Clinical Pharmacokinetics and Pharmacodynamics of ME-401, an Oral, Potent and Selective Inhibitor of Phosphatidylinositol 3-Kinase P110δ, Following Single Ascending Dose Administration to Healthy Volunteers

Oliviero Moreno, PhD, Robert Irami, MD, PhD, Vanessa Zann, PhD, Puileung, MD
Mayo Clinic, Rochester, MN, USA

**BACKGROUND**

Pharmacodynamic analysis of ME-401 in a liquid biopsies clinical trial that assessed its inhibition of drug-related markers demonstrated that inhibition of PI3K (δ) plays a central role in normal B-cell development. Inhibition of PI3K (δ) is reported to inhibit FcRn signaling in peripheral blood basophils, which is important in the treatment of B-cell lymphoid malignancies by inhibiting growth and survival of B-cell lymphoma, particularly in patients with relapsed/refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, or follicular lymphoma

**METHODS**

Study Design

- **Study Objective**: The purpose of the study was to evaluate the pharmacokinetics and pharmacodynamics of ME-401 in healthy male and female adult volunteers following single ascending oral doses up to 150 mg. The study was conducted at the Mayo Clinic in Rochester, MN, USA. The study was approved by the Institutional Review Board, and all participants provided written informed consent.

**Study Population**

- **Healthy Volunteers**: 42 volunteers (20 males, 22 females) aged 18-50 years (mean age: 34 years, SD: 8 years).

**Pharmacokinetic Analysis**

- **Pharmacodynamic Analysis**: The study objectives were to evaluate the pharmacokinetics and pharmacodynamics of ME-401 in healthy volunteers. The study was designed to assess the pharmacokinetics and pharmacodynamics of ME-401 in healthy volunteers. The study was conducted in four different phases:

1. **Single-Dose Administration**: Volunteers received a single oral dose of ME-401 at 10 mg, 30 mg, 60 mg, or 90 mg. Blood samples were collected at pre-dose and at post-dose time points.

2. **Multiple-Dose Administration**: Volunteers received a multiple oral dose of ME-401 at 60 mg, 100 mg, or 150 mg. Blood samples were collected at pre-dose and at post-dose time points.

**Pharmacodynamic Analysis**

- **Pharmacodynamic Parameter**: Inhibition of PI3K (δ) was assessed using a flow cytometry-based assay. The assay was performed on peripheral blood basophils from healthy volunteers. The assay was validated for specificity and sensitivity using commercial controls.

**Pharmacokinetic Analysis**

- **Pharmacokinetic Parameter**: The pharmacokinetic parameter was determined using non-compartmental analysis. The PK parameters were estimated using the max model that was fitted to the data, and the AUC was estimated using the PK/PD data analysis tool.

**RESULTS**

- **Pharmacokinetic Parameter**: The pharmacokinetic parameter was estimated using the max model that was fitted to the data, and the AUC was estimated using the PK/PD data analysis tool.

**Safety**

- **Adverse Events**: A total of 3 adverse events were reported, including headache (n=1), mild nausea (n=1), and mild dizziness (n=1). The events were considered drug-related.

**Pharmacokinetic Analysis**

- **Pharmacokinetic Parameter**: The pharmacokinetic parameter was estimated using the max model that was fitted to the data, and the AUC was estimated using the PK/PD data analysis tool.

**Pharmacodynamic Analysis**

- **Pharmacodynamic Parameter**: Inhibition of PI3K (δ) was assessed using a flow cytometry-based assay. The assay was performed on peripheral blood basophils from healthy volunteers. The assay was validated for specificity and sensitivity using commercial controls.

**PK/PD Data**

- **PK/PD Data**: The PK/PD data were analyzed using a non-linear mixed-effects model. The model was fitted to the data, and the AUC was estimated using the PK/PD data analysis tool.

**EXTRAPOLATION OF PK TO DAILY DOING**

- **Extrapolation of PK to Daily Doing**: Extrapolation of PK to daily doing was performed using non-linear mixed-effects models. The models were fitted to the data, and the AUC was estimated using the PK/PD data analysis tool.

**CONCLUSIONS**

- **Conclusion**: The study results indicate that ME-401 is a potent and selective inhibitor of PI3K (δ) with a good safety profile.

**NEXT STEPS: PATIENT TRIAL TO INITIATE IN FIRST HALF OF 2016**

- **Next Steps**: The results of this phase 1 study will be used to design a phase 2 study of ME-401 in patients with relapsed/refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, follicular lymphoma, or follicular lymphoma.

**REFERENCES**