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## PURPOSE

ME-401, a potent and selective inhibitor of the p110 $\delta$  isoform of phosphatidylinositol 3 kinase (PI3K), is in clinical development for the treatment of lymphoid malignancies. Preclinical toxicology and safety pharmacology data supported initial clinical assessment in healthy volunteers.

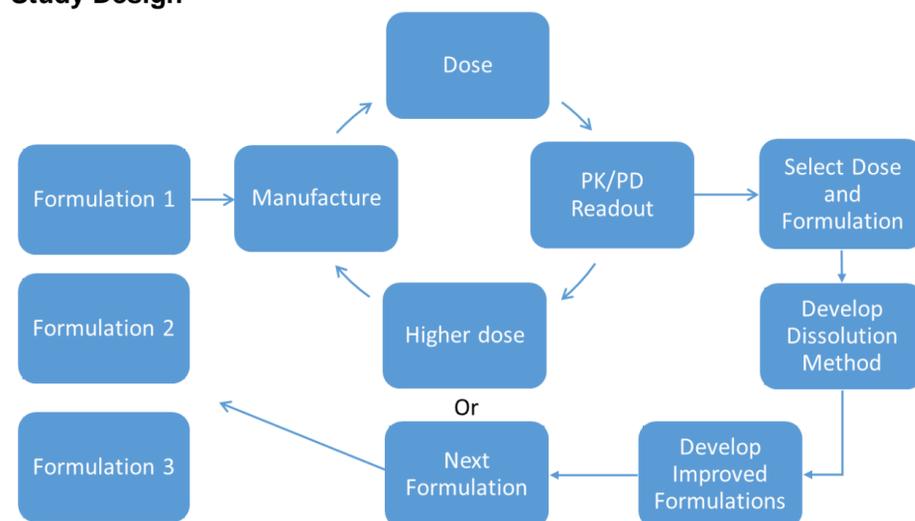
Since ME-401 is a potential best-in-class drug, early identification of the ultimate formulation platform is important to streamline clinical development and commercialization.

The objectives of the study were to:

- Assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD)
- Identify a formulation and dosing schedule to advance into patient trials

## METHODS

### Study Design



- Three formulations, representing three platforms, were developed and prioritized for clinical evaluation based on manufacturability and stability: 1. powder blend, 2. lipid suspension, and 3. spray dried dispersion
- The clinical study was conducted using the Translational Pharmaceuticals® platform, which enables rapid real-time PK/PD analysis and GMP manufacture of drug products between dosing periods.
- Blood samples were taken to assess ME-401 plasma levels, and for testing with a PD assay of target inhibition: basophil activation assessed via CD63 expression by flow cytometry following *ex-vivo* stimulation with an anti-FCeR1 monoclonal antibody<sup>1</sup>.
- Interim decisions after dosing periods, based on emerging data.
- Dissolution studies were performed using a biorelevant pH switch dissolution method in USP apparatus II: pH 1 fasted state simulated gastric fluid (FaSSGF); followed by pH 6.8 fasted state simulated intestinal fluid (FaSSIF).
- Selected dose strengths were further improved for smaller capsule size (higher drug loading) and scalability of manufacturing

## METHODS

### Clinical Study Parameters

- Open label, in healthy male subjects (18-65 years).
- 3 sequential groups (A n=3, B n=6 and C n=6).
- Planned dose levels: 10, 30, 60, 90, and 150 mg
- Optional groups (D & E n=6) included in protocol to allow for further optimization of the selected formulation.
- Each subject administered up to 2 single doses across 2 study periods
- Safety parameters evaluated included adverse events, vital signs, electrocardiogram, and physical examination

## RESULTS

- 15 volunteers were enrolled in Groups A-C, and all planned dose levels were completed with Formulation 1 (powder blend)
- One subject experienced 2 treatment-emergent adverse events (TEAEs) that were considered drug-related: pain and headache, graded as mild, after dosing with 60 mg ME-401.
- ME-401 demonstrated linear increases in exposure up to the highest dose tested (150 mg, Table 1).
- Analysis of PK/PD data indicated that daily dosing of  $\geq 60$  mg is expected to afford trough plasma levels that lie on the plateau of the effectiveness/dose-response curve<sup>1</sup>
- Exposure expected from daily dosing of 60 mg, were far below the no adverse effect levels (NOAEL) observed in 28-day preclinical toxicology studies (Figure 1)
- Formulation 1 was further improved to enable scalable manufacturing of 60 mg and 120 mg dose strengths, using smaller capsules; tested in optional group D
- The improved 60 mg formulation was comparable to the original formulation, and the 120 mg formulation demonstrated a proportional increase in exposure (Figure 2)

**Table 1. Geometric Mean (Geometric CV%) PK Parameters for All Dose Levels (Groups A-C)**

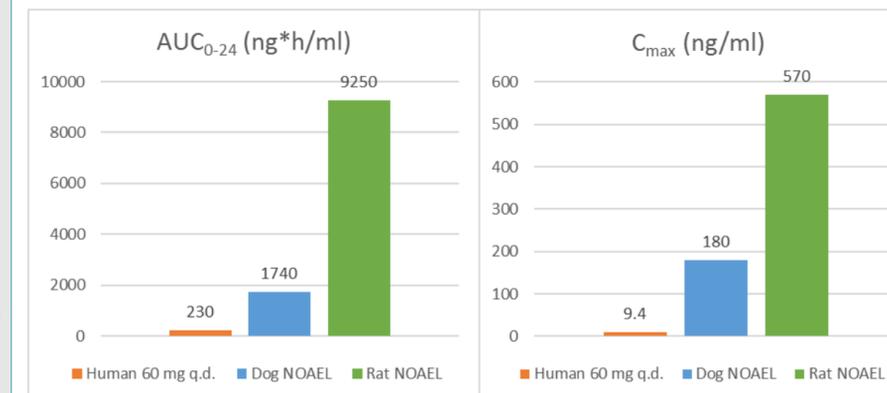
PK Parameter	10 mg (n=3)	30 mg (n=3)	60 mg (n=6)	90 mg (n=6)	150 mg (n=6)
$T_{max}^*$ (h)	5.0 (5.0 – 6.0)	5.0 (5.0 – 6.0)	5.0 (5.0 – 6.0)	5.0 (3.0 – 6.0)	5.0 (1.5 – 6.0)
$C_{max}$ (ng/mL)	1.61 (8.9%)	3.89 (66.8%)	9.39 (32.2%)	13.6 (44.1%)	34.8 (55.2%)
$AUC_{(0-last)}$ (ng*h/mL)	18.2 (70.5%)	77.3 (50.1%)	162 (32.6%)	299 (36.6%)	654 (61.8%)
$AUC_{(0-inf)}$ (ng*h/mL)	24.9 (106.8%)	117 (44.7%)	234 (21.6%)	466 (44.7%)	939 (62.2%)
$T_{1/2}$ (h)	9.362 (138.8%)	29.229 (38.1%)	27.775 (36.2%)	27.560 (46.6%)	28.094 (31.1%)

AUC: area under the concentration-time curve;  $C_{max}$ : maximum plasma concentration; PK: pharmacokinetics;  $T_{1/2}$ : plasma half-life;  $T_{max}$ : time to maximum plasma concentration

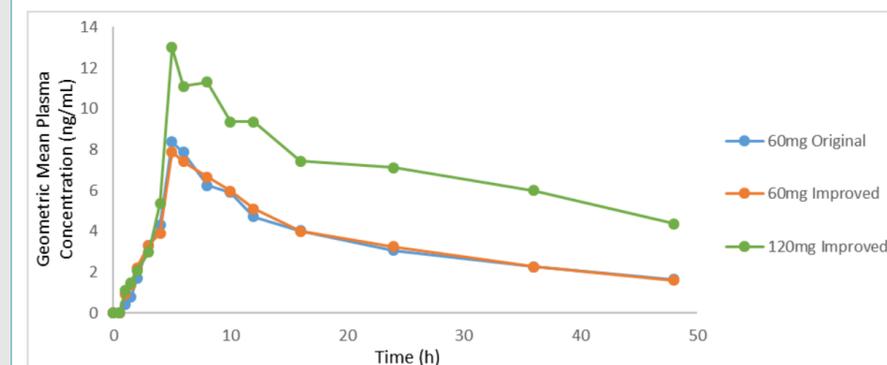
\*Median (range)

## RESULTS

**Figure 1. AUC and  $C_{max}$  expected from 60 mg q.d., compared to rat and dog NOAEL (D28) from preclinical toxicology studies**



**Figure 2. Plasma concentration time profile for the Original and Improved 60 mg capsule and 120 mg capsule formulation**



## CONCLUSIONS

- An ME-401 formulation platform was identified, with desired manufacturability and stability attributes, achieving desired exposure levels, and linear increase in exposure over the dose range tested.
- Exposure margins based on clinical PK/PD data and preclinical toxicity suggests favorable therapeutic window from repeat dosing.
- A dissolution method was developed based on clinical data, and implemented to develop improved 60 mg and 120 mg formulations for oncology patient trials.
- The value of performing formulation selection and improvement in a FIH trial in healthy volunteers was confirmed

Reference:

<sup>1</sup>Clinical Pharmacokinetics and Pharmacodynamics of ME-401, an Oral, Potent and Selective Inhibitor of Phosphatidylinositol 3-Kinase P110 $\delta$ , Following Single Ascending Administration to Healthy Volunteers. Ofir Moreno, Robert Imani, Vanessa Zann, Pui Leung. Poster presented at 2016 American Association of Cancer Research Annual Meeting.