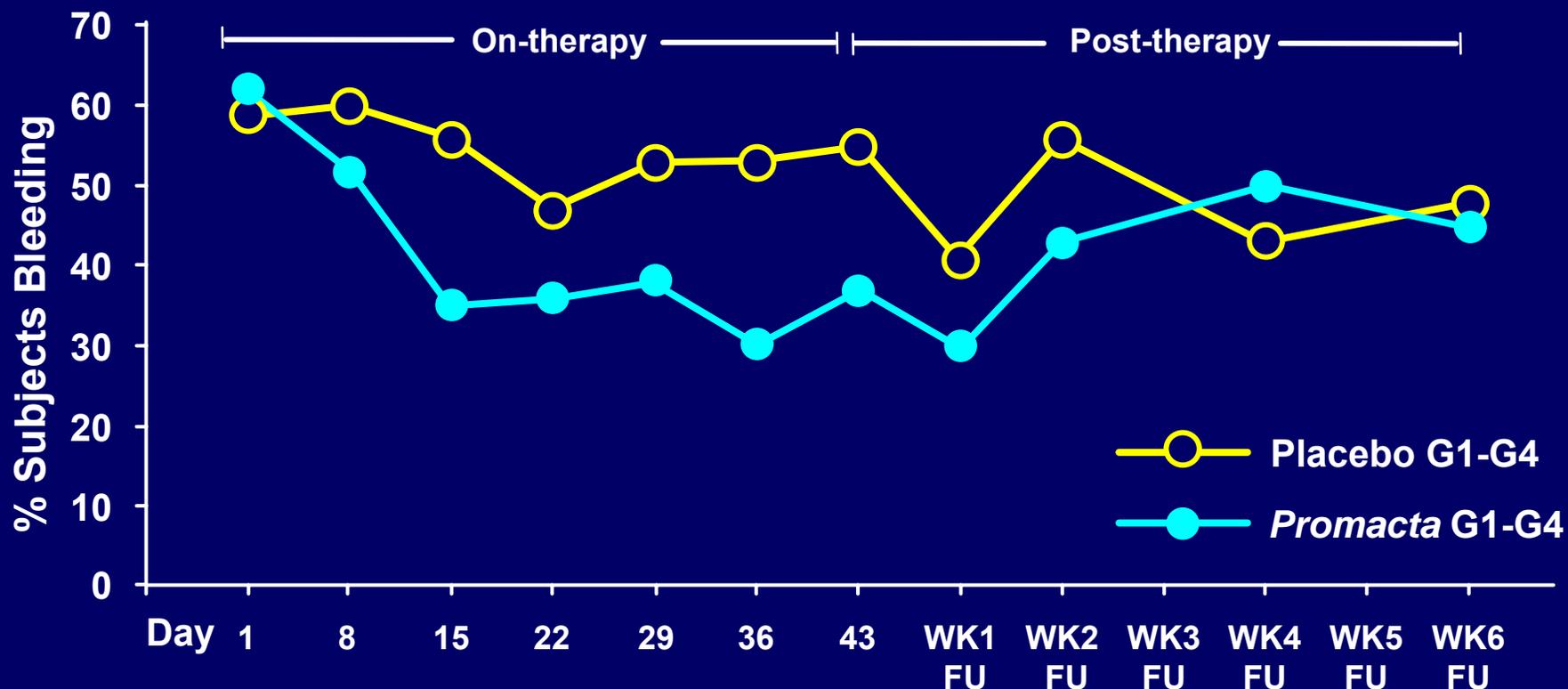
## Pooled TRA100773A and TRA100773B



Bars represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles

# Reduction in Bleeding (Pooled TRA100773A and TRA100773B)

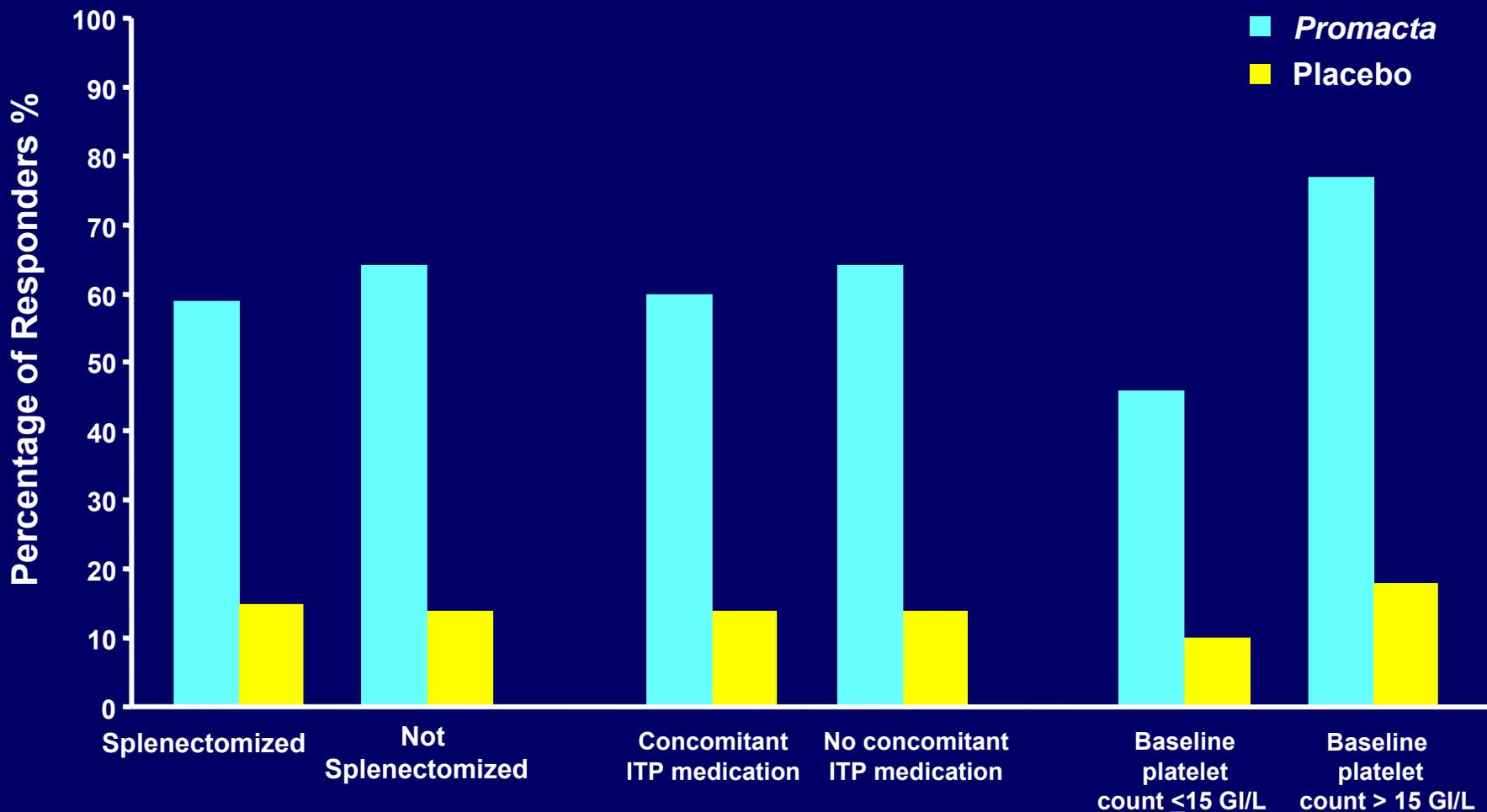
Bleeding symptoms are reduced in 50% of patients



Odds Ratio = 0.49 [0.26, 0.89], p = 0.021 (Days 8-43)

# Effectiveness Across Study Strata

(Pooled TRA100773A and TRA100773B)



No statistically significant interaction with treatments

# **Promacta - Hemostatic Challenges**

**(Pooled TRA100773A and TRA100773B)**

**7 challenges in 7 subjects**

## **Promacta**

- **Cholecystectomy**
- **Laparoscopic Cholecystectomy**
- **Teeth extraction**
- **Car accident**

**No rescue medication or bleeding reported in Promacta patients**

## **Placebo**

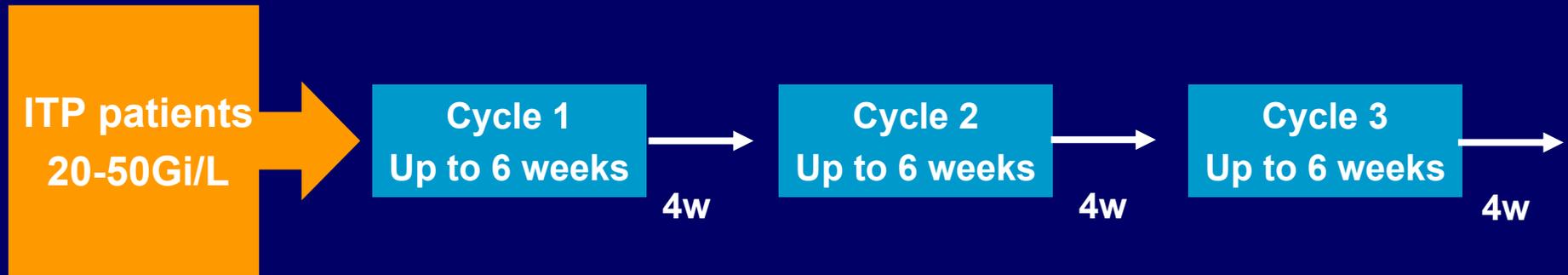
- **Trabeculectomy of right eye (IVIg)**
- **Total hip replacement (IVIg/platelet transfusion)**
- **Removal of a 'papillomatous change' in throat (tranexamic acid)**

# REPEAT

## Ongoing, Open-label, Intermittent Dosing Study

### Primary Endpoint:

Proportion of subjects with a response ( $\geq 50\text{Gi/L}$  + at least 2x baseline) in Cycles 2 or 3 given a Cycle 1 response

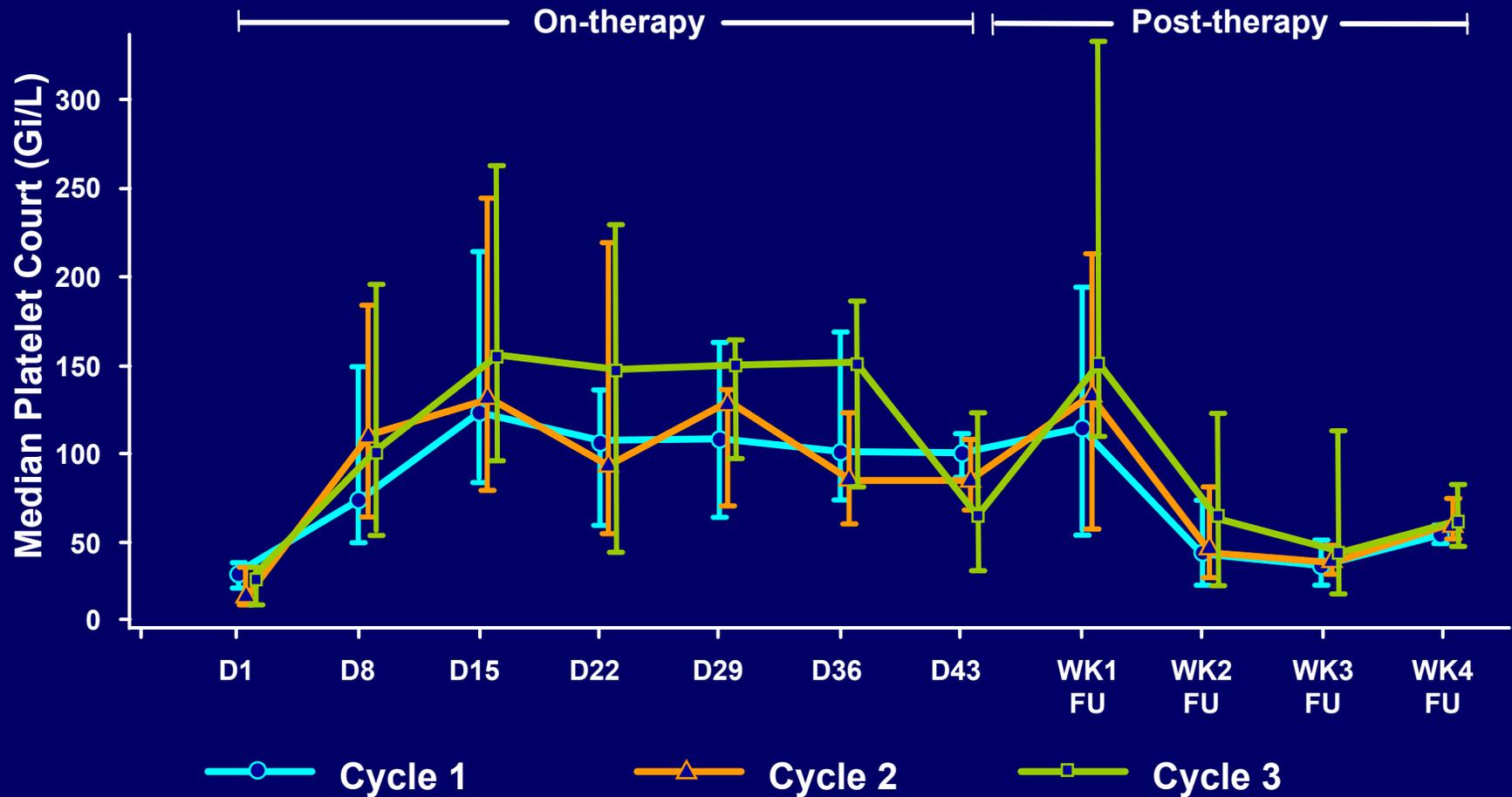


# REPEAT Primary Endpoint – Consistent Platelet Response Across 3 Cycles

## Primary endpoint achieved

	<i>Promacta</i> 50mg N=66
Response in Cycle 1, n (%) 95% CI	51 (82) (71, 93)
Evaluable in Cycle 2 or 3, n <b>Responders in Cycle 1 and in Cycle 2 or 3, n(%)</b> 95% CI	33 <b>29 (88)</b> (72, 97)
Evaluable in Cycle 2 and 3, n <b>Responders in Cycle 1 and in Cycle 2 and 3, n(%)</b> 95% CI	16 <b>13 (81)</b> (54, 96)

# REPEAT - Consistent Platelet Count Dynamics Across 3 Cycles



Bars represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles

# REPEAT - Reduction in Bleeding Across 3 Cycles

WHO Bleeding Scale	Cycle	Baseline	Day 43
Grade 1-4: Any bleeding	1	49%	8%
	2	59%	8%
	3	32%	50%*
Grade 2-4: Clinically Significant bleeding	1	16%	0
	2	9%	8%
	3	11%	0*

\* 4 evaluable subjects at Day 43 in Cycle 3

**No rescue medication was given between cycles**

# REPEAT - Hemostatic Challenges

- 8 procedures in 7 subjects
- All patients were responders
- **No abnormal bleeding reported and no rescue medications were required:**
  - transurethral prostatectomy
  - cardiac catheterization
  - sinus operation
  - colon polypectomy
  - tooth extraction
  - colonoscopy (n=2)
  - dental cleaning

# EXTEND

## Ongoing, Open-label, Long-term, Extension Study

Primary endpoint: Long term safety and tolerability in subjects previously enrolled in *Promacta* ITP studies



Stage 1: Initiate *Promacta* Dosing

Stage 2: Taper Concomitant Medication

Stage 3: *Promacta* Dose Modulation

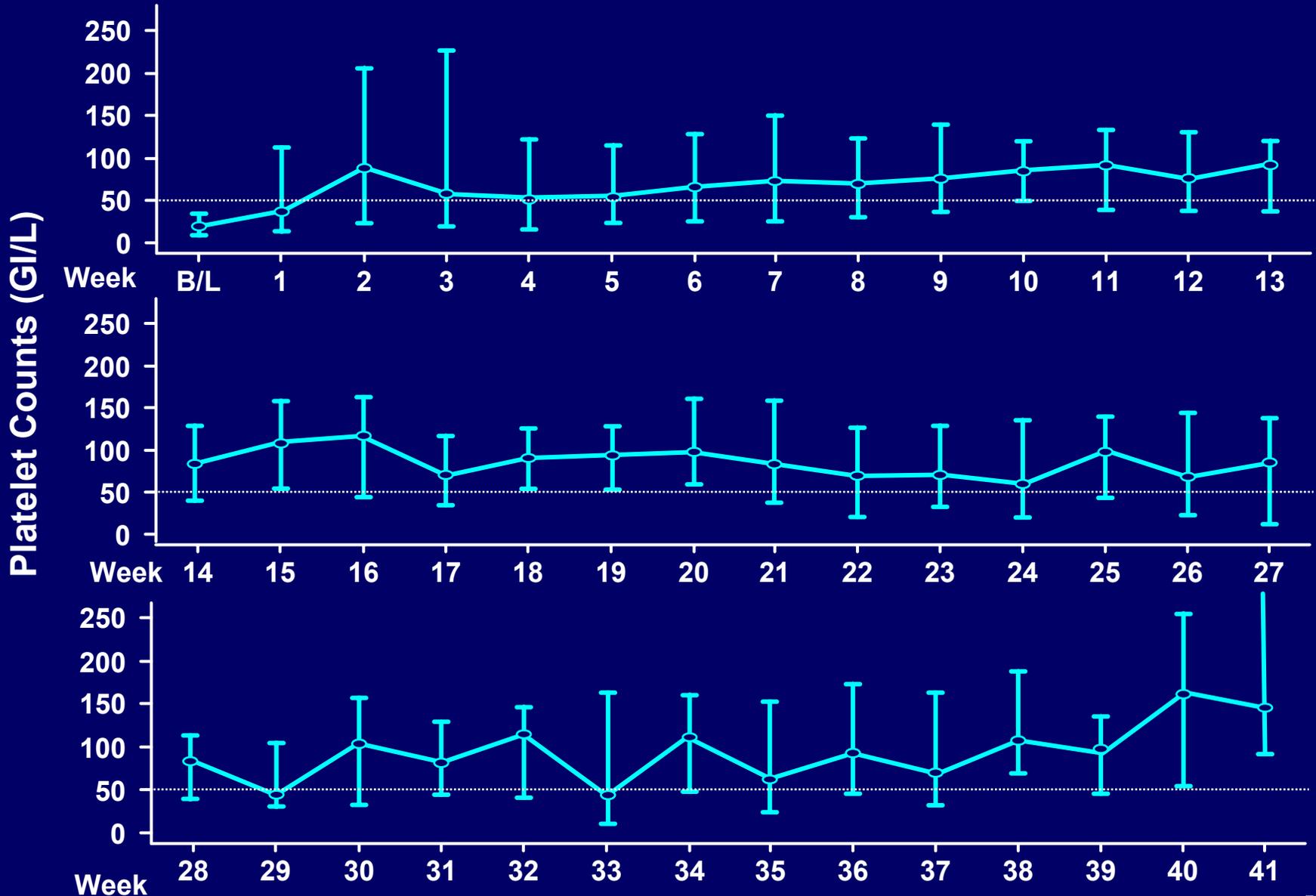
Stage 4: *Promacta* Maintenance

## **EXTEND: Key Efficacy Results**

- **Durable platelet count elevation**
- **Short-term efficacy predicts long-term efficacy**
- **Patients previously on placebo respond to Promacta**
- **Durable bleeding reduction**
- **Reduction/discontinuation of concomitant medications**

# EXTEND – Durable Platelet Count Elevation

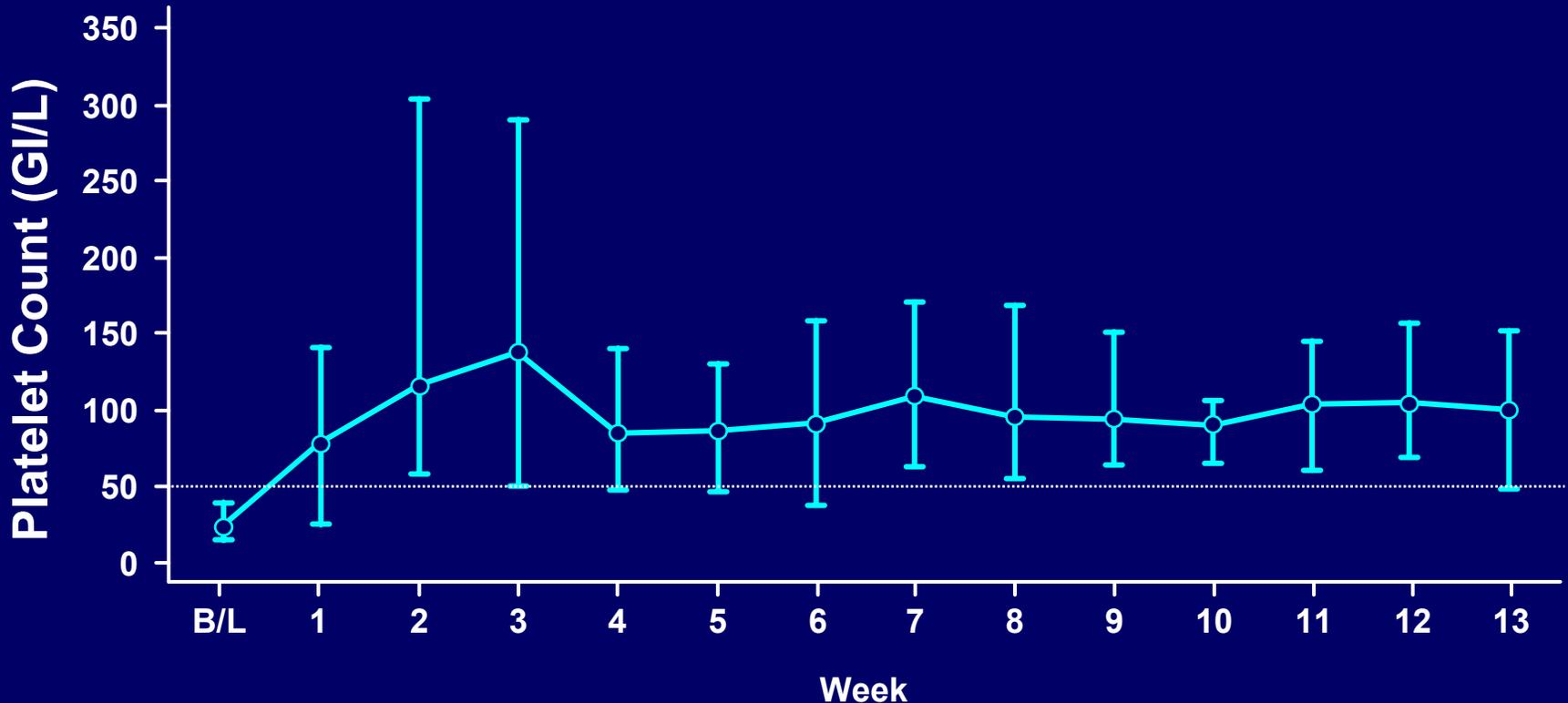
54% of subjects had a continuous elevation  $\geq 50$  Gi/L for  $\geq 10$  weeks



Bars represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles

# Short-term Efficacy Predicts Long-term Efficacy

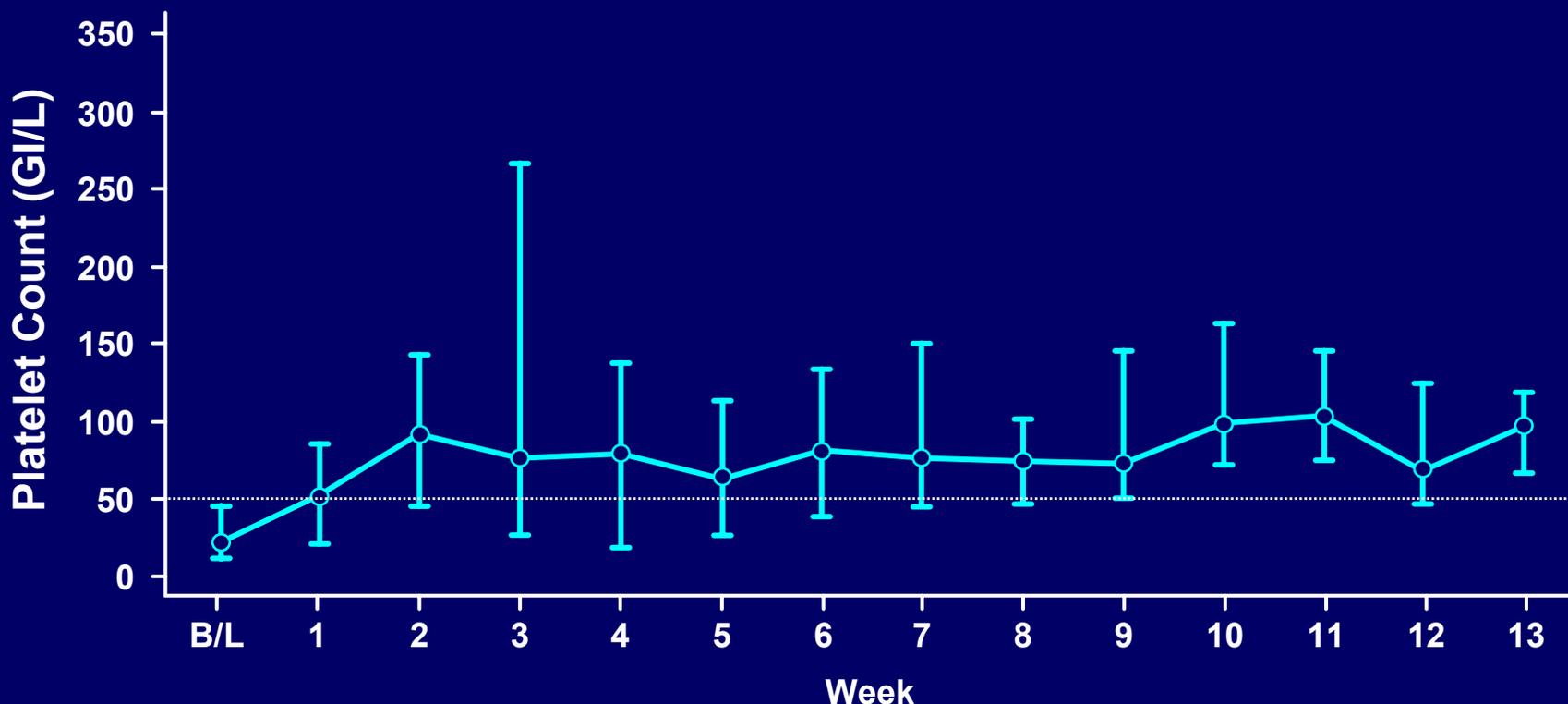
92% of responders in short term trials respond again



Bars represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles

# EXTEND: Patients Previously on Placebo Respond to Promacta<sup>1</sup>

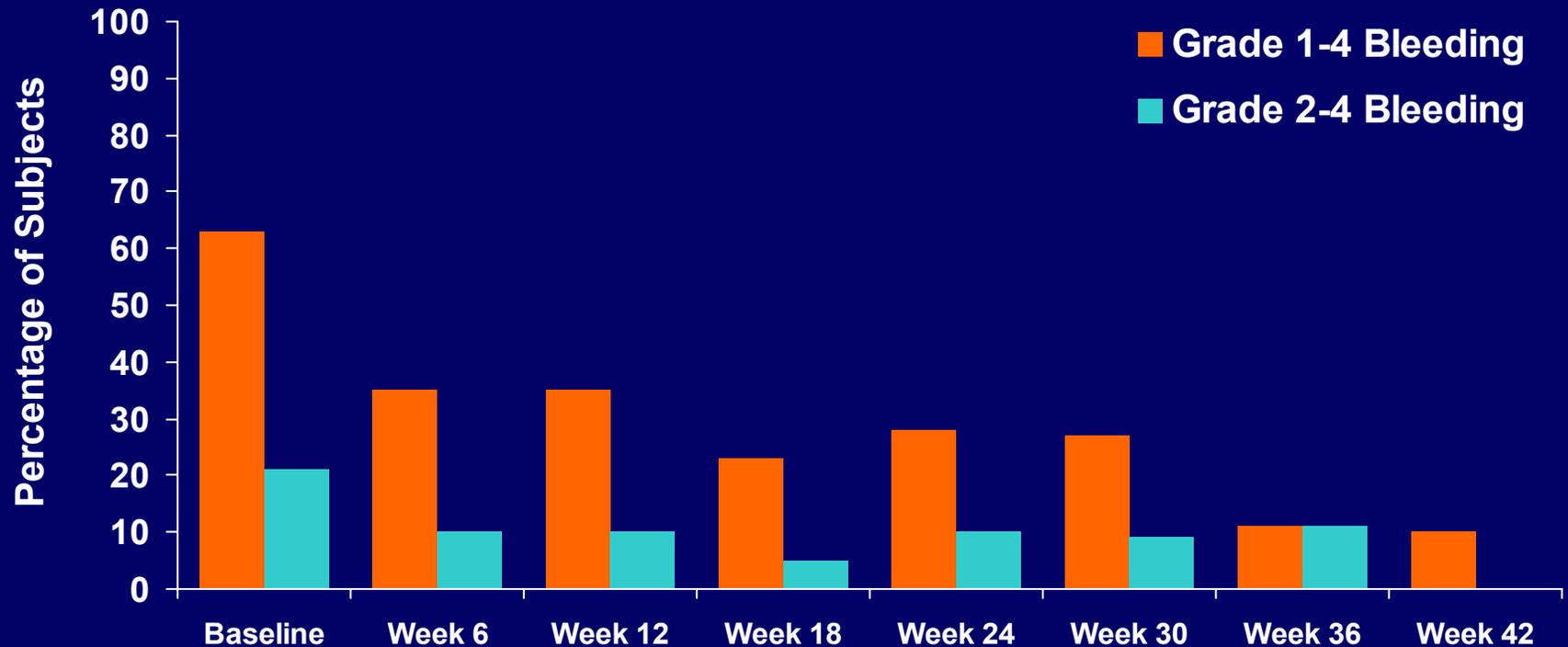
63% achieved platelet counts  $\geq 50$  Gi/L in EXTEND for >75% of assessments



<sup>1</sup> Received placebo in TRA100773A and TRA100773B (n=30)

Bars represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles

# EXTEND - Durable Bleeding Reduction



# **EXTEND - Hemostatic Challenges**

- **13 subjects had at least one procedure during the study including:**
  - **CT guided aspirate of lung**
  - **Colonoscopy**
  - **Uterine polypectomy**
  - **Arthroscopy**
  - **Esophagogastroduodenoscopy**
  - **Endoscopic retrograde cholangiopancreatography**
- **No abnormal bleeding was reported**

# **EXTEND: Reduction/discontinuation of Concomitant Medications**

- **40 subjects reported use of ITP medications**
- **24 attempted to reduce/discontinue**
- **18 subjects (75%) successfully discontinued or reduced concomitant ITP medications**
  - **14 discontinued**
    - **3 danazol + corticosteroids**
    - **8 corticosteroids**
    - **2 androgenic steroids**
    - **1 mycophenolic acid**
  - **4 reduced corticosteroids**

# Overall Efficacy Conclusions

- **Clinical benefit observed in 4 studies**
  - Increased platelet counts
  - Reduced bleeding
  - Patients overcame hemostatic challenges
- **Short-term efficacy predicted long-term efficacy**
- **Clinical benefit seen with short-term treatment, intermittent and long-term therapy**

# Exposure to *Promacta* in ITP Studies

<b>Data included 120-day update</b>	<b>N=493</b>
<b>Exposure to Promacta</b>	<b>460*</b>
<b>≥ 1 day</b>	<b>458</b>
<b>≥ 6 months</b>	<b>155</b>
<b>≥ 12 months</b>	<b>39</b>
<b>≥ 15 months</b>	<b>12</b>

Mean daily dose = 50mg

Median exposure = 70 days (Range 2, 560)

\*Includes estimated 2/3 RAISE patients exposed to Promacta

# Most Common Adverse Events\*

(Pooled TRA100773A and TRA100773B)

Preferred Term	Placebo N=67 n (%)	<i>Promacta</i> 50mg N=106 n (%)
Any AE, n (%)	32 (48)	60 (57)
Headache	10 (15)	9 (8)
Nasopharyngitis	3 (4)	6 (6)
Nausea	0	6 (6)
Fatigue	5 (7)	4 (4)
Arthralgia	4 (6)	2 (2)

**No clinically meaningful differences  
between Promacta and Placebo**

\*Regardless of causality

# Grade 3/4 Laboratory Abnormalities

(Pooled TRA100773A and TRA100773B)

	<b>Placebo</b> N=67 n (%)	<b>Promacta 50mg</b> N=106 n (%)
Hemoglobin	4 (7)	5 (5)
Lymphocytes	3 (5)	6 (6)
WBC/Neutrophils	7 (10)	3 (3)
ALT/AST	2 (3)	5 (5)
Bilirubin	1 (2)	1 (<1)
Glucose	3 (5)	1 (<1)
Sodium	2 (3)	0
Potassium	1 (2)	2 (2)

**No clinically meaningful differences  
between Promacta and Placebo**

# Safety: SAEs, Withdrawals Due to AEs and Deaths<sup>1</sup>

Similar incidence of SAEs and withdrawals due to AEs in placebo and *Promacta* across studies

	Short-term and Intermittent Dosing Studies, n (%)			Long-term Studies, n (%)	
Subjects	Placebo N=67	<i>Promacta</i> 50mg N=106	REPEAT N=66	EXTEND N=207	RAISE Blinded N=196
Any SAEs	5 (7)	4 (4)	1 (2)	17 (8)	26 (13)
Deaths	0	0	0	2 (1) <sup>2</sup>	1 (<1) <sup>3</sup>
Withdrawals due to AEs	5 (7)	5 (5)	1 (2)	8 (4)	14 (7)

<sup>1</sup>On-therapy+1 day

<sup>2</sup>Car accident; sudden death (no autopsy)

<sup>3</sup>Brain stem hemorrhage (blinded)

# Bleeding SAE – TRA100773A and B

- **On therapy – all in non responders, all <15Gi/L**
  - **Placebo – 3%**
    - GI hemorrhage/Cerebral hemorrhage/hematuria – day 15
    - Ruptured varicose vein – day 13
  - **Promacta – 1%**
    - GI hemorrhage – day 16
    - Cerebral hemorrhage – day 12
- **Off therapy – all <15Gi/L**
  - **Promacta – 3%**
    - Rectal hemorrhage (+9), subarachnoid hemorrhage (+39), epistaxis (+32), menorrhagia\*(+16), petechiae\* (+22),

\*responder during treatment

# Safety Assessments of Special Interest

- Hepatobiliary laboratory abnormalities
- Transient decrease of platelet counts following discontinuation of *Promacta*
- Thromboembolic events
- Bone marrow reticulin

# Hepatobiliary Laboratory Abnormalities

Analysis performed according to FDA draft guidance document for drug-induced liver injury (10/2007):

- ALT  $\geq$  3x ULN or AST  $\geq$  3x ULN *or*
- Total Bili > 1.5x ULN *or*
- AP > 1.5x ULN

	TRA100773A and TRA100773B		REPEAT	EXTEND	RAISE
	Placebo N=67 n (%)	Promacta (30, 50, 75mg) N=164 n (%)	Promacta N=66 n (%)	Promacta N=207 n (%)	Blinded N=196 n (%)
On-therapy+ 30 d	5 (8)	16 (10)	3 (5)	12 (6)	20 (10)

Reversible and without evidence of impaired liver function

# Hepatobiliary Laboratory Abnormalities

- **3 patients with AT > 3x ULN *and* total bilirubin > 1.5xULN:**
  - Multiorgan failure probably due to sepsis of pulmonary origin (TRA100773A)
  - Cholangitis; history of biliary disease (EXTEND)
  - Indirect Hyperbilirubinemia (EXTEND)
- **All 3 cases were confounded**
- **No Hy's law cases**

# Post-therapy Decrease in Platelet Counts

- Reoccurrence of thrombocytopenia after treatment discontinuation is expected
  - Natural disease fluctuation
  - Imprecision of platelet count measurements below 10Gi/L
- Transient decrease: <10Gi/L and 10Gi/L less than baseline within 4 weeks of discontinuation<sup>1</sup>

TRA100773A and TRA100773B		REPEAT	EXTEND
Placebo N=67 n (%)	Promacta 50mg N=106 n (%)	Promacta N=66 n (%)	Promacta N=78 n (%)
4 (6)	11* (10)	7 (11)	5 (6)

\* 2 patients had bleeding AEs

(Grade 3 menorrhagia and Grade 1 gingival bleeding)

# Thromboembolic Events

- **11 subjects had an event**
  - PE (5), DVT (4), TIA (1), PRIND (1)
- **No association with platelet count**
  - 6 patients with  $<100\text{Gi/L}$  at time of event
- **All had risk factors:**
  - Hospitalization and no prophylactic anti-coagulation (n=4)
  - IVIg 5-8 days before event (n=3)
  - Other, such as advanced age, smoking, oral contraception, screening tests positive for lupus anticoagulants, varicose veins

# Thromboembolic Events

- Thromboembolic events across Promacta ITP program
  - **Frequency: 2.6%**
  - **Incidence rate: 5.1/100 patient years**
  - 3.2% prior to study participation - none of these patients had TE events in Promacta studies
- Thromboembolic events (TE) reported in other series of ITP patients
- Frequency:
  - 3% (Aledort et al 2004)
  - 4.4% Romiplostim (3/08 ODAC)
  - 6.9% (GSK epidemiology study)
- Incidence rate:
  - 5.2/100 patient years (GSK epidemiology study)
  - 7/100 patient years (Romiplostim 3/08 ODAC)

# Bone Marrow Reticulin

- Limited information available in the medical literature:
  - Mild / moderate reticulin observed in ITP patients and hematologically normal individuals<sup>1</sup>
- *Promacta* Intermittent and Long-term Dosing Trials:
  - No routine baseline bone marrow biopsies required
  - Frequent automated WBC
  - Manual blood smear if automated WBC differential abnormal
  - Bone marrow biopsy if smear suggested findings not consistent with ITP
  - Bone marrow biopsies requested in patients > 12 months on EXTEND

<sup>1</sup>Mufti, 2007; Beckman, 1990; Bauermeister, 1971

# Bone Marrow Reticulin

- **Results:**
  - No blood smear abnormalities led to BM biopsies
  - 19 BM biopsies available from EXTEND
    - 7 with reticulin (n=5) and/or collagen fiber (n=2) increase detected (documented pre-existence of reticulin in 2 subjects)
- **No AEs or clinical consequences**

# ***Promacta* Safety Conclusions**

- ***Promacta* was well-tolerated**
- **Most common AEs – headache, nasopharyngitis, nausea**
- **Hepatobiliary laboratory abnormalities are generally mild and reversible and without clinical sequelae**
- **Post-treatment reoccurrence of thrombocytopenia:**
  - **Observed on Placebo and *Promacta* groups**
  - **Not accompanied by clinically meaningful increases in bleeding symptoms**

# Concluding Remarks

- **Unmet medical need**
- **Serious illness**
- **Bleeding in ITP can be serious and life-threatening**
- **Present therapies are often ineffective, have significant side effects, are inconvenient and many are not approved for ITP**
  - **Used for short term elevation**

# Concluding Remarks (2)

## *Promacta*

- **Novel MOA; addresses suboptimal platelet production**
- **Clinical benefit with short term and intermittent treatment**
  - **Increases platelet count, decreases bleeding, overcome hemostatic challenge**
- **Clinical benefit observed with long term treatment**
- **Reliable and convenient**

**Data package includes the two largest reported controlled studies in ITP**

## Concluding Remarks (3)

### *Promacta*

- Well tolerated with no safety issues that preclude approval
- Potential safety issues addressed in comprehensive risk-management plan

**Benefit risk profile should allow approval of *Promacta* in patients with chronic ITP**

**Promacta is indicated for the short-term treatment of previously-treated patients with chronic ITP to increase platelet counts and reduce or prevent bleeding**

**NDA 22-291**  
**PROMACTA<sup>®</sup> (eltrombopag)**

**GlaxoSmithKline Presentation to the  
Oncologic Drugs Advisory Committee**

**30 May 2008**

# TRA100773A – Platelet Response >200Gi/L and >400Gi/L

Platelet Counts	Placebo	Promacta (30mg)	Promacta (50mg)	Promacta (75mg)
	N=27	N=29	N=27	N=26
>200Gi/L, n (%)	1 (4)	4 (14)	10 (37)	13 (50)
>400Gi/L, n (%)	1 (4)	1 (3)	6 (22)	4 (15)

# REPEAT Primary Endpoint – Consistent Platelet Response Across 3 Cycles

## Final Analysis

	<i>Promacta 50mg</i> (N= 66)
<b>Response in Cycle 1</b>	<b>52 (80)</b>
Evaluable in Cycle 2 or 3, n	52
<b>Responders in Cycle 1 and in Cycle 2 or 3, n(%)</b>	<b>45 (87)</b>
95% CI for Proportion (Exact Methods)	(0.74, 0.94)
Evaluable in Cycle 2 and 3, n	48
<b>Responders in Cycle 1 and in Cycle 2 and 3, n(%)</b>	<b>34 (71)</b>
95% CI for Proportion (Exact Methods)	(0.56, 0.83)

# WHO Bleeding Scale - Examples

<b>Grade 0 None</b>	<b>Grade 1 'Petechiae'</b>	<b>Grade 2 Mild Blood Loss</b>	<b>Grade 3 Gross Blood Loss</b>	<b>Grade 4 Debilitating Blood Loss</b>
None	Occasional bruises/ petechiae	Ecchymoses	Extensive ecchymoses/frank bleeding	Life-threatening requiring transfusion ± shock
None (normal period)	Petechiae	Multiple blood blisters	Continous bleeding from gums or oral cavity	Hemoptysis requiring transfusion ± shock
	Blood when blowing nose	Spontaneous epistaxis controlled by simple pressing	Continuous epistaxis requiring packing or other procedure	Major ICH with neurological deficit
	Occult blood	Macroscopic blood in stool	Profuse bleeding	
	Microscopic hematuria	Macroscopic hematuria	Frank blood	
	Spotting	Unexpected bleeding > heavier than normal menses	Profuse bleeding/menorrhagia	
	Occasional flecks of blood in sputum	Moderate hemoptysis	Profuse hemoptysis	
Minor bleed confirmed by CT/MRI				

# Promacta does not affect platelet function

- **In vitro studies in platelets from healthy subjects**
  - Normal aggregation and activation
    - Aggregometry, FACS (p-selectin)
- **In vivo studies in healthy subjects and ITP patients on Promacta treatment**
  - Normal aggregation and activation
    - Healthy: Aggregometry, FACS (PAC-1, p-selectin)
    - ITP: FACS (plt-leuc, p-selectin, GP1b)