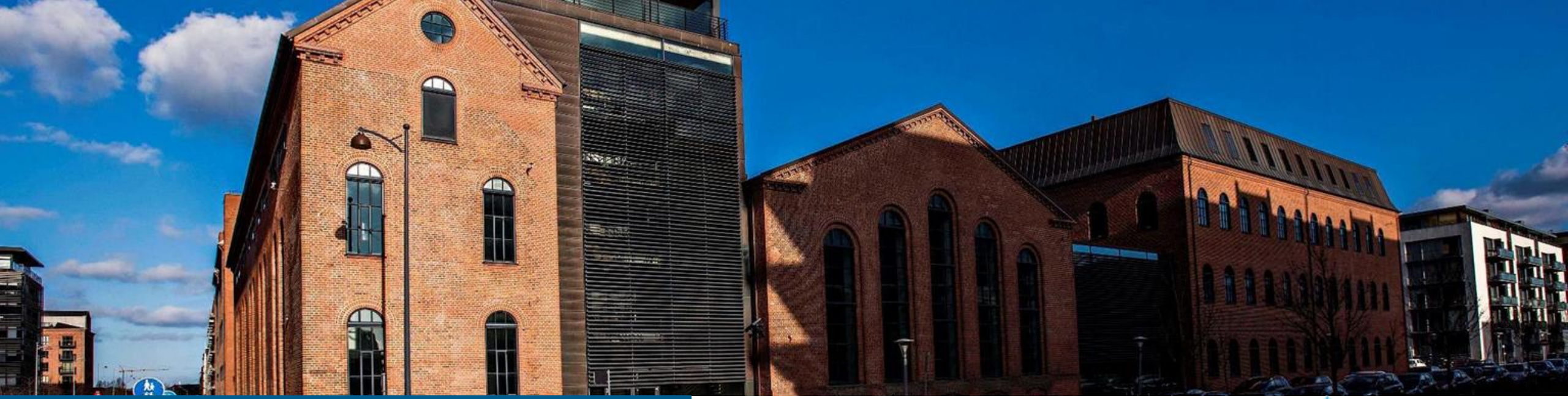

Considerations … on study objectives and outcome parameters.

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Ole Weis Bjerrum
MD, dr med sci.
Clinical assessor, DKMA.

No CoI.

Considerations…

- The EMA guideline
- Clinical trials
- Study design
- Platelets / alternatives
- PROs
- Summary… adults cITP

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SCIENCE MEDICINES HEALTH

20 February 2014
EMA/CHMP/153191/2013
Oncology Working Party

Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia

Agreed by Oncology Working Party	
Agreed by PDCO	July 2012
Adoption by CHMP for release for consultation	November 2012
End of consultation (deadline for comments)	11 March 2013
Agreed by Oncology Working Party	31 August 2013
Adoption by CHMP	13 November 2013
Date for coming into effect	20 February 2014
	1 September 2014
Keywords	***Chronic primary immune thrombocytopenia, ITP, thrombopoietin receptor agonists***

Objectives

- Dose finding
- Conduct clinical trials, RCT
- Study impact on the QoL
- Compare efficacy
- Describe safety risks
- Prevent splenectomy in ITP

Outcomes

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- Dose-response, PK/PD study
- Platelet count used as a valid surrogate endpoint in ITP
- Increment / duration
- Pt Reported Outcomes
- Reduction concomitant medication (glucocorticoids)
- Rescue treatment
- Reduce bleeding
- Register Adverse Events

Considerations...

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The primary endpoint

- Platelet response on pre-specified time point(s) should in general be expected as the primary endpoint.
- The increase in blood platelet count (CR or R) should be considered as primary endpoint.
- The exact definition of the endpoint will depend on the stage of the clinical development.
- The primary endpoint is expected to provide the most clinically relevant evidence of efficacy related to the primary objective.

Considerations....Pivotal RCTs

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Drug	Design < 30 x10^9/L	Primary endpoint
Eltrombopag[1]	Phase 2, double-blind, vs placebo, 6 weeks	A platelet count of ≥50 ×10^9/L on day 43
Romiplostim[2]	Phase 3, double-blind, vs placebo, 24 weeks	Durable response - platelet count ≥50 ×10^9/L during 6 or more of the last 8 weeks of treatment
Avathrom-bopag[3]	Phase 3, double-blind vs placebo, 6 months	Cumulative number of weeks of platelet count ≥50 x 10^9/l without rescue therapy for bleeding / 6 months
Fosfamatinib[4]	Phase 3, double-blind vs placebo, 24 weeks	Stable response platelets ≥50 x 10^9/l at >4 of 6 biweekly visits, weeks 14-24, w/o rescue therapy
Rilzabrutinib[5]	Phase 3. double-blind, vs placebo, 24 weeks	Durable platelet counts ≥50 × 10^9/L for two-thirds or more of at least 8 nonmissing weekly scheduled platelet counts during the last 12 weeks, in the absence of rescue therapy

1: Bussel et al, NEJM 2007; 357: 2237 – 2247. NCT00102739
2: Kuter et al, Lancet 2007; 371: 395 – 403. NCT00102336
3: Jurczak et al, Br J Haematol 2018; 183: 479–490. NCT01438840
4: Bussel et al, Am J Hematol 2018; 93: 921–930. (NCT02076399
5: Kuter et al, Blood 2025; 145: 2914–2926. NCT04562766

Contextualisation....in progress

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Drug	Design < 30 x10^9/L	Primary endpoint
Ianalumab NCT05885555	Phase 2, single-arm trial, 24 weeks	Platelet count ≥50 x 10^9/L at two (or more) consecutive assessments at least 7 days apart, in the absence of rescue or treatment change
Efgartigimod NCT06544499	Phase 3, double-blind, vs placebo, 24 weeks	Number of cumulative weeks during the treatment period with platelet counts of at least 50 × 10^9/L
Sovlepenib NCT05029635	Phase 3, double-blind, vs placebo, 24 weeks	Platelet count ≥50 × 10^9 /L on at least 4 of 6 scheduled visits of week14-week 24

Response: platelet count ≥ 30 x 10^9/L and at least double the base line count confirmed at least 2two consecutive occasions 1 week apart and absence of bleeding;
Complete response: count ≥ 100 x 10^9/L and at least double the base line count confirmed at least 2two consecutive occasions 1 week apart, absence of bleeding.

Al-Samkari: Am J Hematol 2024; 99: 2178 – 2190. Rodeghiero et al, Blood 2009; 113: 2386 – 2393.

Considerations…study design

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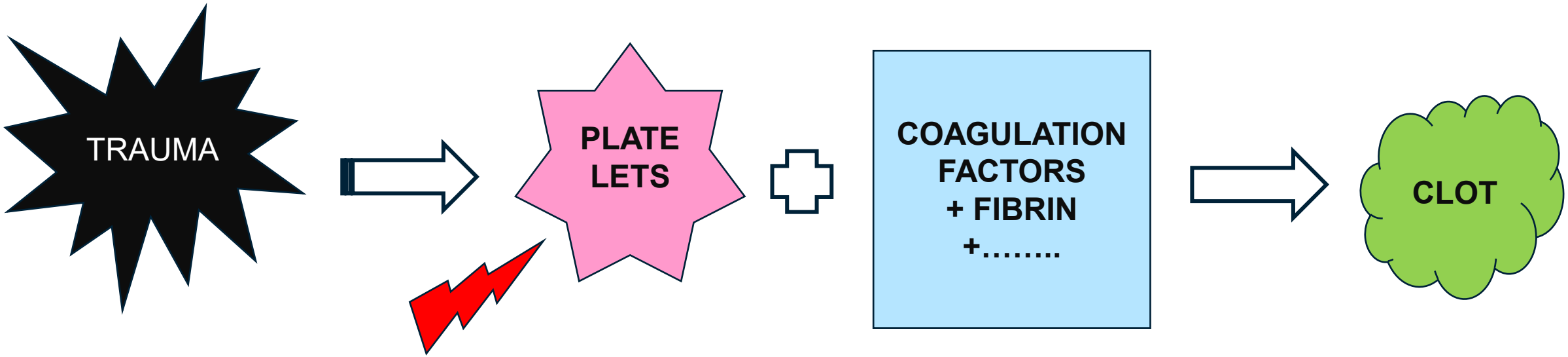
- **Blind RCT experimental drug vs active comparator(s)**
- **Intended for long-term treatment of ITP Phase 2 - Phase 3**
- **Available approved therapies, ethics, relevant guidelines**

May need to discuss:

- **Durable "safe" platelet count > 50 x10^9/L? 12 – 24+ weeks?**
- **Termination of treatment (Rx) and Adequate follow-up**
- **Combine approved drug(s) or off-label agent (Repurposing)**

...Alternative to platelet counts



- **Involved in ITP:** **immunecomplexes, autoantibodies, megakaryocyte dysfunction, T-cells (Reg. Th1,Th17), B-cells, platelet clearance, monocytes, spleen activity, TPO, C-activation, interleukines, epigenetic control, metabolites such as xanthosine, 2′-deoxyadenosine, lithocholic acid 3-O-sulfate, and 20-HETE correlating with key genes (PNP, GADPH, etc), vWF and V-CAM (endothelial)….BLEEDING, and more**

Cooper et al, NEJM 2019; 381: 945; Efat et al, Clin Appl Thromb Hemost 2021; 27: 1 - 8.
Allegra et al, Int J Mol Sci 2023; 24: 4438. Xu et al, Sci Rep Nature 2024; 14: 9040. Wang, BBRC 2025; 779: 152470.
Pincez et al, Res Pract Thromb Haemost 2025; 9:103210.

Considerations...cITP in adults

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An *objective* variable as part of the primary endpoint

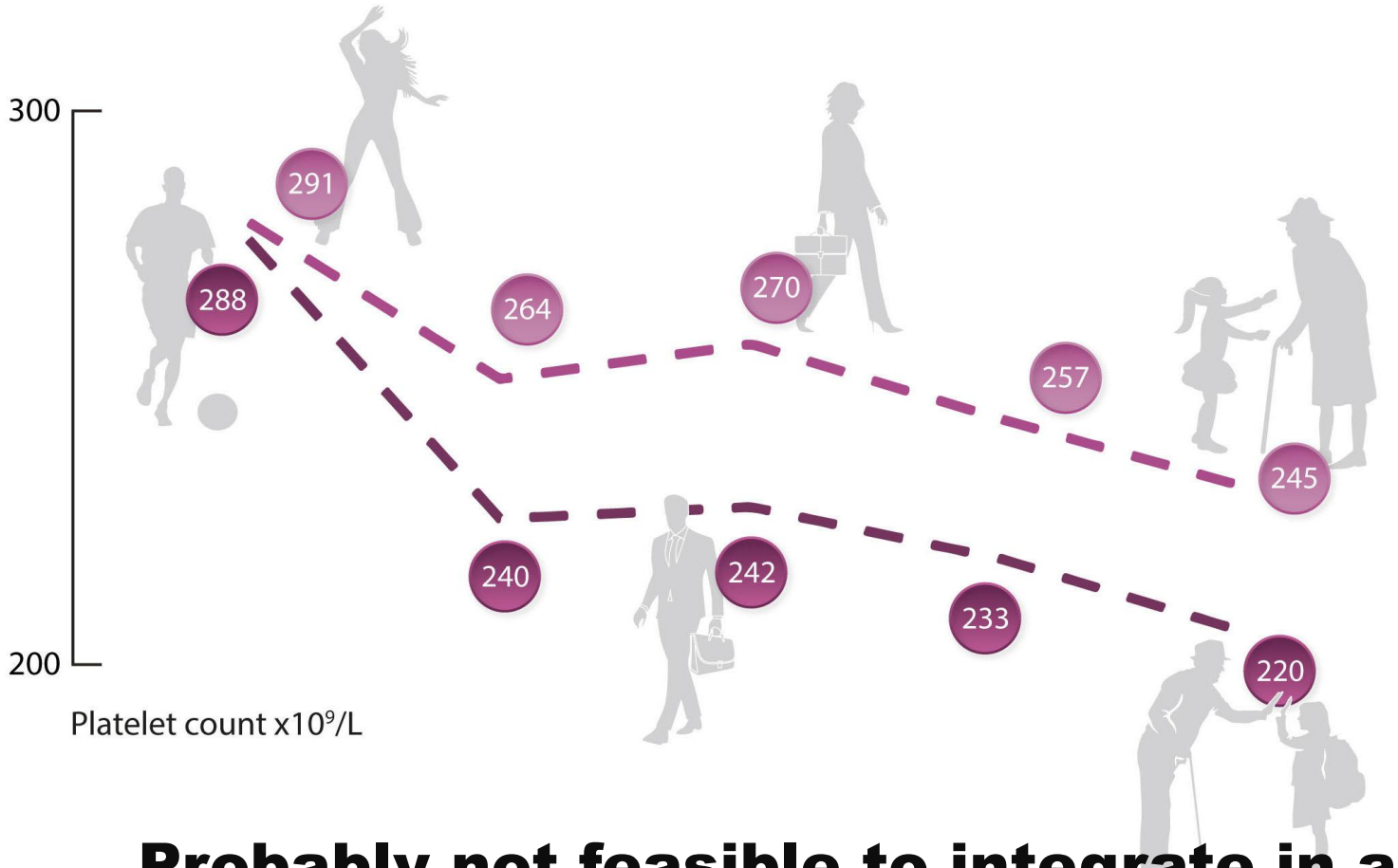
- **easy to measure, standardized, low cost, one analysis**
- **reproducible, local lab; clinically meaningful**
- **in ITP: pseudothrombocytopenia, volumen, reproducibility ↓**
- **validated surrogate and statistically practical**

....balance Sponsor / Academia, EMA assessment (FDA)

....considering alternatives: *stick to platelet counts*

EMA guidelines; Kordecka et al, Health Pol Analysis 2019; 22: 884; Siebert et al, Clin Trials 2026; 17407745261437363.

… age and the platelet count



The number of platelets is normally higher in females than in males (races). Not at Dx in ITP.

Risk factors for bleeding in ITP:

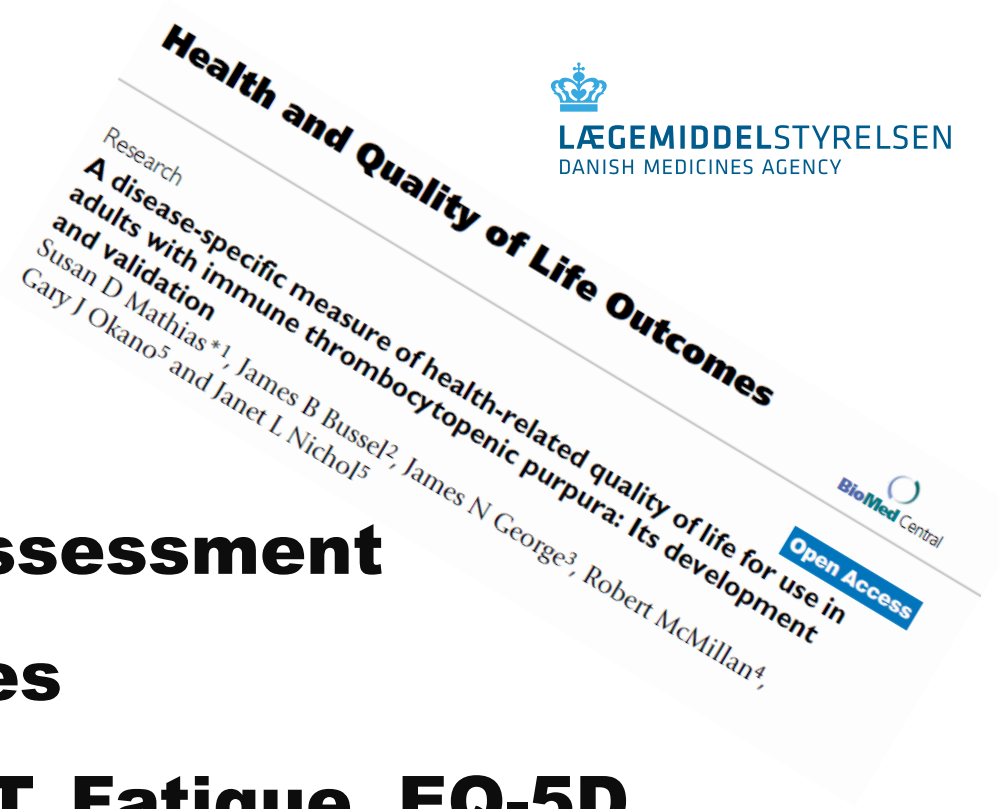
- Platelet count
- Comorbidity and treatments
- Physical activity and risks
- Invasive procedures
- Female gender
- History of bleeding

The platelet count decreases with age. After 15 years of age, women have more platelets than men.

Probably not feasible to integrate in a clinical trial context

Bain: J Clin Pathol 1996; 49: 664 – 666; Frederiksen & Schmidt, Blood 1999; 94: 909 – 913. Piel-Julian et al, J Thromb Haemostas 2018; 16: 1830 – 1842. Gaetano et al,Haematologica 2023; 108: 1473 – 1475. Sabrkhany et al, Haematologica 2023; 108: 1667 – 1670.

Considerations… PROs



- **Crucial information in treatment**
- **One 44-item ITP-specific Patient Assessment**
- **Questionnaire (ITP-PAQ) No updates**
- **Additional PROs: EORTC-Q30, FACIT_Fatique, EQ-5D…**

…respondent burden needs to be considered to avoid high rates of missing data and poor reporting of PRO results … may impact quality of data for regulatory decision making and clinical care. Data more robust in blinded trials.

Reflection paper (EMA/CHMP/292464/2014 / EMA PROs integrated in several guidelines; Mathias et al, Health QoL Outcomes 2007; 5: 11; Mathias et al, Curr Med Res Opin 2009; 25: 375 – 383; Sestøl et al, Exp Rev Hematol 2018; 11: 975 – 985. Aiyegbusi et al, Nature Comm 2022; 13: 6026; Aiyegbusi et al, Nature Med 2024, 30: 650 – 659.

Considerations…Summary

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- EMA guideline on ITP – still valid, progress since 2014 in pathophysiology, and management
- Study design to contextualise results, definition of response, head-to-gead studies, termination of treatment, combo-studies

- Platelet count remains …but ”safe level” / durability
- PROs crucial information, take care of data quality

- Thank You for your attention and consideration, as well