M-CERSI FDA workshop: Clinical Pharmacology concepts to support subgroup analyses in drug development

May 8th/9th 2024

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Presenting on behalf of IQ D&I WG

Conflicts of interest:

- I am an employee and shareholder of AstraZeneca
- The views and opinions expressed here are of my own and do not have any bearings to AstraZeneca

Outline

- Basic principles of Sub-Group Analysis
- Overview of guidance
- Case studies
  - Race/ethnicity
  - Age
- Challenges and opportunities in conducting Sub-group Analysis

Basics of sub-group analysis: When, Why, and How of it

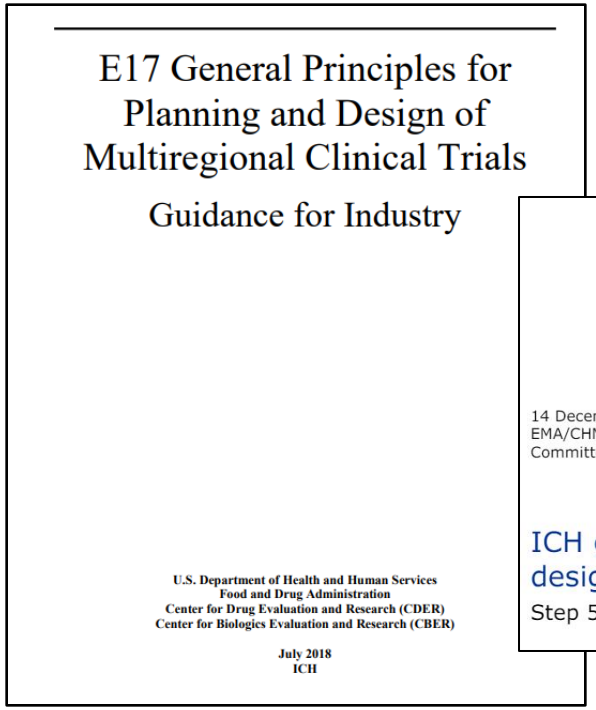
- Sub-group[1]: *"subset of the clinical trial population defined by one or more intrinsic and extrinsic factors, usually measured at baseline"*

- ICH E9[2,3] recommends evaluating differential treatment effects using subgroup analyses:
    - Demographic
    - Disease
    - Environment
    - Clinical considerations

- May be inferential, supportive, or exploratory

1. Guideline on the investigation of subgroups in confirmatory clinical trials ; 2. Guidance for Industry E9 Statistical Principles for Clinical Trials; 3. Sub-group analyses in oncology trials; Amatya et al. Clin Cancer Res. 2021 Nov 1; 27(21): 5753–5756.

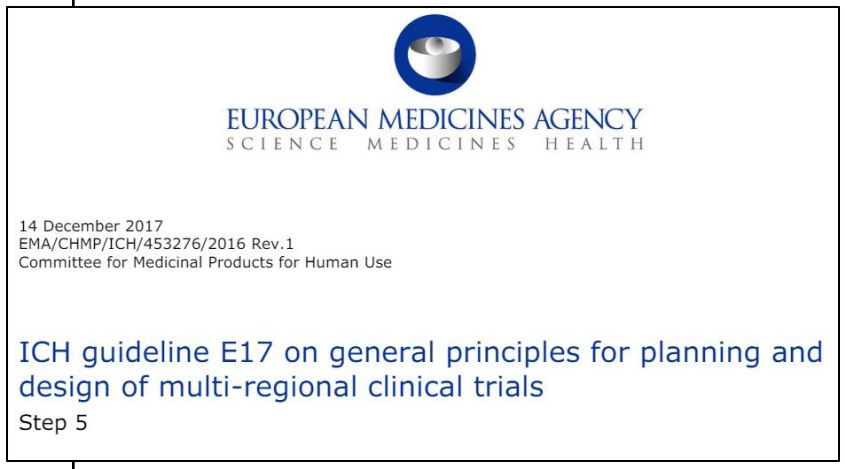
Sub-group analysis: Clinical Pharmacology considerations


E17 General Principles for Planning and Design of Multiregional Clinical Trials

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2018
ICH


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

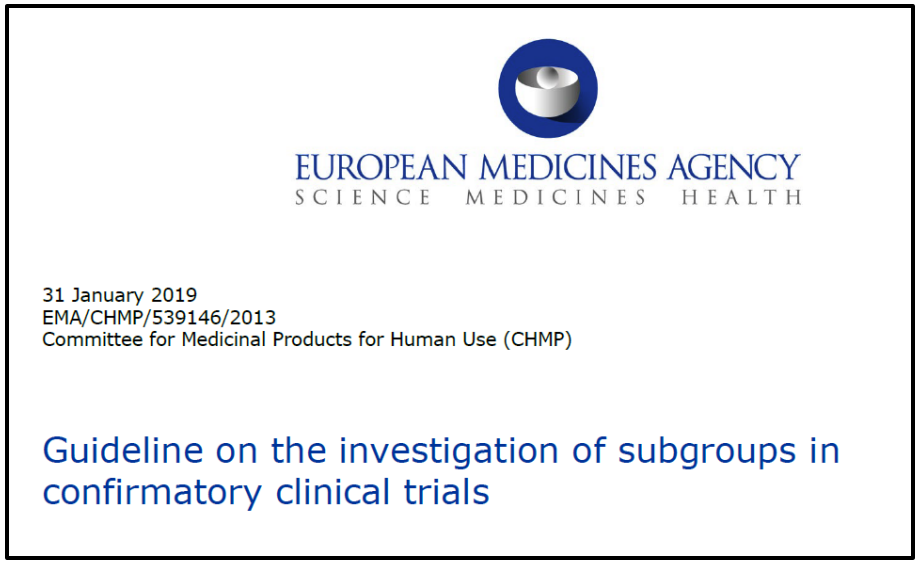
14 December 2017
EMA/CHMP/ICH/453276/2016 Rev.1
Committee for Medicinal Products for Human Use

ICH guideline E17 on general principles for planning and design of multi-regional clinical trials

Step 5

ICH E17:

"Subjects' responses to different drugs may be more or less sensitive to ***intrinsic factors, leading to regional variability. For example, genetic polymorphisms in drug metabolism or receptor sensitivity (described in ICH E5 Appendix D) or body weight and age may impact PK-pharmacodynamics (PD)****, as well as efficacy and safety of the drug."*


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

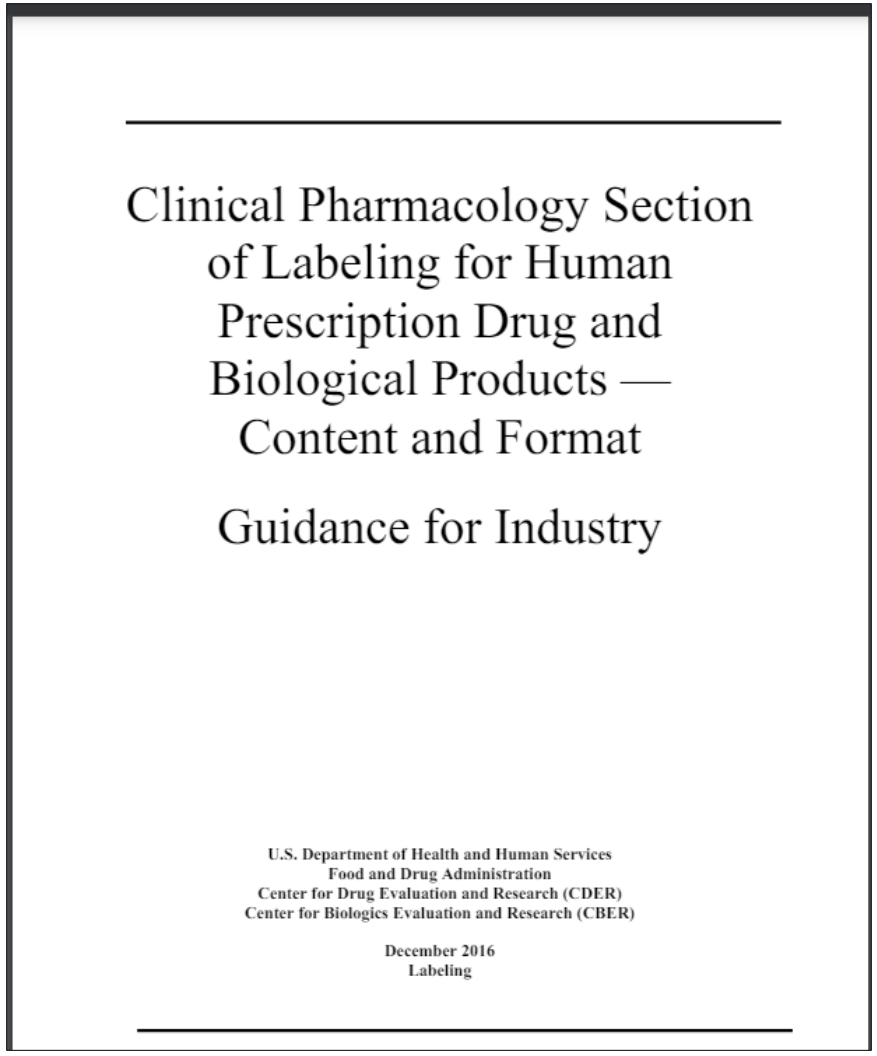
31 January 2019
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the investigation of subgroups in confirmatory clinical trials

Guidelines for investigation of sub-group analysis:

"genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population" and the CHMP Points to consider (PtC) on multiplicity issues in clinical trials states ***"Some factors are known to cause heterogeneity of treatment effects such as gender, age, region, severity of disease, ethnic origin, renal impairment, or differences in absorption or metabolism",*** *and indicates that* ***"analyses of these important subgroups should be a regular part of the evaluation of a clinical study".***

Clinical Pharmacology considerations for Labeling: outputs of sub-group analysis



Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2016
Labeling

- *This heading should include results of studies or analyses that evaluate the potential for PK differences in subpopulations defined by* ***age, sex, race/ethnicity, renal function, hepatic function, and pregnancy.*** ***We recommend that the following subheadings be used for consistency unless the specific population was not assessed: Geriatric Patients, Pediatric Patients, Male and Female Patients, Racial or Ethnic Groups, Patients with Renal Impairment, Patients with Hepatic Impairment, and Pregnant Women.***

- ***Explicit dosage modifications or population-specific therapeutic management should be included in other sections as appropriate (e.g., DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and USE IN SPECIFIC POPULATIONS)***

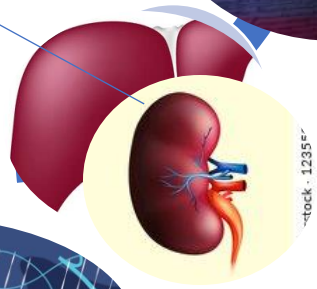
Trial diversity : Learn and confirm during drug development

Phase 1/2a/2b → Phase 2b/3 → Label

Age

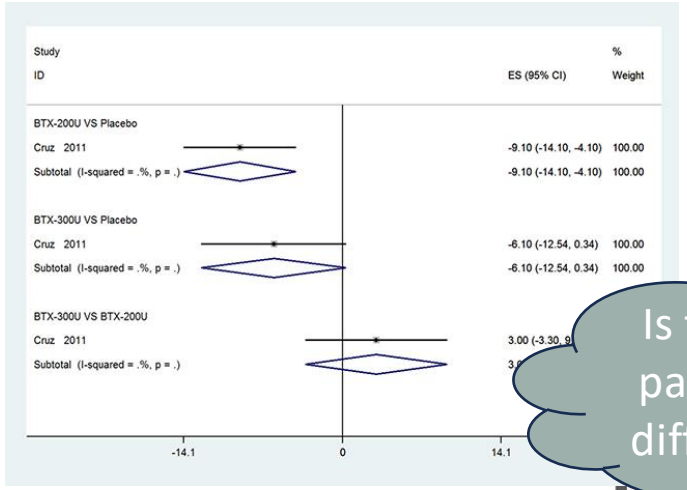
Race/ ethnicity

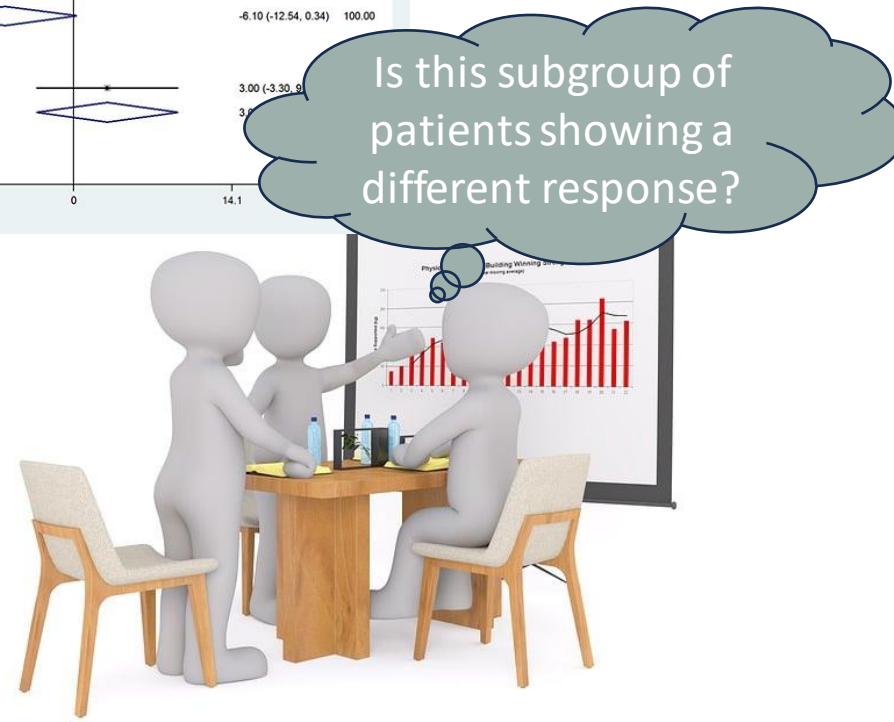
Gender



Organ insufficiencies

Genotypes

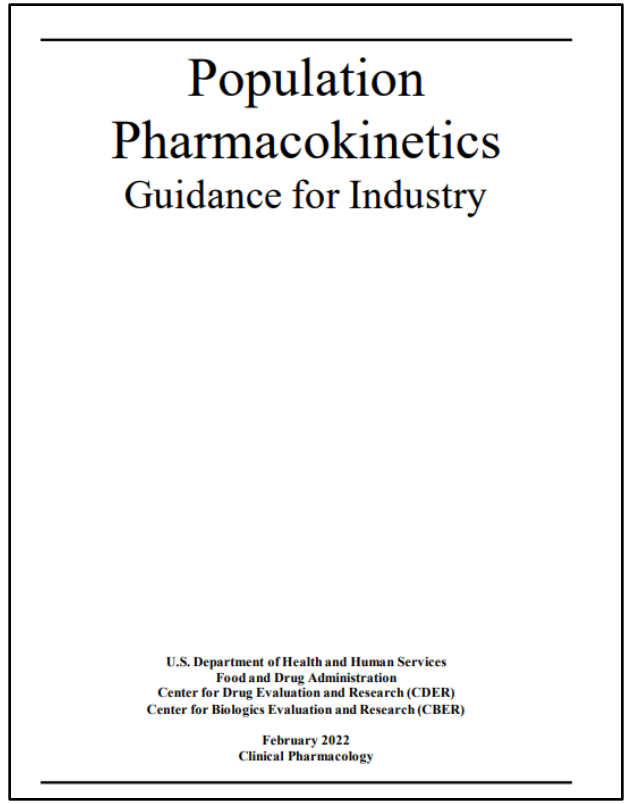




How about the others? Environmental? Treatment related?

Choice of Sub-groups, analysis plan, and outputs

- Visualization of treatment effects by sub-groups
- Sufficient sample size
- Sufficient exposure data at informative time points.
- Distribution of data across subgroups/covariates categories
- Relevance of covariates on PK parameters, ER etc.


Population
Pharmacokinetics
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2022
Clinical Pharmacology

Clinical meaningfulness of outcomes and relevance to dosing considerations?

Case study #1: Osimertinib

- Osimertinib is a potent, oral, selective, CNS active, irreversible EGFR-TKI, approved[1] as a First-line agent in EGFRm NSCLC patients.
- During early trials osimertinib was determined to be well absorbed and a systemic $t_{1/2}$ that afforded once daily dosing in NSCLC populations.
- During early clinical development, prevalence of NSCLC with EGFRm in Asian populations were evident

1. Ramalingam et al; JCO 2018, 36(9):841-849;

Osimertinib sub-group analyses by race/ethnicity using global trials data[1]

AURA Phase 1 (N=210)

- Dose escalation in NSCLC EGFRm patients
- Patients with advanced NSCLC and progressive disease after EGFR TKI
- Dose range of osi.: 20-240 mg, once daily
- Primary end-point: Safety and tolerability

AURA extension (N=211)

- Fixed dose
- Patients with advanced NSCLC and progressive disease after EGFR TKI
- Dose of osi.: 80 mg, once daily
- Primary end-point: Safety, tolerability, and efficacy

Distribution of participants by race as a subgroup (N=780)

Race	%
Caucasian	24
Asians (non-J or non-Chinese)	24
Chinese	15
Japanese	19
Others	6
Missing	11

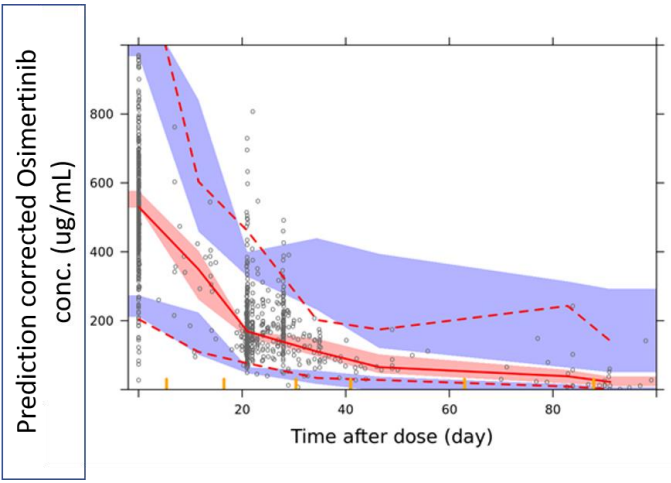
AURA Phase 2 (N=311)

- Open label, single arm, fixed dose, multi-centre
- Patients with advanced NSCLC and progressive disease after EGFR TKI. T790M+
- Dose: 80 mg, once daily (DR: 40 mg, once daily)
- Primary end-point: Efficacy and safety

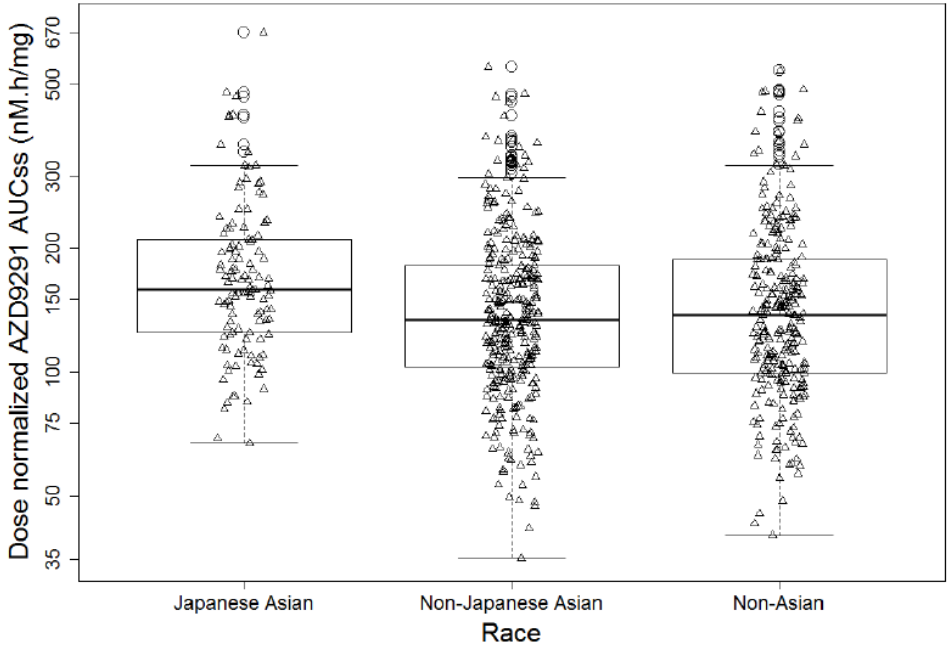
1. K. Brown et al; Br J Clin Pharmacol (2017)831216–1226

PopPK analysis to evaluate the impact of race[1,2,3]

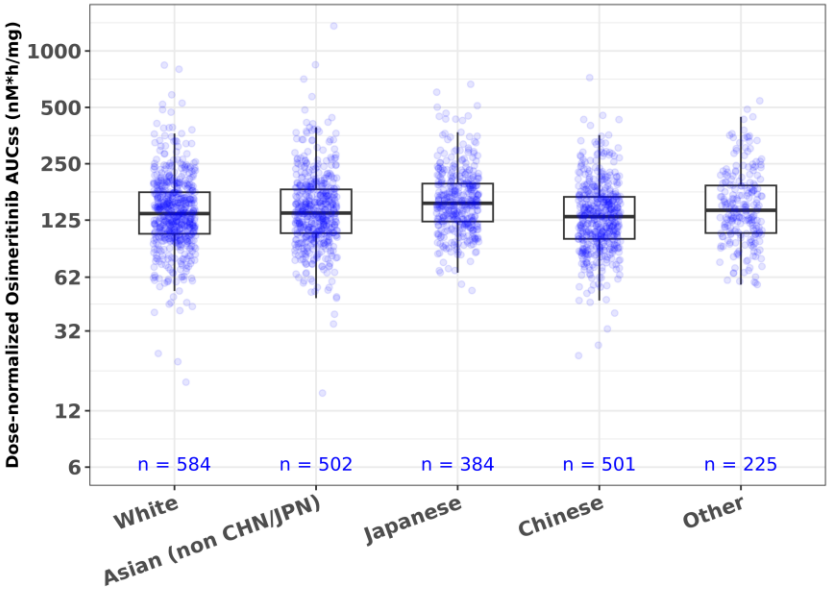
PopPK analysis assessing race as covariate



Sub-group analyses on race



Updated assessments from FLAURA2



No effect of race/ethnicity on CL/F or V/F of osimertinib

- **No significant differences in Osimertinib dose normalized AUCss when stratified by race**

No dose adjustments required by race/ethnicity

PopPK assessments consistent with no differences in treatment effect by race

1. K. Brown et al; Br J Clin Pharmacol (2017)831216–1226; 2. Planchard et al CancerChemother Pharmacol 2016; 77: 767–76.; 3. Yang et al; AACR 2024; Manuscript in Progress

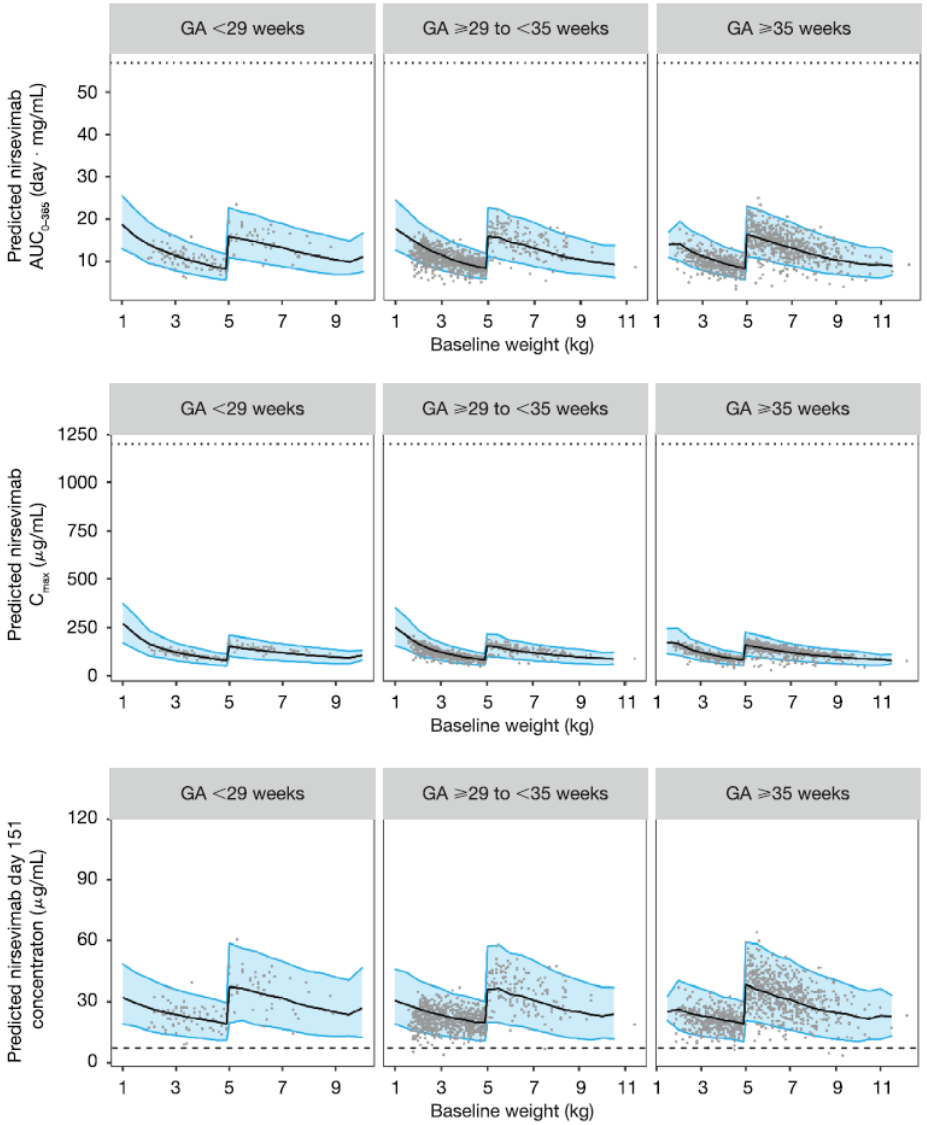
Case study#2 Nirsevimab

- Efficacy was established in healthy infants that were full term and preterm (≥29 wGA) during the first RSV season in two global, pivotal, placebo-controlled studies (MELODY, Phase IIb)
- MEDLEY study evaluated safety and PK of nirsevimab in infants at higher risk for severe RSV LRTI (included: Infants <29 wGA and with CHD or CLD) Vs palivizumab
- Dosing by weight band: Single IM dose; 50 mg if <5kg, 100 mg if ≥5kg body weight at baseline

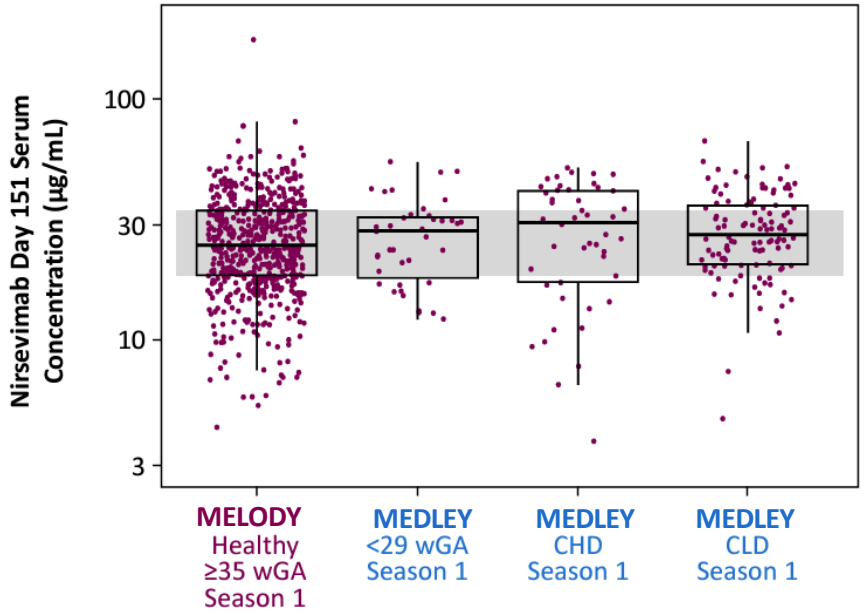
wGA = weeks gestational age

Nirsevimab extrapolation of efficacy & safety based on PK[1]

Exposure range for the dosing regimen was comparable across weight range



Observed PK in support of **efficacy Extrapolation** to infants <29 wGA, and infants with CHD and CLD



- CHD and CLD were tested as covariates[2] and showed no significance supporting exposure similarity across subgroups
- similar of exposures using healthy infants as a reference, where efficacy was established, supporting protection against RSV across infant populations.

Ref. Nirsevimab Advisory Committee meeting, June 2023

1. *Simoes et al, Lancet Child Adolesc Health 2023;* 2. Clegg et al, J Clin Pharmacol, 2024

Caveats in Subgroup analyses: data collection, testing, and interpretation

- Potential for insufficient data during early drug development
  - Recruiting sub-groups may be a challenge
- Post hoc analyses is supportive or exploratory
  - Minimize sub-group dilution and testing procedures
- Potential for inherent bias in outcomes depending on the patients enrolled in each subgroup
- Planned analyses, post-marketing and/or dedicated subgroup trials outcomes (if feasible), may be required for complete assessment

In Conclusion…..

- Subgroup analyses should be conducted during drug development, to support clinical trial diversity

- Clinical relevance of outputs should be considered based on overall study outcomes

- Subgroup analyses leading to additional dedicated trials may warrant further considerations:
  a) feasibility of enrollment
  b) sufficient sample size
  c) Relevance of subgroup to real world patient populations
  d) Minimal delay in access to the drug product in intent-to-treat population

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