A mechanism-based model was developed to adequately describe quemiclustat PK, sCD73, and its inhibition of CD73 enzyme activity. The model provided rationale for selecting a dose of 100 mg Q2W for future clinical trials for quemiclustat.

**RESULTS**
- A preliminary population PK-PD model, consistent with target-mediated disposition of quemiclustat, adequately described the quemiclustat PK and sCD73 profiles over the dose range of 0.1 to 125 mg.
- The model established a power relationship was explored and the final value was selected based on objective function values.
- The model predicted quemiclustat at doses ≥100 mg would yield exposure throughout the dosing interval in majority of patients with gastrointestinal (GI) malignancies.
- A power relationship was established between the dose, quemiclustat PK profiles, soluble CD73 (sCD73) measurements, and CD73 enzyme activity.
- The model predicted quemiclustat at doses ≥100 mg would yield exposure throughout the dosing interval in majority of patients with gastrointestinal (GI) malignancies.
- The model provided rationale for selecting a dose of 100 mg Q2W for future clinical trials for quemiclustat.

**OBJECTIVES**
- Develop a population PK-PD model capturing the relationship between dose, quemiclustat PK profiles, soluble CD73 (sCD73) measurements, and CD73 enzyme activity.
- Use model simulations to guide dose selection for future clinical trials.

**METHODS: Clinical Study Design**

- **Study Design**: Single and multiple ascending dose, placebo controlled.
- **Population**: Patients with gastrointestinal (GI) malignancies.
- **Number of subjects per dose level**: 20.
- **Quemliclustat dose**: Single dose, IV, Q2W, subcutaneous.
- **Number of subjects**: 480 ng/mL.
- **Data modeled**: Quemliclustat PK, sCD73, CD73 activity, plasma CD73 activity.

**METHODS: Population PK-PD Model Structure**
- **A Mechanistic Pharmacokinetic-Pharmacodynamic (PK-PD) Model of Quemliclustat (AB680), a Small-Molecule Inhibitor of CD73, in Healthy Volunteers and Patients with Gastrointestinal Malignancies**
  - PRESENTER: Kai Hsin (Ken) Liao
  - INTRODUCTION
    - The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A2a and A2b receptors on immune cells, leading to an ineffective anti-tumor response.
    - CD73 enzyme and tissue non-specific alkaline phosphatase (TNAP) are primarily responsible for the conversion of extracellular adenosine mono-phosphate (AMP) to adenosine.
    - Quemliclustat is a potent, selective, small-molecule inhibitor of soluble and membrane-bound CD73 developed with the aim of eliminating adenosine-mediated immunosuppression in the tumor microenvironment.
  - METHODS: Clinical Study Design
    - **Study Design**: Single and multiple ascending dose, placebo controlled.
    - **Population**: Patients with gastrointestinal (GI) malignancies.
    - **Number of subjects per dose level**: 20.
    - **Quemliclustat dose**: Single dose, IV, Q2W, subcutaneous.
    - **Number of subjects**: 480 ng/mL.
    - **Data modeled**: Quemliclustat PK, sCD73, CD73 activity, plasma CD73 activity.
  - **Methods: Population PK-PD Model Structure**
    - **A Mechanistic Pharmacokinetic-Pharmacodynamic (PK-PD) Model of Quemliclustat (AB680), a Small-Molecule Inhibitor of CD73, in Healthy Volunteers and Patients with Gastrointestinal Malignancies**
    - PRESENTER: Kai Hsin (Ken) Liao
    - INTRODUCTION
      - The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A2a and A2b receptors on immune cells, leading to an ineffective anti-tumor response.
      - CD73 enzyme and tissue non-specific alkaline phosphatase (TNAP) are primarily responsible for the conversion of extracellular adenosine mono-phosphate (AMP) to adenosine.
      - Quemliclustat is a potent, selective, small-molecule inhibitor of soluble and membrane-bound CD73 developed with the aim of eliminating adenosine-mediated immunosuppression in the tumor microenvironment.
  - METHODS: Population PK-PD Model Structure
    - **Parameter Estimates**
      - **Cmax (mean) [100 mg] (95% CI)**: 0.50 (0.44, 0.60)
      - **Vp (mean) [100 mg] (95% CI)**: 3.0 (2.7, 3.3)
      - **CL (mean) [100 mg] (95% CI)**: 0.00 (0.00, 0.00)
      - **T1/2 (mean) [100 mg] (95% CI)**: 0.5 (0.4, 0.6)
      - **Kd (mean) [100 mg] (95% CI)**: 0.05 (0.04, 0.06)
      - **Km (mean) [100 mg] (95% CI)**: 1.0 (0.9, 1.1)
      - **Fraction of soluble target at total target**: 63% (59%, 66%)
      - **Fraction of soluble target at total target**: 63% (59%, 66%)
      - **Kp (mean) [100 mg] (95% CI)**: 1.0 (0.9, 1.1)
      - **Kp (mean) [100 mg] (95% CI)**: 1.0 (0.9, 1.1)
      - **Residual variability for soluble target concentration**: 28% (20%, 38%)
      - **Residual variability for soluble target concentration**: 28% (20%, 38%)
      - **Residual variability for drug concentration**: 28% (20%, 38%)
      - **Residual variability for drug concentration**: 28% (20%, 38%)
      - **PK: Production rate for target complex**: 0.74 (0.66, 0.83)
      - **PK: Production rate for target complex**: 0.74 (0.66, 0.83)
      - **PK: Distribution clearance of unbound drug**: 0.74 (0.66, 0.83)
      - **PK: Distribution clearance of unbound drug**: 0.74 (0.66, 0.83)
      - **PK: Distribution clearance of unbound drug**: 0.74 (0.66, 0.83)
      - **PK: Distribution clearance of unbound drug**: 0.74 (0.66, 0.83)
      - **PK: Distribution clearance of unbound drug**: 0.74 (0.66, 0.83)
      - **PK: Distribution clearance of unbound drug**: 0.74 (0.66, 0.83)
  - **Graphical and other statistical analyses, including evaluation of NONMEM outputs, were performed using R version 3.6.2 for Windows**