Phase I/II, Open-Label, Adaptive Study of Oral Bruton Tyrosine Kinase Inhibitor PRN1008 in Patients With Relapsed/Refractory Primary or Secondary Immune Thrombocytopenia

David J. Kuter,[1] Ralph V. Boccia,[2] Eun-Ju Lee,[3] Merlin Efraim,[4] Nikolay Tzvetkov,[5] Jiri Mayer,[6] Marek Trněný,[7] Milan Kostal, MD,[8] Roman Hajek,[9] Vickie McDonald,[10] Olga Bandman,[11] Regan Burns,[11] Ann Neale,[11] Dolca Thomas,[11] and Nichola Cooper[12]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Center for Cancer and Blood Disorders, Bethesda, MD, USA; [3]Department of Medicine, Weill Cornell Medical College-New York, Presbyterian Hospital, New York, NY, USA; [4]Multiprofile Hospital for Active Treatment Sveta Marina EAD, Bulgaria; [5]MHAT Dr. Georgi Stranski, Clinic of Hematology, Pleven, Bulgaria; [6]Department of Internal Medicine, Hematology and Oncology, Masaryk University Hospital, Brno, Czech Republic; [7]Charles University Hospital, Prague, Czech Republic; [8]Faculty of Medicine Hradec Kralove, Charles University, Prague, Czech Republic; [9]Department of Haematooncology, University Hospital Ostrava and Faculty of Medicine University of Ostrava, Ostrava, Czech Republic; [10]Barts Health NHS Trust, The Royal London Hospital, London, United Kingdom; [11]Principia Biopharma Inc, South San Francisco, CA, USA; and [12]Department of Medicine, Hammersmith Hospital, London, United Kingdom

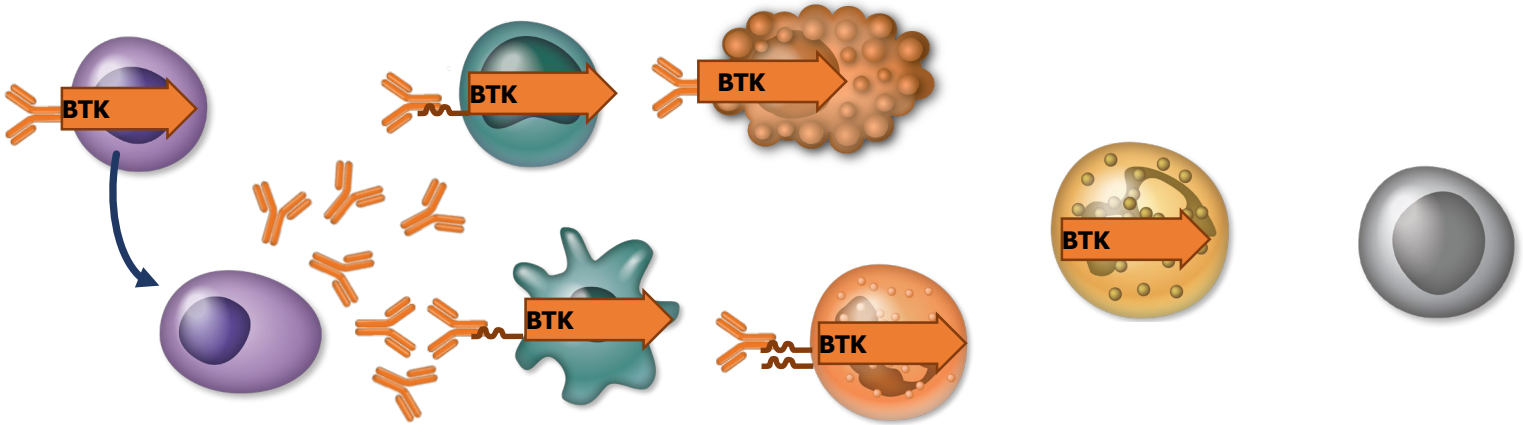
Immune Thrombocytopenia (ITP)

- ITP is characterized by immune-mediated platelet destruction and impairment of platelet production, leading to thrombocytopenia, a predisposition to bleeding, and adverse impact on patient quality of life (QOL)
- Current therapies for adults with ITP include
  - Initial: IVIG, corticosteroids (CS)
  - Subsequent: splenectomy, thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, and other immunosuppressive therapies (MMF, cyclosporine)
- Unmet needs in relapsed or refractory ITP
  - Improved remission rates and durability
  - Avoid rapid increase of platelet counts/thrombosis risk
  - Steroid-free regimens
  - A tolerable and safe therapy that ensures good patient QOL

IVIG, intravenous immune globulin; MMF, mycophenolate mofetil.

1. Neunert C, Cooper N. *Hematology Am Soc Hematol Educ Program.* 2018;2018:568-575. 2. Cooper N, Ghanima W. *N Engl J Med.* 2019;381:945-955.

Bruton Tyrosine Kinase (BTK) Inhibition Mechanisms for Targeting Drivers of Immune-Mediated Disease[1,2]



B cells, plasma cells	Monocyte, macrophage	Mast cells, basophils	Neutrophils	T cells
Blocks B-cell receptor Inhibits plasma cell differentiation and antibody production	Blocks IgG-mediated FcγR activation, phagocytosis, inflammatory mediators	Blocks IgE-mediated FcεR activation and degranulation	Inhibits activation, adhesion, recruitment, oxidative burst	No effect
BTK inhibition				

FcγR, Fcγ receptor; FcεR, Fcε receptor; Ig, immunoglobulin.

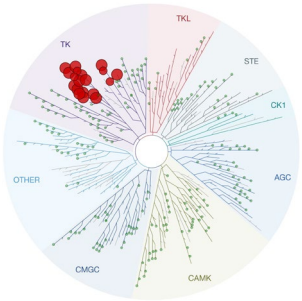
1. López-Herrera G, et al. *J Leukoc Biol.* 2014;95:243-250. 2. Langrish C, et al. *JID (ESDR).* 2019;139:S216 (abstract 011).

PRN1008: Reversible, Covalent Inhibitor Selects for BTK High Occupancy, Low Systemic Exposure for Use in Immunology

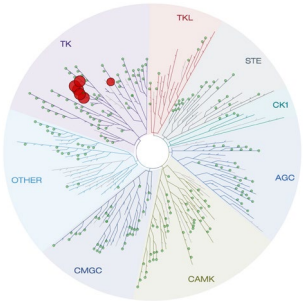
PRN1008 has improved kinase selectivity

In a 251-kinase panel, >90% inhibition was achieved in
- 21 kinases for ibrutinib (1 μM)
- 6 kinases for PRN1008 (1 μM)

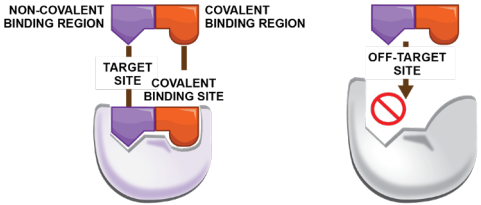
Ibrutinib Kinase Selectivity



PRN1008 Kinase Selectivity

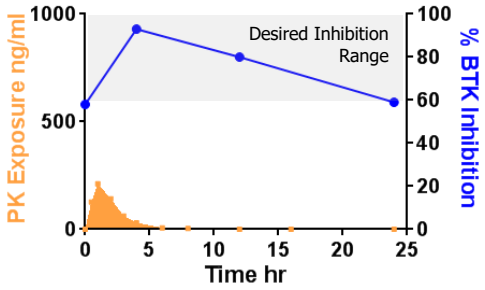


PRN1008 is designed with **Tailored Covalency®** for optimized clinical activity with minimal drug exposure and benefits of reversibility



PRN1008 With Reversible Covalent Binding

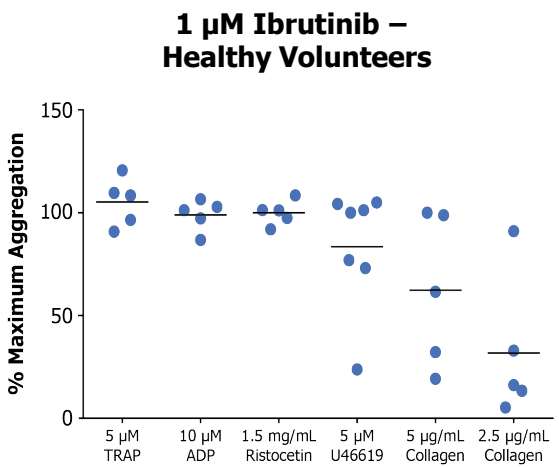
PRN1008



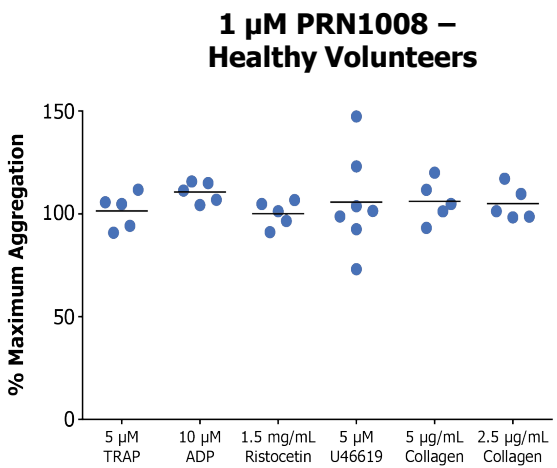
1. Langrish C, et al. *JID (ESDR).* 2019;139:S216 (abstract 011). 2. Bradshaw JM, et al. *Nat Chem Biol.* 2015;11:525-531. 3. Data on file, Principia Biopharma Inc.

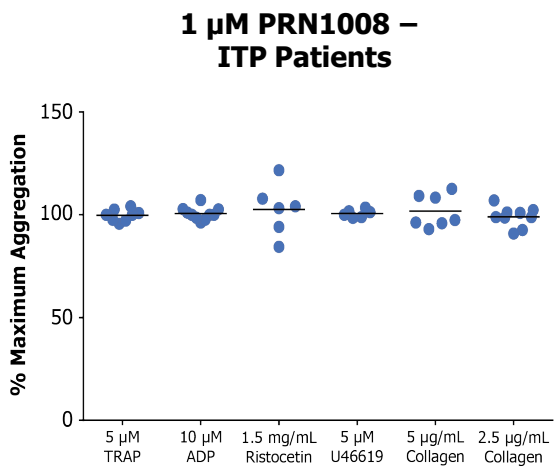
PRN1008: No Impact on Platelet Function

Ibrutinib has significant effects on platelet aggregation in HV



PRN1008 does not alter platelet aggregation in blood taken from healthy volunteers or ITP patients





Platelet-Rich Plasma (PRP) was adjusted to 200,000-300,000 in healthy volunteers. Platelet count >125,000 in ITP patients was required for inclusion in the study.

ADP, adenosine diphosphate; TRAP, thrombin receptor activating peptide.

1. Langrish C, et al. *Blood (ASH).* 2017;130(suppl, abstr):1052. 2. Data on file, Principia Biopharma Inc.

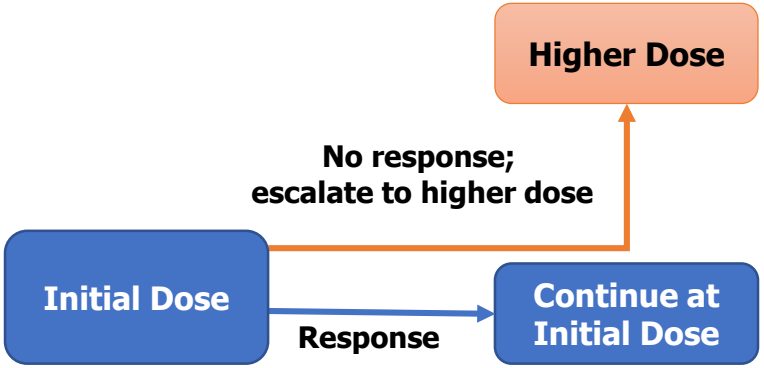
Adaptive, Open-Label, Dose-Finding, Phase I/II Study of PRN1008 in Relapsed/Refractory Immune Thrombocytopenia (ITP)

Key inclusion criteria (N ≤ 40)

- Adults age 18-80 y
- Relapsed/refractory ITP
- Primary or secondary to other diseases (eg, SLE, CLL)
- No other available/approved treatment options
- ≥ 2 platelet counts < 30,000/μL at study entry
- Adequate hematologic, hepatic, and renal function
- Stable concomitant CS or TPO-RA was allowed

Intrapatient dose escalation of PRN1008

- **PRN1008 doses* (24 wk)**: 200 and 400 mg qd
  300 and 400 mg bid
- 3+3 design
  - If response was observed in 1 of 3 patients, then 3 more patients were added to the dose level
  - If no response in 3 patients for 28 d, dose was dropped and patients were escalated to higher doses and all subsequently enrolled patients started treatment at the higher dose



NCT03395210; EudraCT 2017-004012-19.
bid, twice daily; CLL, chronic lymphocytic leukemia; qd, once daily; SLE, systemic lupus erythematosus.
*Dose escalation part of the study was completed with all patients currently treated with the 400 mg bid dose.

Key Study Endpoints

Primary Endpoint

Two or more consecutive platelet counts ≥ 50,000/μL without requiring rescue medication

Additional endpoints

- Any 2 platelet counts ≥ 50,000/μL
- Platelet responses over time, by duration of treatment, and clinical benefit (≥ 30,000/μL)
- Stable response - defined as platelet counts ≥ 50,000/μL at ≥ 50% visits during last 8 weeks of active treatment (4 of 8)
- Safety

Patient Demographics and Prior ITP Therapy

Demographics	N = 31
Median age, y (range)	50 (21-74)
Female, n (%)	18 (58)
ITP classification, n (%)	
Primary ITP	29 (94)
Secondary ITP	2 (6)
Median duration of ITP, y (range)	7.8 (0.5-42.4)
Median baseline platelet count, $x10^9$/L (range)	13 (3-28)

Prior ITP Therapy	N = 31
Median number of prior ITP therapies (range)	6 (1-41)
Splenectomy, n (%)	8 (26)
Prior ITP therapies, n (%)	
Corticosteroids	26 (84)
TPO-RA	17 (55)
IVIG/Anti-D	11 (35)
Rituximab	10 (32)

- At enrollment, patients had ITP for a median duration of 7.8 y, were heavily pretreated (median of 6 prior therapies), and 26% had undergone a prior splenectomy
- During the study, 10 patients (32%) received PRN1008 monotherapy and 21 patients (68%) were on ≥ 1 concomitant ITP medication

Data cut-off 13Nov2019.

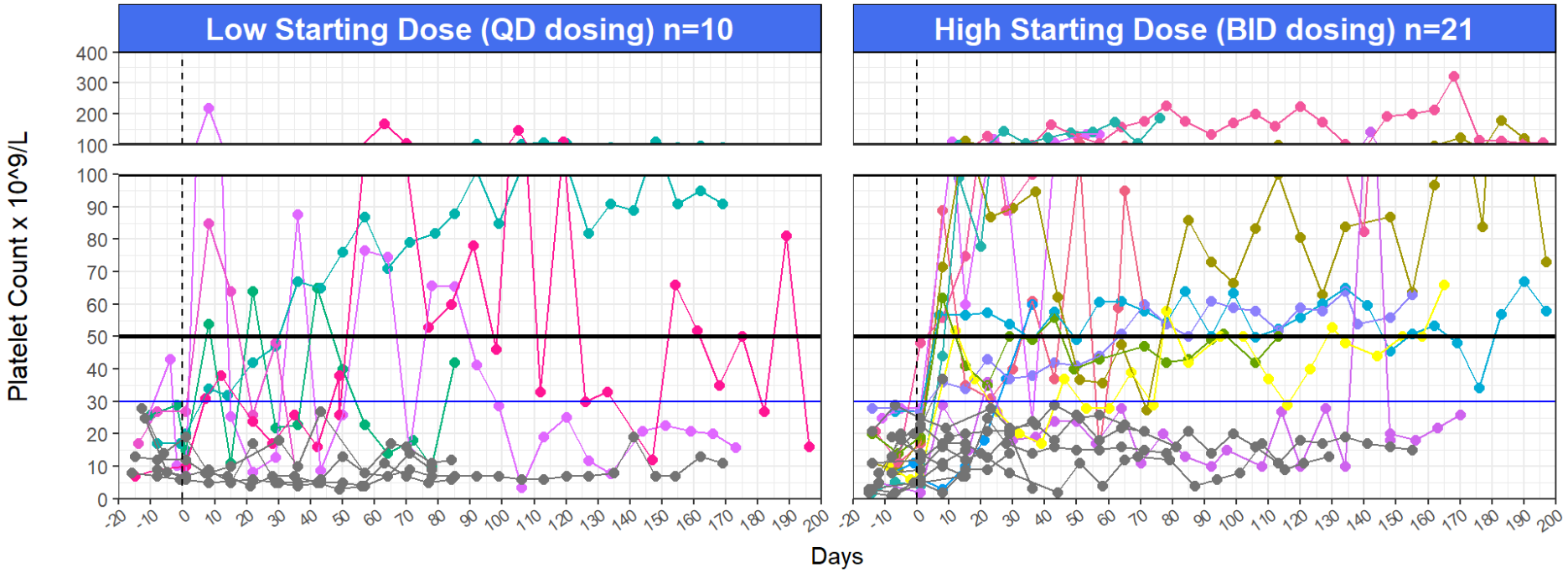
Summary of Platelet Response by Treatment Duration and Dose

Treatment Duration and Dose (data cut-off 13Nov2019)	Patients Achieving Platelet Counts ≥ 50 × 10^9/L (80% CI)		
	Primary Endpoint* 2 consecutive	**Any 2**	**4 of Final 8**
All patients enrolled (N = 31)	**39% (28%-50%)**	45% (34%-57%)	29% (20%-40%)
≥ 4 wk, all doses (n = 26)	46% (34%-59%)	54% (41%-66%)	35% (24%-47%)
≥ 12 wk, all doses (n = 17)	47% (33%-62%)	59% (43%-73%)	35% (22%-51%)
≥ 12 wk at 300 and 400 mg bid (n = 13)	54% (37%-70%)	62% (44%-77%)	39% (23%-56%)

- Primary endpoint was met in 39% of all patients
- Platelet response was further improved with longer treatment and at higher doses of PRN1008

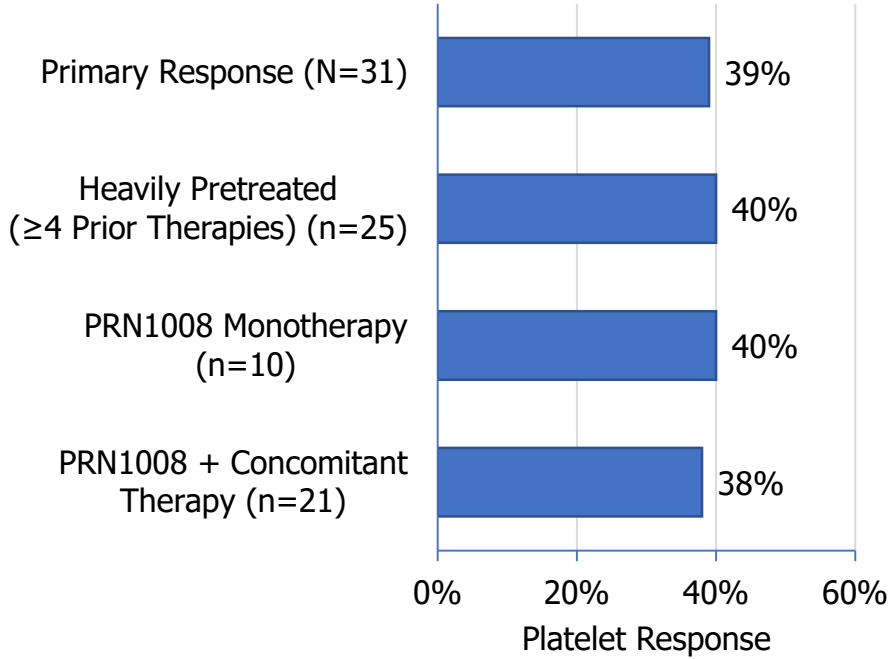
*Primary endpoint was defined as 2 consecutive platelet counts ≥ 50,000/μL without requiring rescue medication.

Individual Platelet Counts By Dose Levels Over Time to Date



Data cut-off 13Nov2019.
*Patients who achieved ≥ 50,000/μL platelet counts at least once.

Subset Analyses of Primary Platelet Responses*



- Overall, 39% of patients met the primary endpoint independent of dose or time on treatment*
- PRN1008 showed 10/25 (40%) heavily pretreated patients responding (≥ 4 prior therapies)
- Similar responses were achieved in patients receiving PRN1008 monotherapy (4/10 patients) and concomitant therapy (8/21 patients)

Data cut-off 13Nov2019.

*Primary endpoint was defined as 2 consecutive platelet counts ≥ 50,000/µL without requiring rescue medication.

PRN1008 Treatment Was Well-Tolerated in ITP Patients (N = 31)

- Median treatment duration at data cut-off was 12.0 weeks (range, 0.1-41.9)
- Related TEAEs were reported in 11 patients (35%); all were grade 1 or 2
- No treatment-related bleeding or thrombotic events
- No significant changes in the ITP-BAT bleeding scale from baseline to last visit
- No dose-limiting toxicities
- Safety profile is consistent with safety observed to date in pemphigus[1]

Related TEAEs (≥ 2 Patients), n (%)	**Grade 1/2**
All TEAEs	11 (35)
Nausea	8 (26)
Diarrhea	7 (23)
Abdominal distension	3 (10)
Fatigue	3 (10)

Data cut-off 13Nov2019. TEAEs, treatment-emergent adverse events.

1. Murrell D, et al. *AAD.* 2018:LBA 10086.

Unrelated Serious Adverse Events (Grade 2-3)

Patient	Serious Adverse Event	Description
0211-003	Rectal hemorrhage, grade 2 Start: study day 37, 400 mg bid Stop: study day 42	Patient was discontinued from the study because rescue medications were used during hospitalization. Platelet counts: 16×10^9/L at baseline (average of 3 counts); 3×10^9/L on study day 29.
0213-005	Iridocyclitis, grade 2 Start: study day 73, 400 mg bid Stop: study day 76, 400 mg bid	Patient was hospitalized due to a need for monitoring. Event as ”secondary to ulcerative colitis and due to autoimmune predisposition”. There were no changes to the study drug dosing. Platelet counts: 8×10^9/L at baseline (average of 2 counts); 14×10^9/L at study day 70
0434-001	Head contusion (due to fall), grade 3 Start: study day 29, next day after the last dose of 300 mg bid Stop: study day 30	Rescue medications were used during hospitalization. This event was the reason for drug and study discontinuation. Platelet counts: 3×10^9/L at baseline (average of 3 counts); 14×10^9/L on study day 28.
0102-002	Gastrointestinal bleeding, grade 3 Start: study day 10, 400 mg bid Stop: study day 15	Patient with a history of GERD experienced two episodes of melena and was hospitalized. Treatment included platelet transfusion. Patient was discontinued from the study. Platelet counts: 18×10^9/L at baseline (average of 3 counts), 37×10^9/L at study day 8.

Conclusions

- 54% primary endpoint response rate with bid doses for ≥ 12 weeks
  - Overall 39% response rate in all patients with median of 6 prior therapies (55% had received prior TPO-RA)
- Rapid onset (platelet counts > 30K by the first week of treatment)
- Responses were durable in the majority of patients
- PRN1008 was well-tolerated across all doses (all TEAEs were mild to moderate) with no thrombotic events
- Confirmed optimal safety and efficacy dose is 400 mg bid
- Further studies are being planned