Discussion Points For the "Track B" Breakout Session: In Vivo Tests (PK, PD and Biomarkers)

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Outline

- Basic Necessities 5 min
- PK and Lung Deposition 25 min
- Clinical/PD 30 min
- Dose Response 10 min
- Applicability to BE of Combination Products 15 min
- Summary/Wrap up 5 min

Basic Necessities (5 min) - *Dale Conner*

- A pharmacodynamic (PD)/clinical or pharmacokinetic (PK) measure of drug delivery to the local site of action (lung)
- Ability to objectively quantitative response(s)
- Ability to distinguish between doses of different magnitudes

PK and Lung Deposition in Determination of Equivalence of Local Delivery (25 Min) – *Dale Conner*

- **Pharmacokinetic[1] Evaluations**
  - **Standard PK studies**
  - **Early Bioavailability (30 min)**
  - **Charcoal-block**
    - **Definition of "complete" charcoal block**
    - **Validation of charcoal block**
    - **Acceptable level of blockage**
    - **Drug with very short (few minutes)T_{max}**
- **Lung Deposition**

[1]Systemic levels and/or Urinary excretion

PD/Clinical Outcomes of Equivalence of Local Delivery (30 Min) – *Param Nair*

- **Efficacy**
  - **Bronchodilators**
    - FEV_1 (Bronchodilation, including nocturnal asthma)
    - Methacholine Challenge (Bronchoprovocation/protection)
  - **Corticosteroids**
    - Steroid-naïve vs. steroid-treated patients
    - FEV_1 (Bronchodilation inclusing "Asthma Stability" model)
    - Exhaled Nitric Oxide (eNO)
    - Sputum Eosinophils
    - Adenosine Challenge or other Bronchoprovocations
- **Safety**
  - **Urinary cortisol, osteocalcin, ACTH stimulation, serum markers**

Dose Response (10 Min) - *GJPS*

- **Possibility based on the available biological models**
- **Acceptability:**
  - **Statistical vs. pharmacological**
- **Limitations**
  - Clinical/PD endpoint dependency
  - Approved/labeled dosing regimen
    - The marketed strength may represent the recommended single maximum dose

Applicability to BE of Combination Products (15 Min) - *Robert Hermann*

- PK Evaluations
- PD/Clinical Evaluations
  - Single (e.g., FEV_1) or separate measures based on mode of action
    - ICS + β-agonists
    - β-agonists + Anticholinergics

Summary (5 Min)

Gur Jai Pal Singh