# *What Does a Regulator Need to See Before Approving a HIF-PHIs? PMDA's Perspective*

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# *Disclosures*

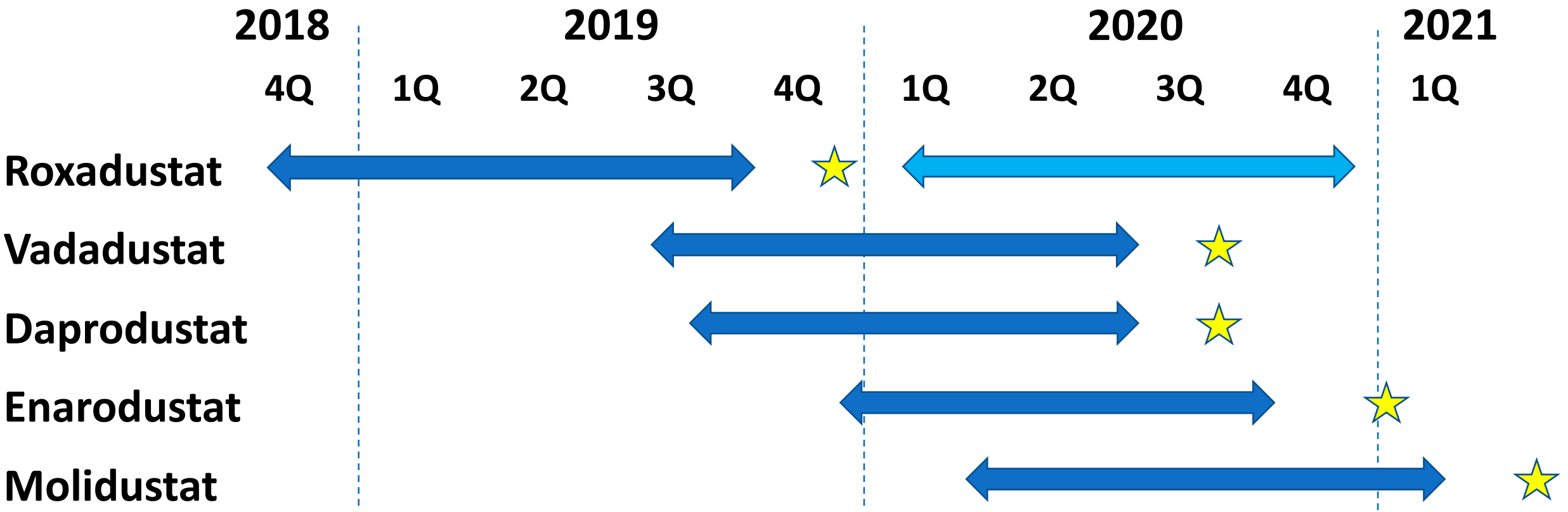
- The authors declare no conflicts of interest

# *Today's Overview*

Pharmaceuticals and Medical Devices Agency


- HIF-PHIs approved in Japan
- What are the efficacy data that are necessary?
- What are the safety data that are necessary?
- How/Why were HIF-PHIs approved early in Japan?
- PMDA's perspective on the benefit-risk assessment for HIF-PHIs in clinical trials in Japan

# *HIF-PHIs approved in Japan*



# *PMDA's Request for the clinical evaluation of renal anemia drugs in Japan*

- At least one double-blind, randomized controlled trial
- Available data on 300 or more Japanese patients treated in comparative studies
- Available data on 100 or more in long term (>52 weeks) studies

*Guideline for clinical evaluation for renal anemia (Japan). PFSB/ELD Notification No. 0930-1(2011) Japanese Ministry of Health, Labour and Welfare.*

# *What are the necessary efficacy data?*

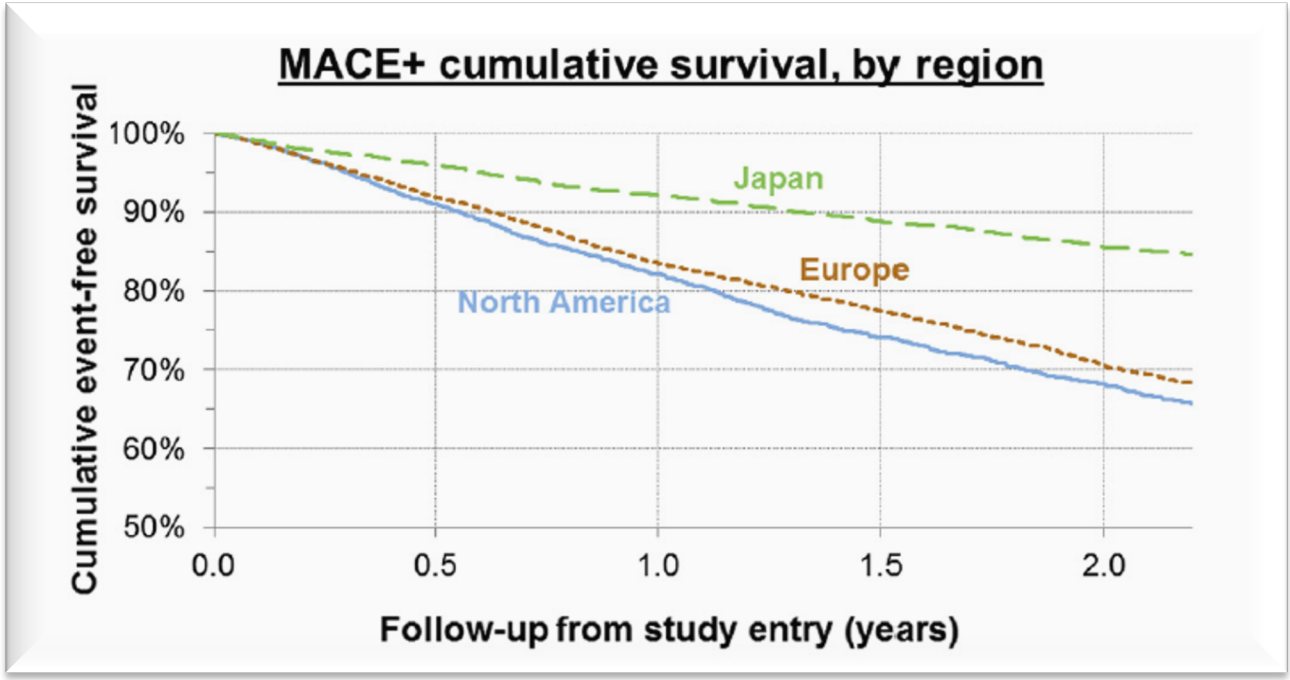
- Whether Hb reached the target level?
- Whether Hb was maintained in the target range?
- Whether switching from ESAs was O.K. in terms of efficacy; non-inferiority to ESAs for maintaining Hb levels?
- Whether there were difference in efficacy among patients with non-dialyzed CKD, HD or PD?

# *What are the necessary safety data?*

- Whether there were no unacceptable risks beyond the expected benefits?
- Whether the safety profiles did not markedly differ from those of ESAs, both in comparative studies and while in switching from ESAs?

# *How/Why were HIF-PHIs approved early in Japan?*

- Differences in clinical practice for renal anemia between Japan and Western countries may lead to choose local trials in Japan
  - ✓ **target Hb levels**
  - ✓ **the dosage of ESAs**
  - ✓ **iron use**




N=16,560（Japan 3,921） *Kidney Int Rep 2019;4:864-872*

- While PMDA considerd the shortage of CV outcome data at the time of submission, it is unfeasible to conduct such trials in Japan since CV risk is much lower in Japan than in Western countries

# *PMDA's perspective on the benefit-risk assessment for HIF-PHIs in clinical trials in Japan*

- **Efficacy**
  - ✓ HIF-PHIs increase/maintain Hb level in patients with non-dialyzed CKD or HD or PD
- **Safety**
  - ✓ No signals for increase in risk of CV events, tumor progression, retinal hemorrhage, and hypertension compared to ESA

# *PMDA's perspective on the R&B assessment (cont'd)*

- **Potential benefit**
  - ✓ Oral administration may reduce hospital visits/pain especially in patients with non-dialyzed CKD and PD
- **Uncertainty**
  - ✓ Long-term safety, such as CV risks
  - ✓ Whether HIF-PHIs are effective in patients with ESA-resistance

# *Core of the Risk Management Plan*

| Important Risks | Roxadustat | Vadadustat | Daprodustat | Enarodustat | Moridustat |
|---|---|---|---|---|---|
| Important ***identified*** risks | ■ Thromboembolism<br>■ Hypertension | | | | |
| | Seizure* | Hepatic injury* | | | |
| Important ***potential*** risks | ● Malignancy<br>● Retinal hemorrhage<br>● Cyst growth in Polycystic Kidney Diseases<br>● CV event/thromboembolism | | | | |
| | # | | | | ## |

* setting mainly based on the result of the global clinical trial

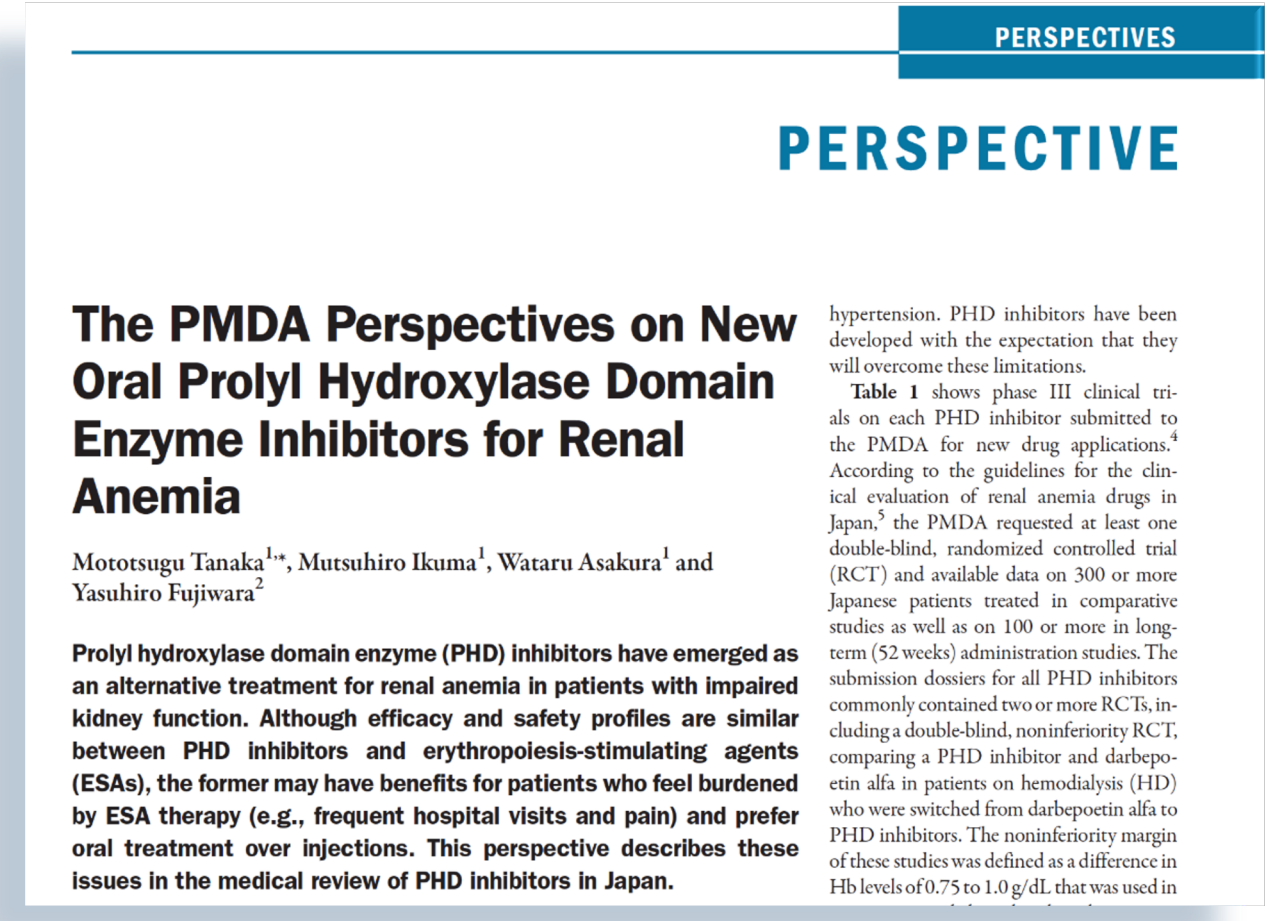
\# plus *interaction with HMG-COA, hepatic injury and serious infections*

\## plus *interstitial pneumonia*

# Regulator's challenge

*What is the **minimum requirement** and how can we approve based on **benefit-risk assessment** for new drug approvals?*

*Collecting extensive data on efficacy and safety is necessary, but request for complete data can delay effective drugs to be available*



PERSPECTIVES

PERSPECTIVE

## The PMDA Perspectives on New Oral Prolyl Hydroxylase Domain Enzyme Inhibitors for Renal Anemia

Mototsugu Tanaka[1,*], Mutsuhiro Ikuma[1], Wataru Asakura[1] and Yasuhiro Fujiwara[2]

**Prolyl hydroxylase domain enzyme (PHD) inhibitors have emerged as an alternative treatment for renal anemia in patients with impaired kidney function. Although efficacy and safety profiles are similar between PHD inhibitors and erythropoiesis-stimulating agents (ESAs), the former may have benefits for patients who feel burdened by ESA therapy (e.g., frequent hospital visits and pain) and prefer oral treatment over injections. This perspective describes these issues in the medical review of PHD inhibitors in Japan.**

hypertension. PHD inhibitors have been developed with the expectation that they will overcome these limitations.

**Table 1** shows phase III clinical trials on each PHD inhibitor submitted to the PMDA for new drug applications.[4] According to the guidelines for the clinical evaluation of renal anemia drugs in Japan,[5] the PMDA requested at least one double-blind, randomized controlled trial (RCT) and available data on 300 or more Japanese patients treated in comparative studies as well as on 100 or more in long-term (52 weeks) administration studies. The submission dossiers for all PHD inhibitors commonly contained two or more RCTs, including a double-blind, noninferiority RCT, comparing a PHD inhibitor and darbepoetin alfa in patients on hemodialysis (HD) who were switched from darbepoetin alfa to PHD inhibitors. The noninferiority margin of these studies was defined as a difference in Hb levels of 0.75 to 1.0 g/dL that was used in

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