

# Is Extrapolation of Foreign QT Data Required? - A Regulatory Perspective

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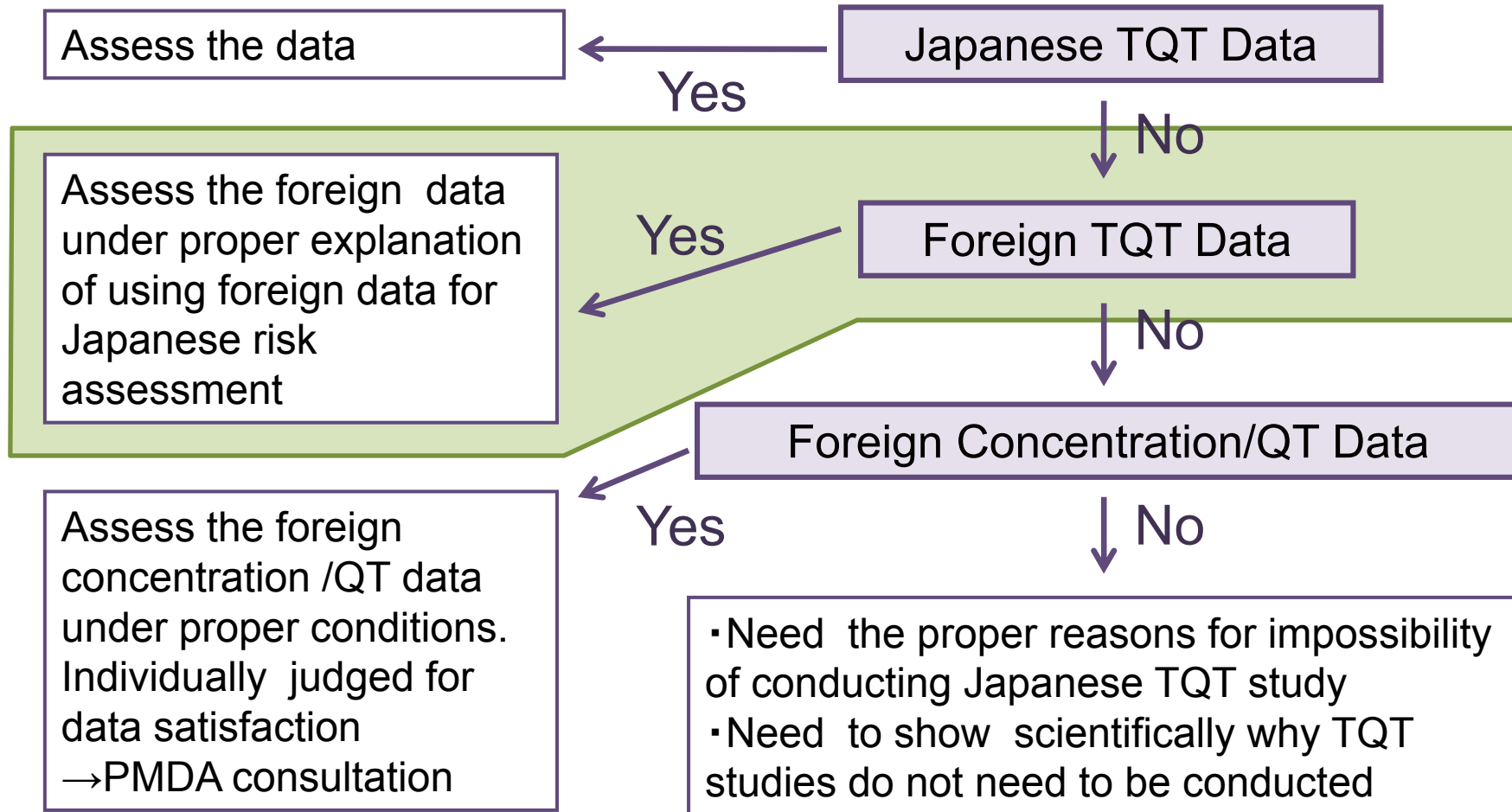


# Outline

- Use of foreign TQT data in Japan
- “Extrapolation “ of foreign TQT data
- TQT in PMDA clinical trial consultation meetings
- Summary



# Use of foreign TQT data in Japan



# Use of foreign TQT studies in Japanese NDA

- The availability of foreign data used to assess the delay of cardiac repolarization should be assessed individually.
- When foreign TQT data is used in Japanese NDAs, a proper explanation of why foreign TQT data is being used for Japanese risk assessment is always necessary.
- The reason foreign TQT data is available for Japanese QT prolongation risk assessments should be included in CTD2.7.2

- Shinagawa, 2<sup>nd</sup> DIA Cardiac Safety WS in Japan. Sep. 2011.



# “Extrapolation” of foreign QT data

- Discussion regarding “extrapolation” of QT data (or TQT) is different from that of confirmatory efficacy trial in bridging strategy.
- TQT study
  - is used to determine whether or not the effect of a drug on the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development.
  - is not intended to identify drugs as being pro-arrhythmic.



# “Extrapolation” of foreign QT data

- It is important to
  - Investigate possible ethnic factors
  - consider cautiously the necessity of additional data collection in Japanese in the late stage drug development in Japan
  - decide the type, amount of additional data in Japanese
  - organize various data for comprehensive evaluation of QT prolongation and proarrhythmia risk in Japanese



# Use of foreign TQT data

Before PII or PIII

Basic characteristics of  
-the drug (and the drugs with similar mechanisms)  
-target disease, target population  
-non-clinical data of the drug

Foreign TQT  
-dosage  
-results

Safety data collected so far in foreign countries  
-Data from both pre- and post- approval phases

Possibility of ethnic difference  
-intrinsic and extrinsic factors  
-difference of PK/PD, different putative dose

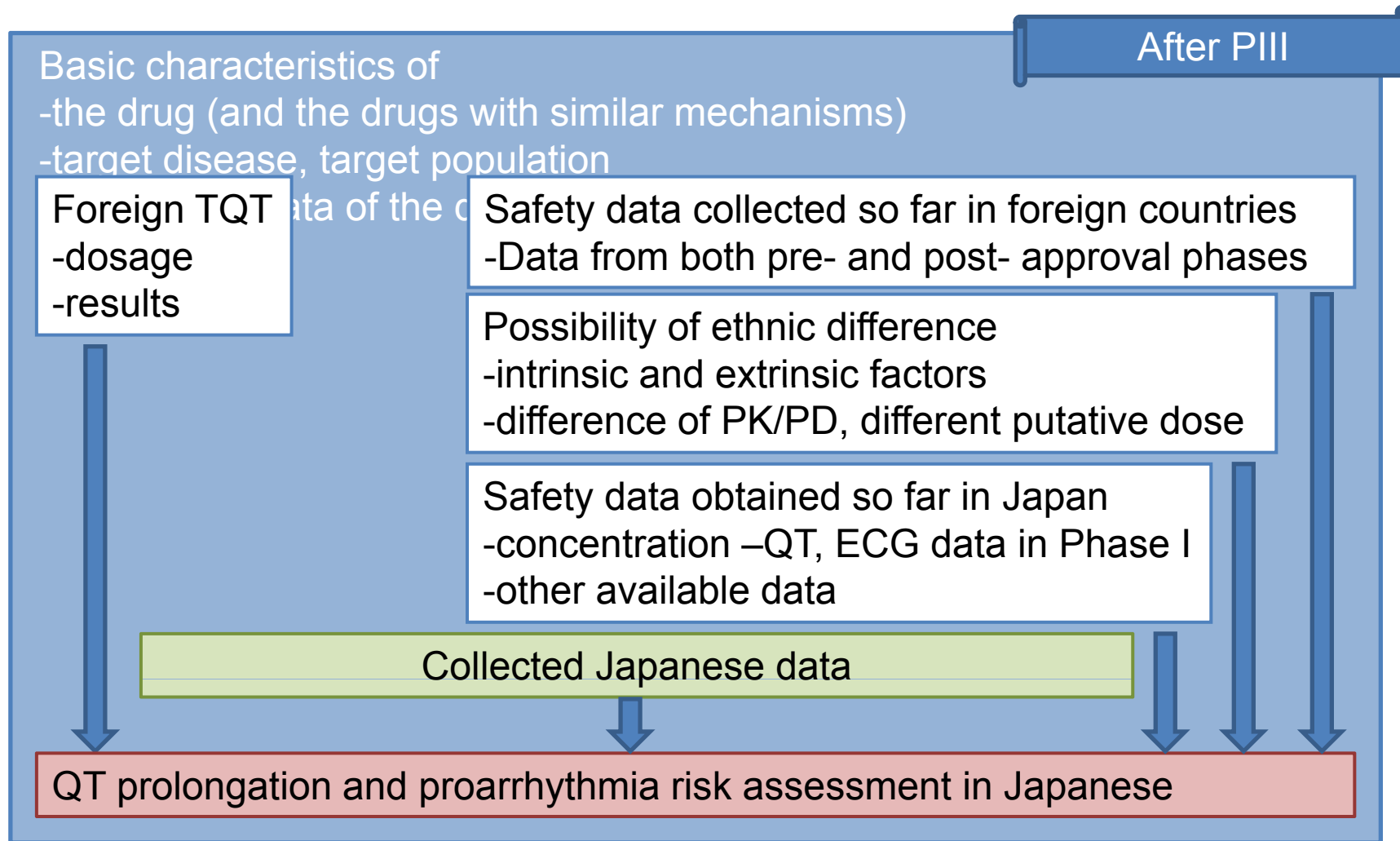
Safety data obtained so far in Japan  
-concentration –QT, ECG data in Phase I  
-other available data

Necessity and amount of data should be collected in  
late-phase clinical development in Japan

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# Use of foreign TQT data



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# TQT in PMDA clinical trial consultation meetings

- We have a certain experience with discussion of
  - clinical data packages including TQT study
  - necessity of TQT study
  - use (possibility of extrapolation) of foreign TQT studiesin PMDA clinical trial consultation meetings.



# TQT in PMDA clinical trial consultation meetings

- Although sufficiency of data packages and the necessity of TQT studies became a focal point in the meetings in many cases, there were several cases with the issue of “extrapolation of foreign TQT data”.



# Discussion points at consultation meetings

- Results of the foreign TQT study
  - Positive or negative
- Relationship between
  - Dosage used in the foreign TQT study
  - (Dosage that showed positive result)
  - Exposure difference between regions (PK/PD, putative clinical dose)
  - Exposure in special population
- Necessity of additional TQT study in Japan



# A positive TQT case

- The foreign TQT study showed positive result.
- Cautious evaluation of safety is needed in subsequent clinical trials.
  - Protecting patients
  - Planning of intensive ECG monitoring
- When planning the subsequent trials, possibility of difference of several factors such as drug exposure between regions.



# A positive TQT case (cont.)

- Since appropriate description of possible risk in the drug labeling will be needed, advance consideration is recommended.
- When evaluating QT prolongation risk in Japanese population, exposure associate with recommended dose (including situation in special population, maximum exposure) should be taken into account.



# A negative foreign TQT case

- The foreign TQT study showed negative result.
- Exposure associate with the dosage of foreign TQT study did not exceed the exposure associate with the maximum putative dose in Japanese.
- Since QT effect in patients with high exposure is still not unclear, ECG monitoring and concentration measurement should be appropriately planned in subsequent clinical trials.



# A negative foreign TQT case (cont.)

- In case like this, necessity of additional TQT study in Japanese may be discussed.
- In such discussion, several aspects should be considered.
  - The objective of TQT study
  - The results of the TQT study
  - Characteristics of the drug
  - Concentration-QT relationship
  - Existing safety event data related to cardiac risk





# TQT in PMDA clinical trial consultation meetings

- Availability of foreign TQT study and how to plan subsequent clinical trials should be discussed on a case-by-case basis.
  - Clinical trial consultation meeting may be recommended
- Sufficient explanation of the risk in Japanese based on the integration of data of foreign TQT study and other information should be focus.
- For considering and collecting necessary and sufficient data in later phase drug development, the timing of TQT study and evaluating its data will be critical.



# Summary

- For efficient use of foreign TQT study for Japanese NDAs, it is important to
  - Investigate possible ethnic factors
  - consider cautiously the necessity of additional data collection in Japanese in the late stage drug development in Japan
  - decide the type, amount of additional data in Japanese
  - organize various data for comprehensive evaluation of QT prolongation and proarrhythmia risk in Japanese



# Summary

- Prospectively planned strategy for
  - exploring possibility of ethnic difference
  - deciding timing and where to conduct TQT study
  - explaining QT prolongation and proarrhythmia risk in various regions based on the TQT data and other safety data

may be important in the era of globally simultaneous clinical development.



Thank you for your attention.

