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

• 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

2018  2019  2020  2021

Roxadustat  Vadadustat  Daprodustat  Enarodustat  Molidustat

- Review
- Selling release
- Additional application (for CKD at predialysis stage)
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

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

- While PMDA considered 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

Graph: MACE+ cumulative survival, by region

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-PHIIs are effective in patients with ESA-resistance
## Core of the Risk Management Plan

<table>
<thead>
<tr>
<th>Important Risks</th>
<th>Roxadustat</th>
<th>Vadadustat</th>
<th>Daprodustat</th>
<th>Enarodustat</th>
<th>Moridustat</th>
</tr>
</thead>
</table>
| Important *identified* risks | | | ■ Thromboembolism  
■ Hypertension | | |
| | Seizure* | Hepatic injury* | | | |
| Important *potential* risks | | | | | |
| | ● Malignancy  
● Retinal hemorrhage  
● Cyst growth in Polycystic Kidney Diseases  
● 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.

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