SANDOZ A Novartis Division

Clinical development of orally inhaled drug products: Bioequivalence Study designs, conduct, subject attributes and analysis - Challenges and Opportunity

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Bill B Brashier (MBBS, Dip Chest Disease, Fellow of ERS)

Group Head Respiratory Clinical Development.

Sandoz Global Clinical Development Center India

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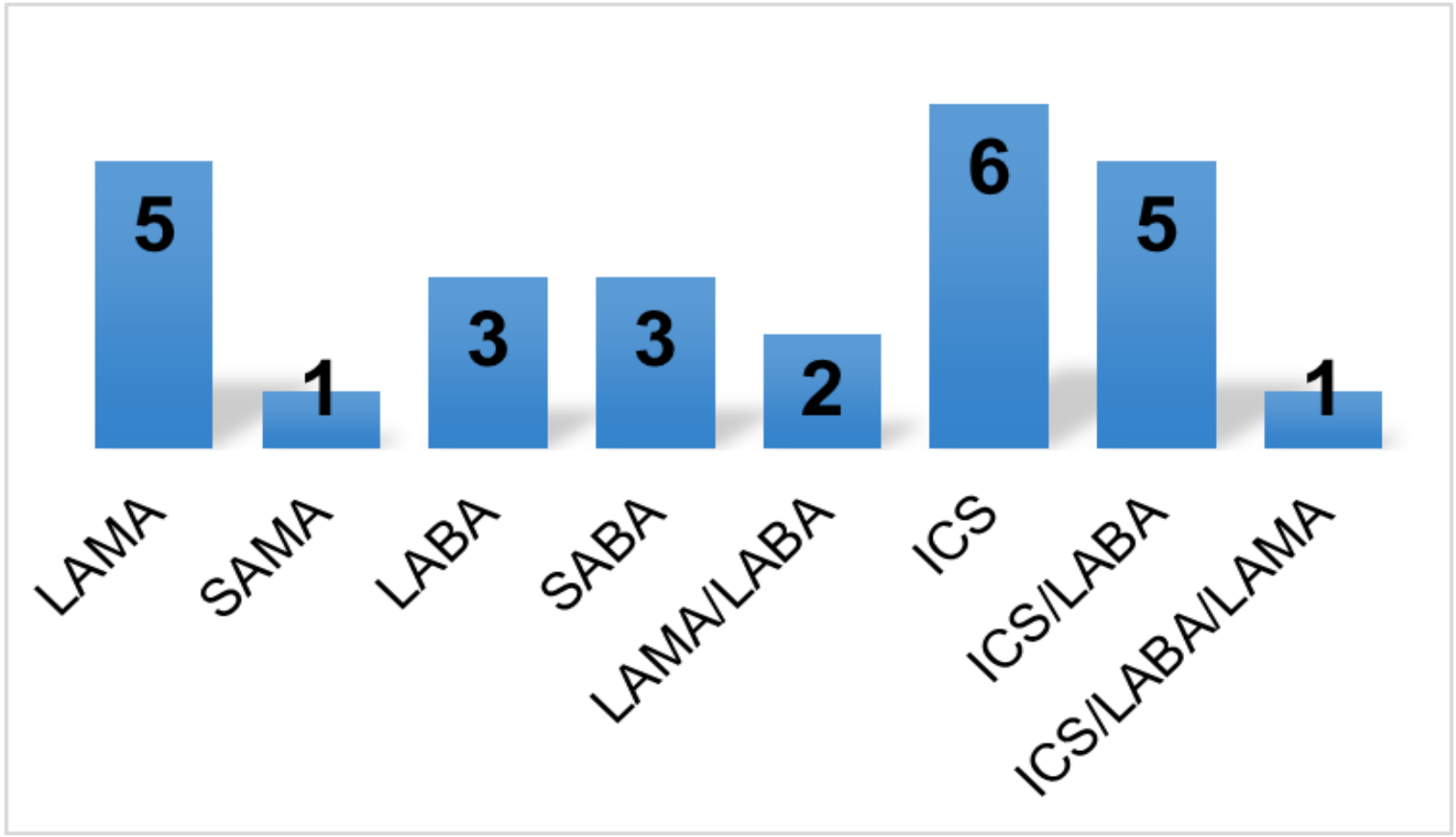
Background- OIDPS with Product specific guidelines-FDA

COPD & Asthma



FDA weight of evidence approach

Invitro

Pharmacokinetic Bioequivalence (all strengths)

Clinical Endpoint study (lowest strength)

LAMA: Long acting muscarinic antagonist, SAMA: Short acting muscarinic antagonist, LABA Long acting beta-2 Agonist, SABA: short acting beta-2 agonist, ICS: Inhaled corticosteroids

FDA Pharmacokinetic study design -OIDPS

Bioequivalence Model-

- **Design**: Single-dose, two-way crossover
- **Dose:** Minimum number of inhalations –analytical method sensitivity
- **Subjects**: Healthy
- **End points**: AUC and Cmax

  T/R ratios limits 80-125%

Adequate and Robust Inhalation training SOPS and protocols

Reference-scaled average BE

- ≥30% Intra-Subject CV – Reference (drug substance)
- Study design -partial replicate: or full replicate

Widening of Equivalence margins=

$$-\left[\ln(1.25)\frac{\sigma_{WR}}{\sigma_{W0}}\right] \leq \mu_T - \mu_R \leq \ln(1.25)\frac{\sigma_{WR}}{\sigma_{W0}}$$

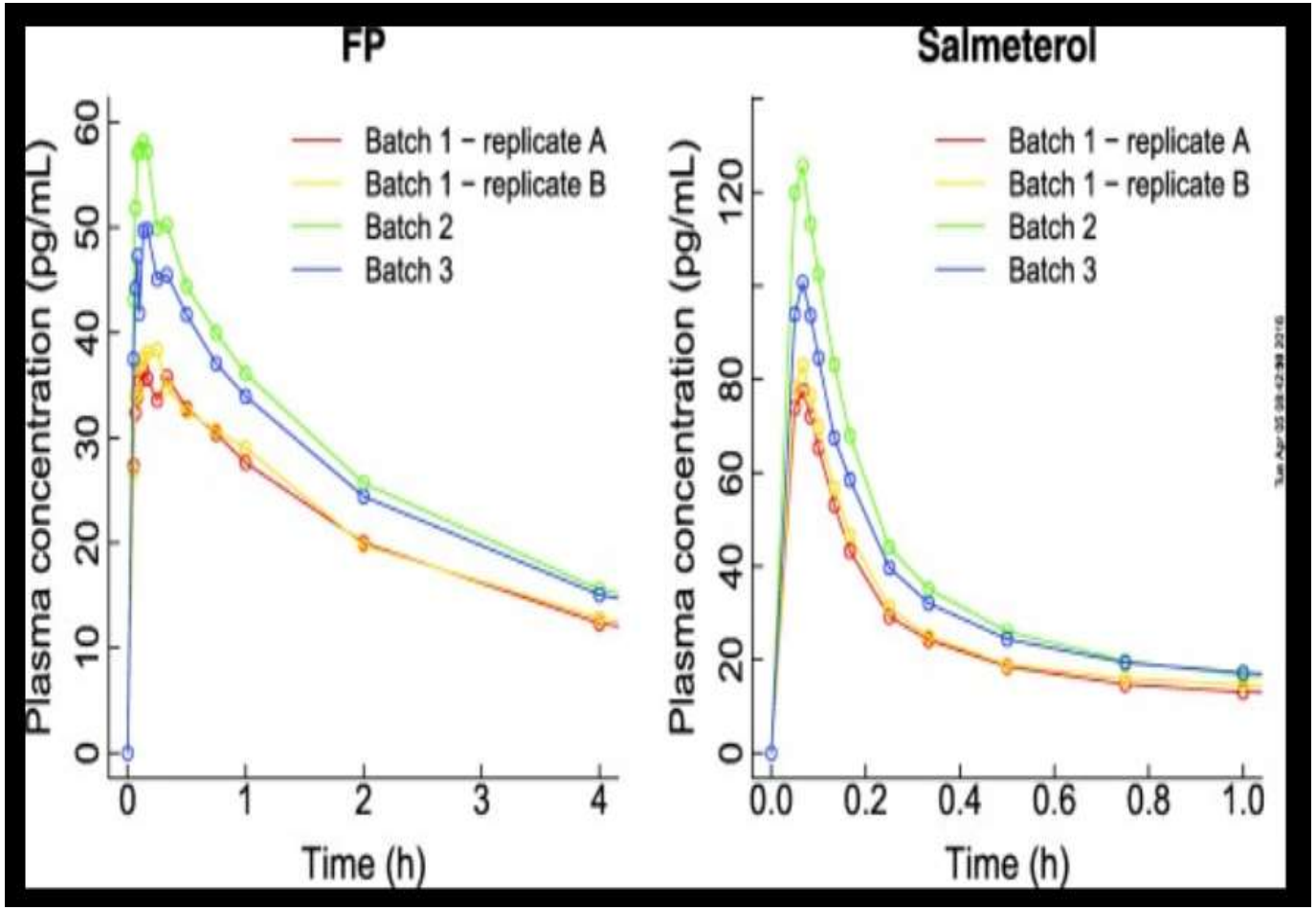
& point estimate within 80-125%

σWR is the population within-subject variance
of the σW0 is a predetermined constant set by the regulatory agency=0.25

Davit et al. The AAPS Journal, 2012 ;14; 4

Inter batch Variation in PK profiling

Advair 100/50 N=28



Getz et al . Clin Pharma & Therap , 100; 3; 2016

*Haughie et al. JAMPDD 33; 2020; 34-42

Plausible-variability R1-R2,

- Manufacturing practice
- Complex product
- Complex Lung anatomy

Low dose

Near expiry batches

Alternative designs

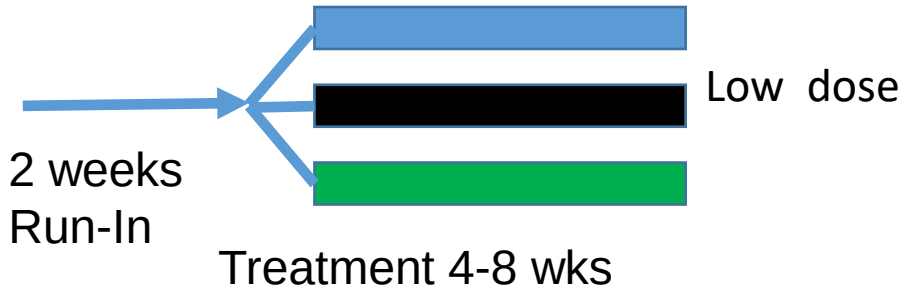
- Increase the number of Puffs
- Multi batch approach

Alignment with FDA

Clinical End-point study in LABA/ICS & ICS in Asthma

Study Design

Parallel Design, Randomized
Placebo controlled

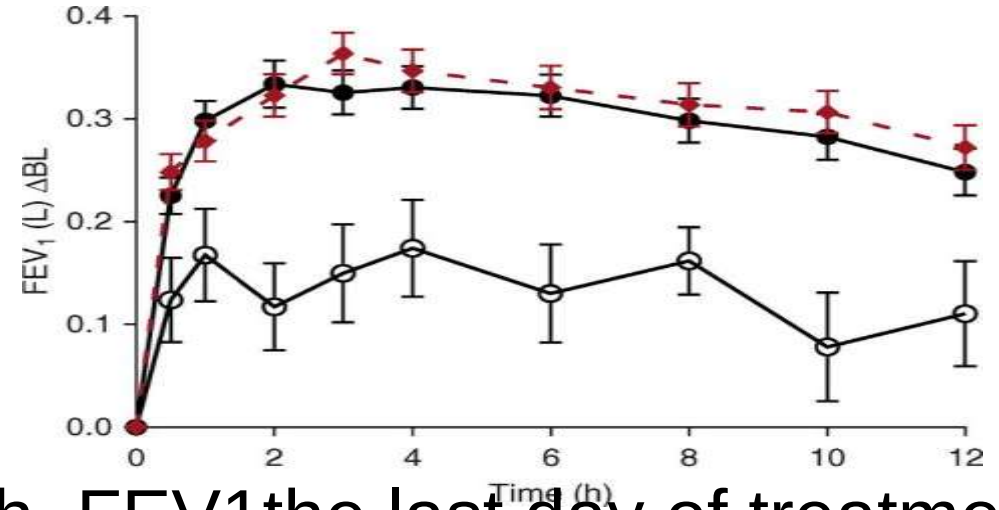


Patient Characteristics

- FEV1% 40-85%

Primary Endpoints

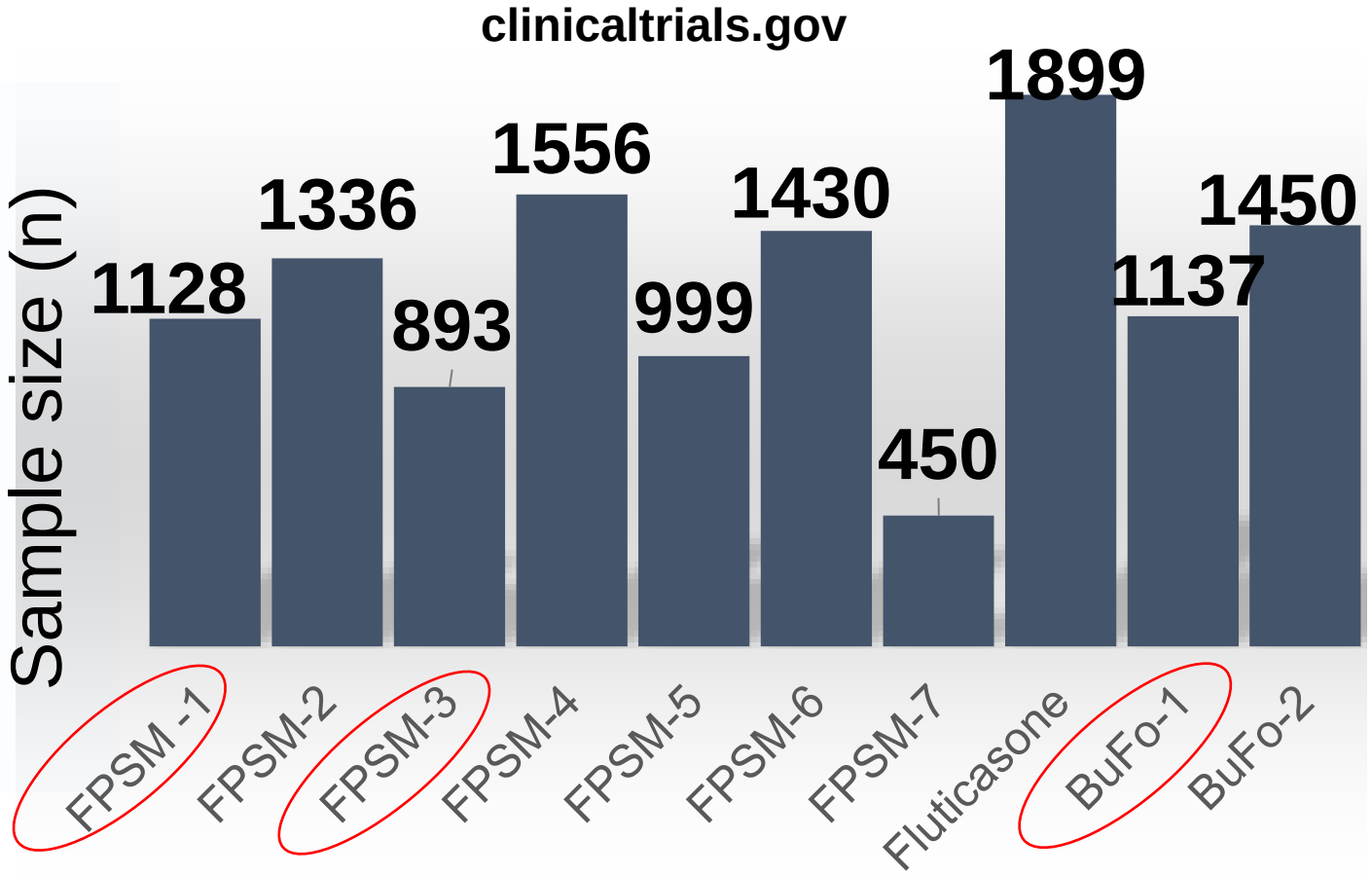
- FEV1- (AUC0-xh) on the first day of the treatment- baseline subtracted



- Trough FEV1the last day of treatment (ΔFEV1)-baseline subtracted
- Superiority of R & T to Placebo

Longphre et al. An ATS, 2017; 14;2

Sample Size and Variability contributors



Contributors to Variance

- Phenotypes - Endotypes#
- Comorbidities
- Exacerbations**
- Low-dose steroid Variable response
- Spirometry attributed Variability

Kerwin et al	NCT02495168	Longphre et al
ΔFEV1 CV%=130	ΔFEV1 CV%=118	ΔFEV1 CV%=123
ΔFEV placebo=57 ml	ΔFEV1 placebo=124 ml	ΔFEV1 placebo=190 ml

#Kuruvilla et al. Clin Rev Allergy Immunol. 2019; 56(2): 219–233.
**Bai et al. ERJ 2007 30: 452-456, Graham et al AJRCCM, 2019; 200; 8; 15; Barr et al . Respir Care. 2008

53(4): 433–441. Kerwin et al. J AERO MED AND PULM DRUG DELIVERY, 2020:33:; 2; 99–10, Longphre-et al An ATS, 2017;14:2

Broncho-protection studies –Asthma-Albuterol

Design

- Single dose, double-blind, double-dummy, randomized, crossover

Patient Characteristics

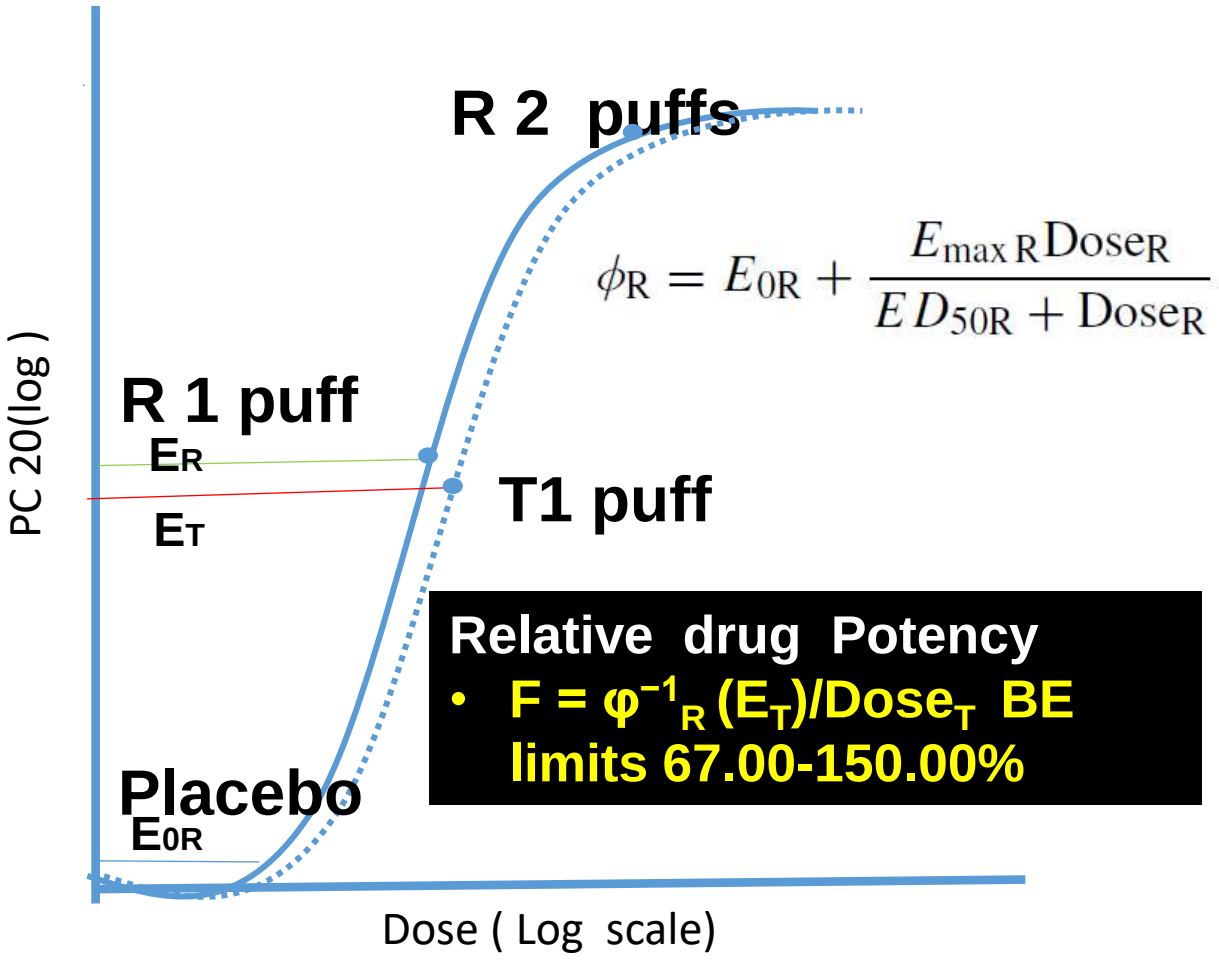
- Asthma (mild).
- PC20 ≤ 8 mg/mL.

Endpoint: Post-dose

- **Trained sites**
- **Standardized Procedure**

$$PC_{20} = \text{antilog}\left[\log C_1 + \frac{(\log C_2 - \log C_1)(20 - R_1)}{R_2 - R_1}\right]$$

Dose-scale analysis – Emax model



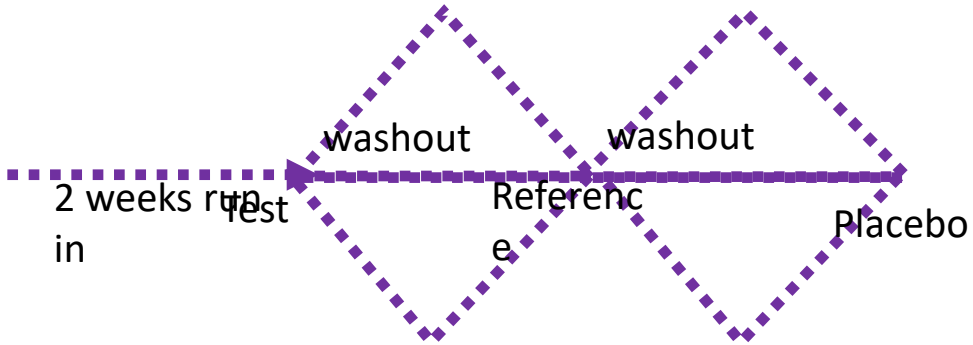
Relative drug Potency

- **$F = \varphi^{-1}{}_R(E_T)/Dose_T$ BE limits 67.00-150.00%**

C1 =concentration preceding C2, C2 =concentration resulting in a 20% or greater fall in FEV1, R1=percent fall in FEV1 after C1, R2 =percent fall in FEV1 after C2

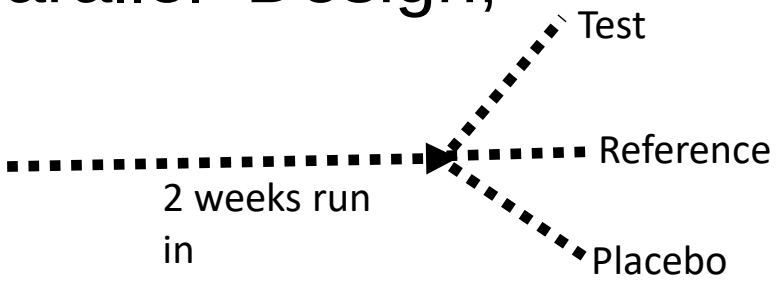
Bronchodilator- Asthma & COPD patients

Crossover Design,
Randomized Single dose,



Allows patient Enrichment

Parallel Design,



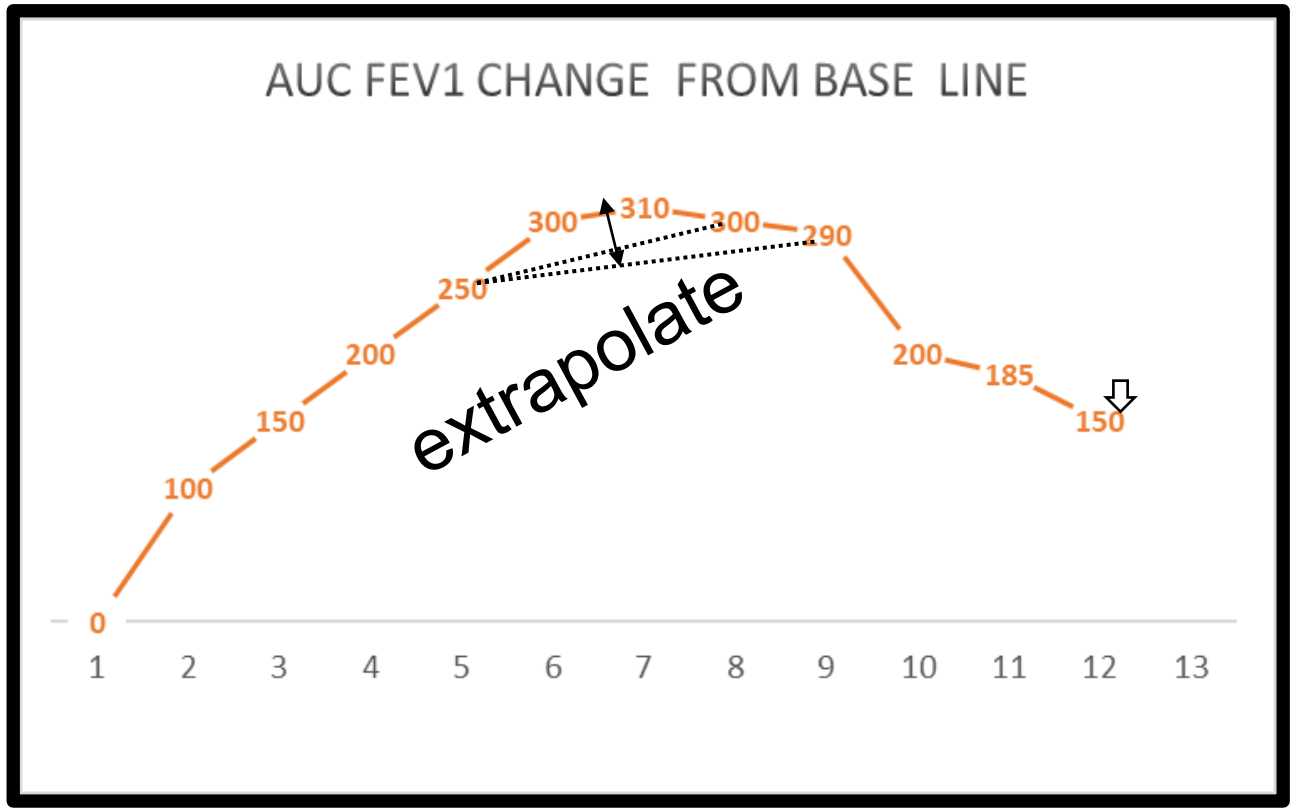
Endpoints

- FEV1-AUC0-xh on the first day of the treatment:

Challenges

- Discontinue- medications (including ICS)- exacerbations
- High patient dropouts

Data Analysis Consideration and Challenges



- **AUC** –Missing time points?

Rescue medications noted in Diary

Key Take aways

BE PK studies:

- Reference variation–Evaluate the reference elaborately
- Standardize Inhalation techniques

CEBE Studies:

Acknowledgment

Sandoz Clinical Development Center-Global

- Clinical Development
- IVIVC
- Pharmaceutical Development
- Regulatory

References

- Guidance for Industry- Bioequivalence Studies with Pharmacokinetic . Endpoints for Drugs Submitted Under an ANDA (pages 1-20) http//:www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
- Product-Specific Guidances for Generic Drug Development. https://www.accessdata.fda.gov

Thank you