EMA EFPIA workshop
Break-out session no.3

Case Study Title: M&S support to the bridging of a drug with Ethnic PK-differences

Disclaimer

The view and opinions expressed in these slides are my own and do not necessarily represent the views of AstraZeneca

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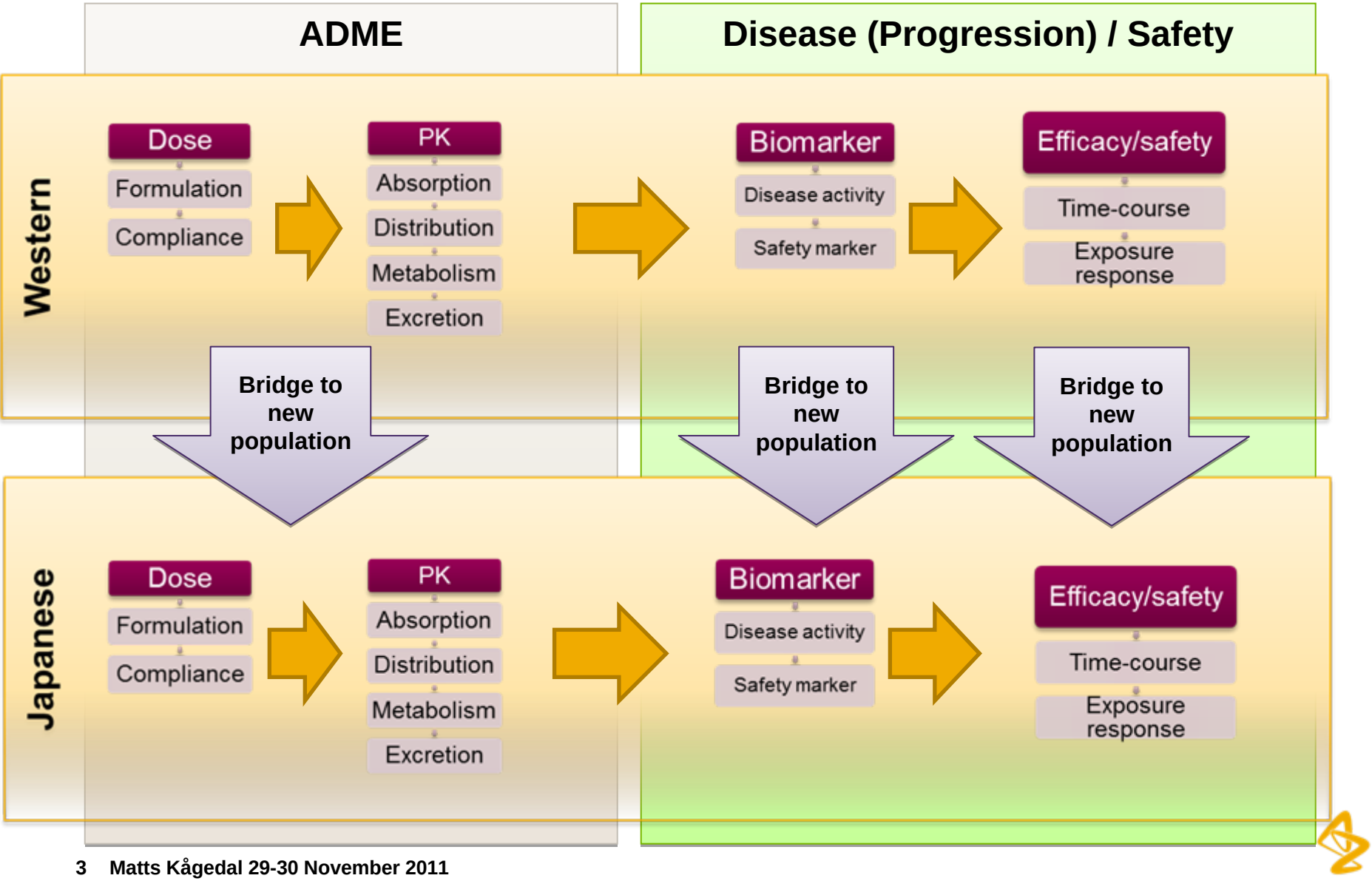
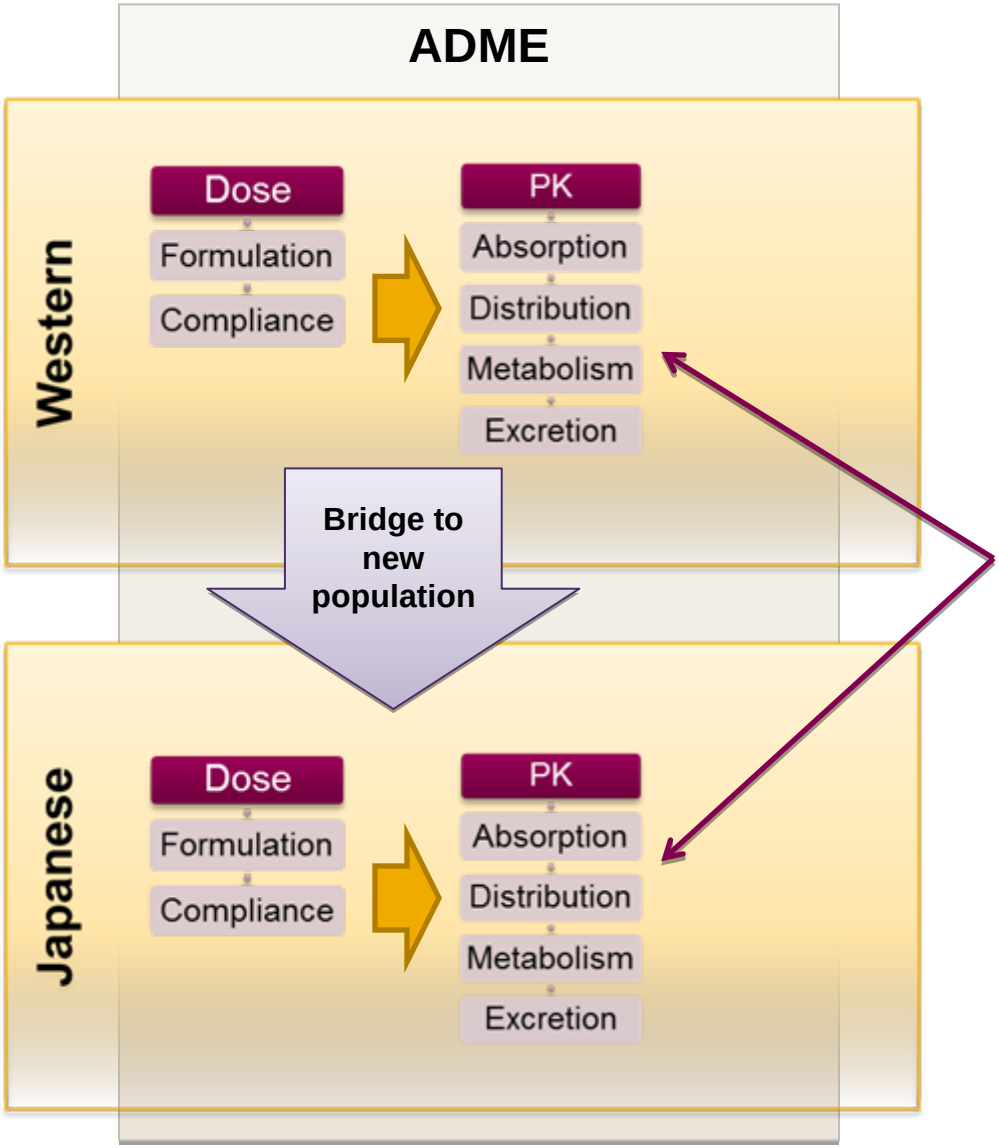
Background, Scope

- **First in class for treatment of neuropathic pain**
- **How can a clinical development plan (CDP), aiming to bridge from Western to Japanese, be designed**
  - Assumptions, sensitivity to assumptions
  - Results from Phase I modeling
  - Modeling to support program design
- **Considerations**

Assumption Framework



Assumption Framework



Sensitivity to ethnic factors:

PK:
Elimination via Metabolism (Enzyme uncertain).

Do PK in Japan early

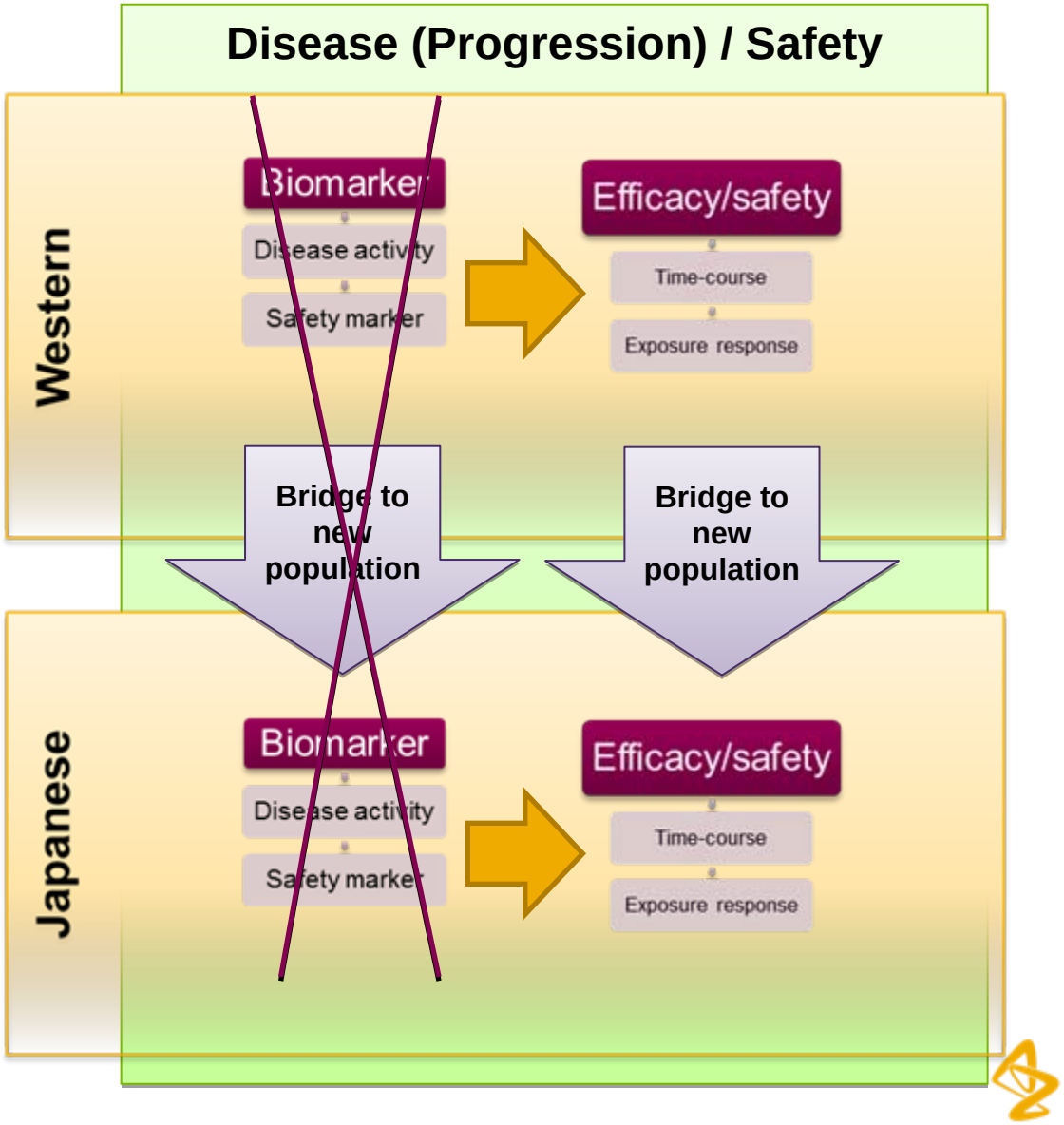
Assumption Framework

Sensitivity to ethnic factors:
(Intrinsic and extrinsic)

Biomarkers:
- No biomarkers available.

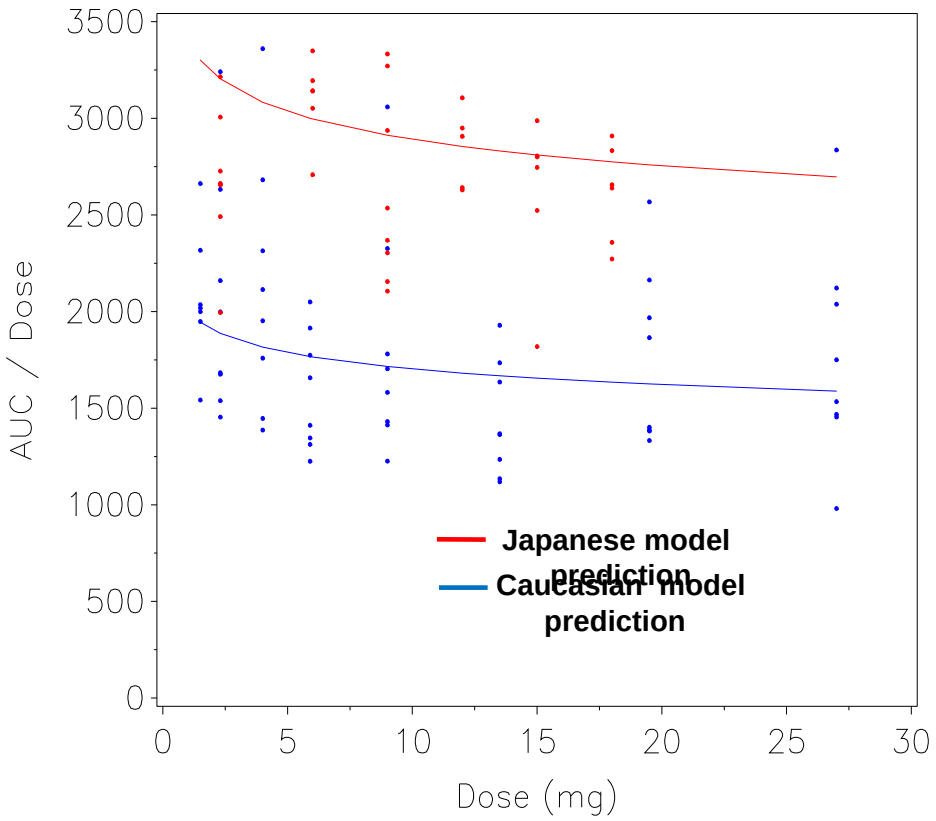
Efficacy/safety:
-First in class!
-Therapeutic index likely to be narrow

Dose response data for Efficacy and safety needed in Japan to bridge results from the West.



Japanese vs Caucasian AUC based on last dose data in MAD and J-MAD

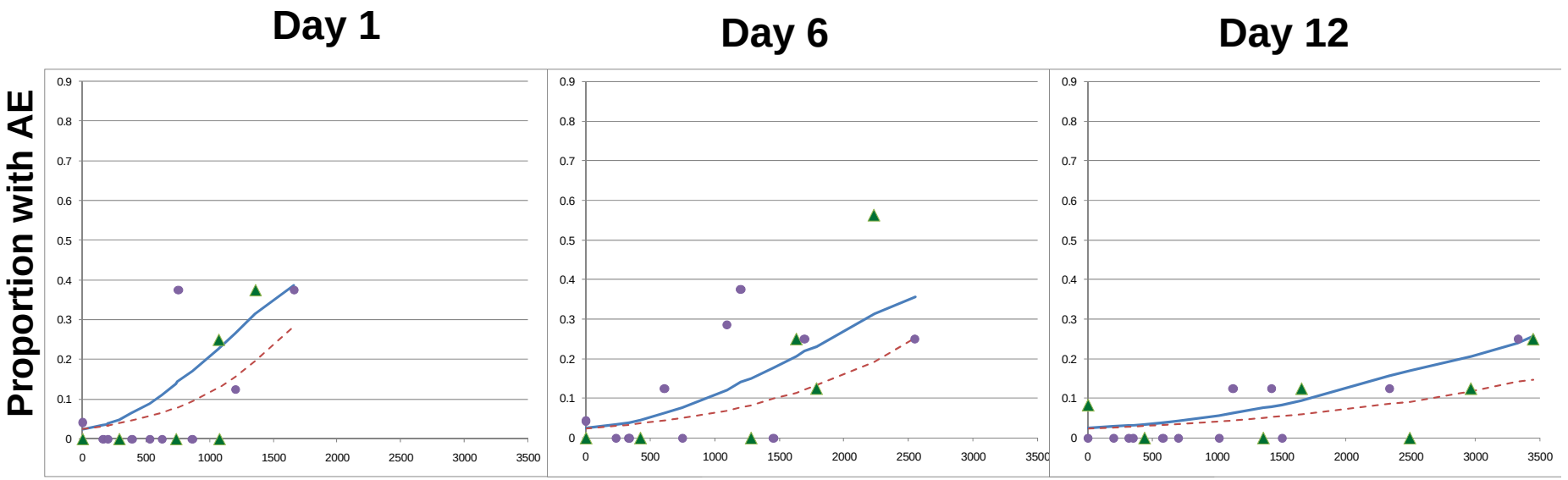
Observed and model predicted AUC/dose for Japanese and Caucasian subjects.



- Higher AUC in Japanese as compared to Caucasian.
- Not explained by body weight
- No ethnic difference in protein binding.

- Additional studies may be needed to understand mechanism behind PK-difference to improve predictions.

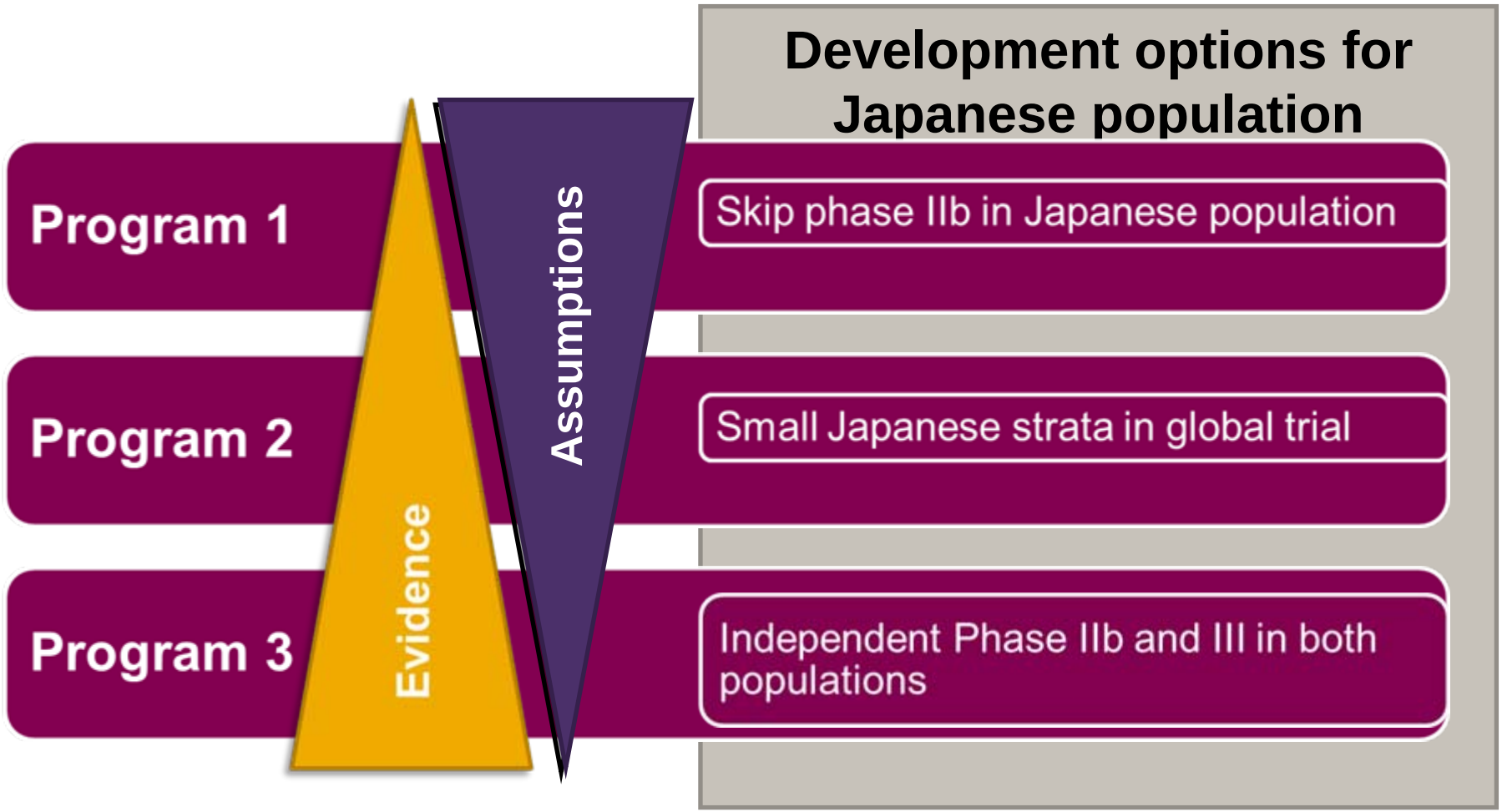
Cmax vs probability of AE



Model is based on logistic regression with tolerance development. Figure showing proportion of subjects with AE in each dose-grope versus the mean Cmax in that group and the model predicted proportion based on simulation.

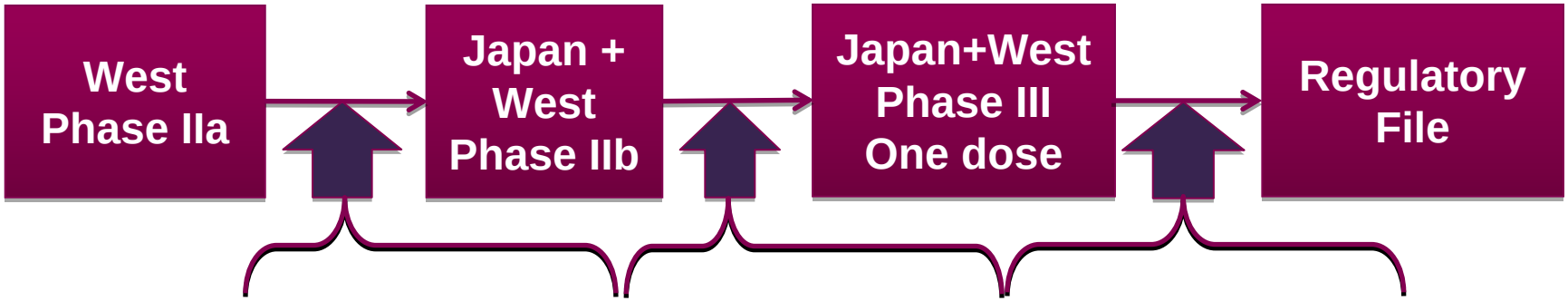
- **Similar PK-safety relationship for West and Japan, but limited data (MAD in western and Japanese subjects)**
- **Tolerance development to side effect indicated.**

Phase II and III program options
(How M&S is used to inform Drug Development)



Empirical support for assumptions in transition between phases

Program 2 -Small strata of Japanese in global trials



Data to support assumptions in the transition between phases

Important Assumptions	IIa -> IIb	IIb -> III	III->File
$CL_{JAP}<CL_W$	SAD, MAD	SAD, MAD, IIb	SAD, MAD, IIb, III
Similar PK-safety	SAD+MAD (limited data)	SAD, MAD, IIb	SAD, MAD, IIb, III
Similar PK-Efficacy	None	IIb	IIb, III

Model based assessment of program

Evaluation conditions (what if):

1. Similar exposure response in Caucasian and Japanese
2. Higher potency in Japanese (e.g. half exposure -> same effect)

Model:

1. PK based on SAD + MAD
2. Placebo model built based on data from previous trials (in-house and literature).
3. Assumed exposure response model based on literature, preclinical data and target product profile

Decision criteria for phase III:

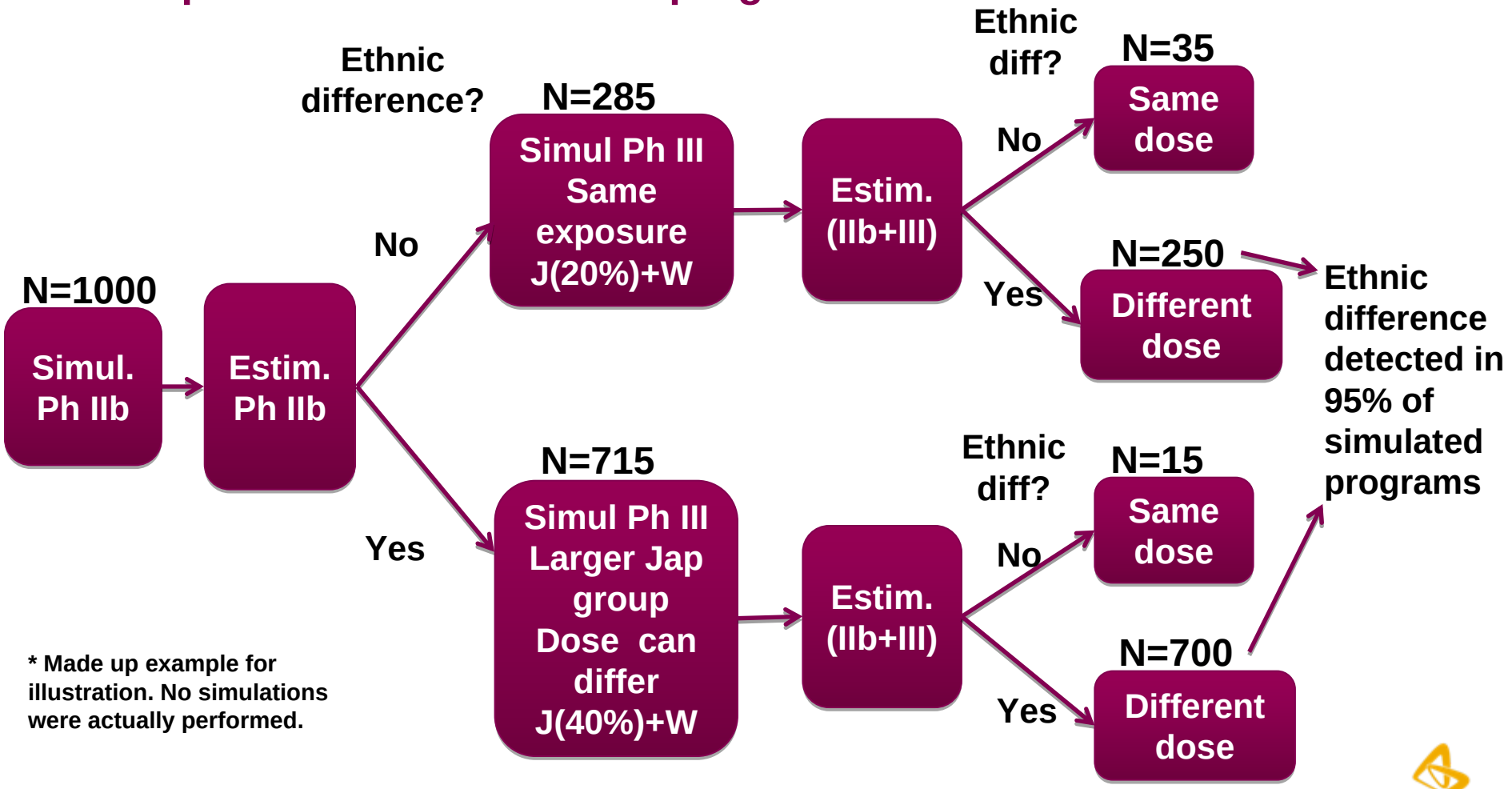
1. Is there an ethnic difference in exposure response

Criteria to judge adequacy of program:

1. Precision and bias in estimation of optimal dose for Japanese and Caucasians
2. Power to detect an ethnic difference in exposure response for Efficacy and Safety

Simulation of program 2 assuming higher potency in Japanese

Example with 1000 simulated programs *

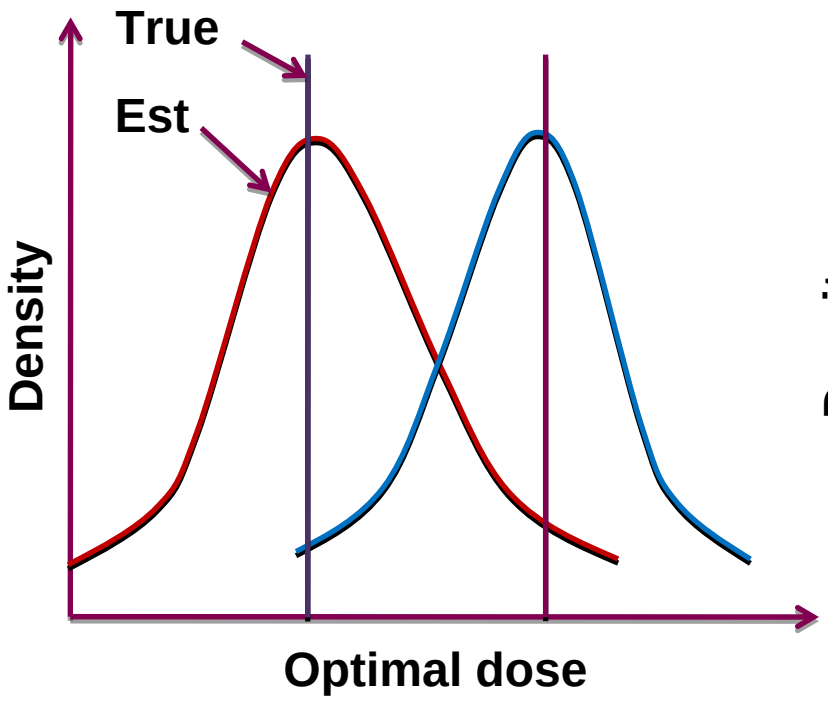


* Made up example for illustration. No simulations were actually performed.

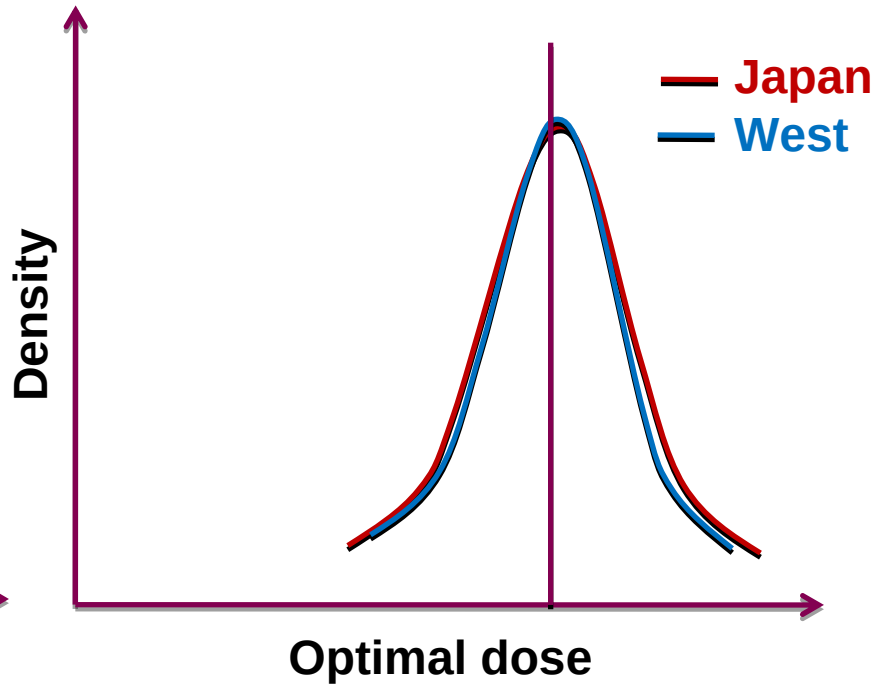
Precision of estimated dose - program 2

(example for illustration)

Two fold difference in potency:
Result: Power=95%



No difference in potency:
5% of studies with detected difference



- Repeat for program 1 and 3 and compare outcome, cost and time
- Different endpoints can be evaluated. E.g. precision of minimum effective dose.

Important considerations

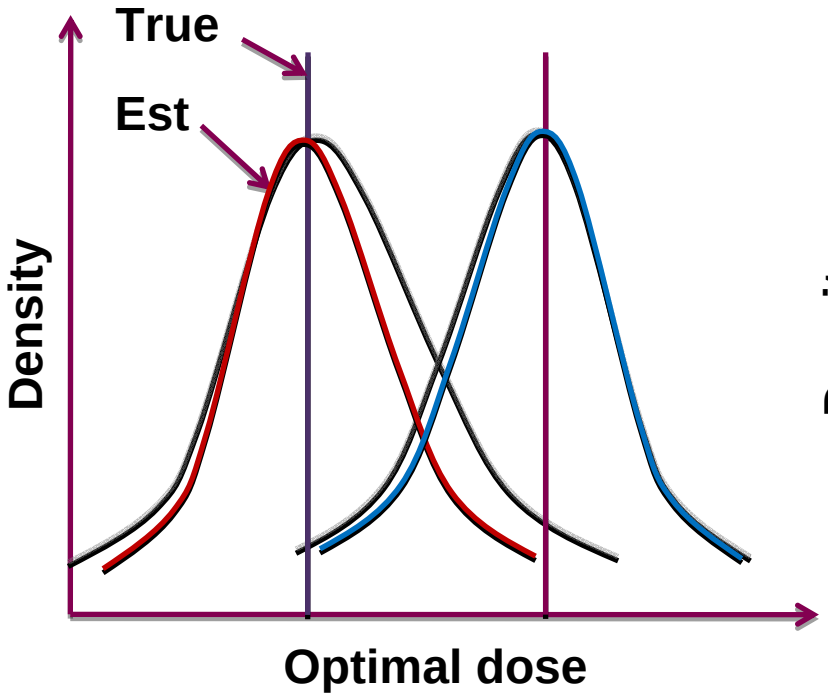
- The required precision in the ethnic comparison needs consideration
- All ethnic groups are important.
- Modeling can allow estimation of the individual components of intrinsic/extrinsic factors, using the data more effectively
- Not all groups will have empirical support. Models built on biological principles can improve predictions. (Eg data on Koreans in Korea and the west can support prediction of response in Japanese in the West)
- Acceptance to base dose selection on target exposure is needed (Phase III dose may not have been studied in one or both populations)

Backups

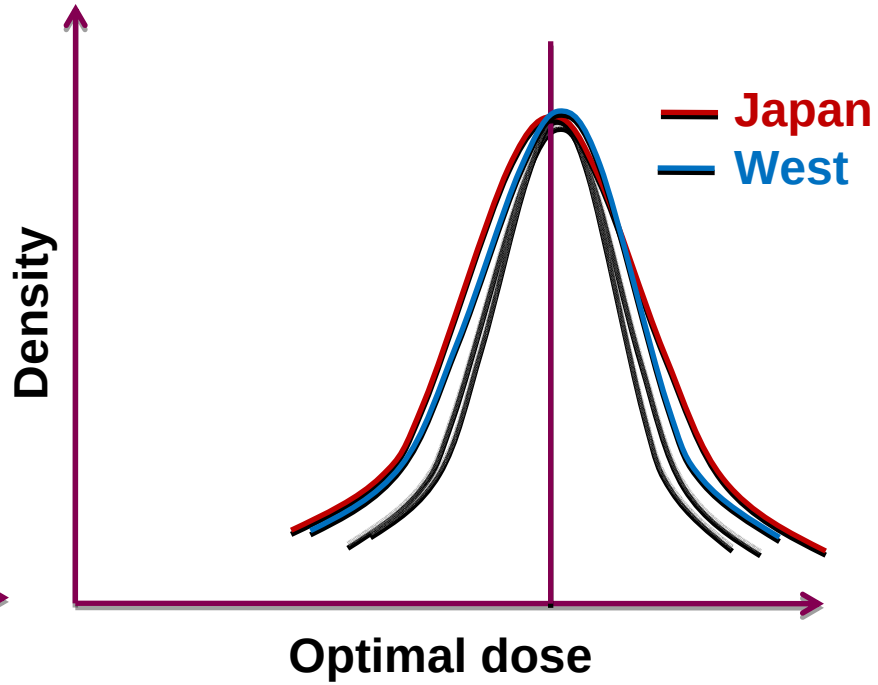
Precision of estimated dose CDP 3

(example for illustration)

Two fold difference in potency:



No difference in potency:



Program is more costly and require more patients. Better precision if there is a 2-fold difference and worse if there is no difference.

(Grey curves= precision based on program 2.)

Similarity West-Japan