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Formulation selection and development for ME-401, an oral, potent and selective inhibitor of phosphatidylinositol 3-kinase P110δ during a first-in-human study in healthy volunteers

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PURPOSE

ME-401, a potent and selective inhibitor of the p110δ 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.

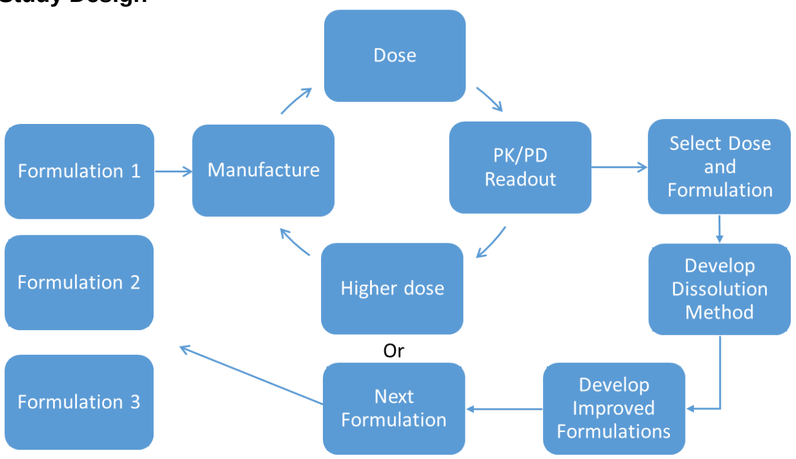
Since ME-401 is a potential best-in-class drug, early identification of the ultimate formulation platform is important to streamline clinical development and commercialization.

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 Pharmaceutics® 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[1].
- 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 ≥ 60 mg is expected to afford trough plasma levels that lie on the plateau of the effectiveness/dose-response curve[1]
- 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%)
$AUC_{(0\text{-}last)}$ (ng*h/mL)	18.2 (70.5%)	77.3 (50.1%)	162 (32.6%)	299 (36.6%)	654 (61.8%)
$AUC_{(0\text{-}inf)}$ (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

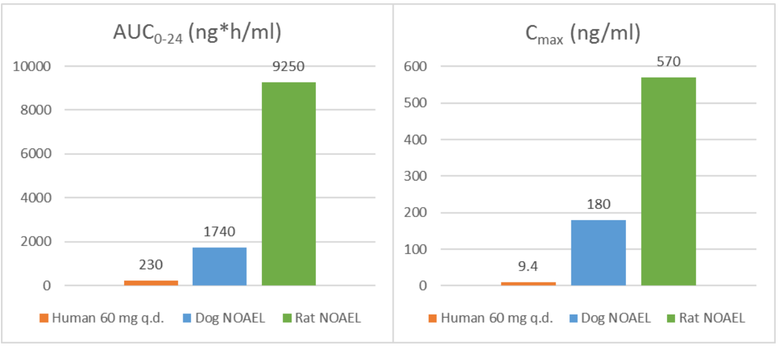
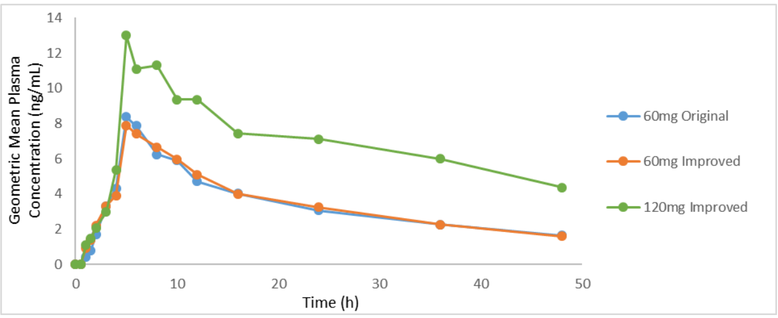


Figure 2. Plasma concentration time profile for the Original and Improved 60 mg capsule and 120 mg capsule formulation



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:
[1]Clinical Pharmacokinetics and Pharmacodynamics of ME-401, an Oral, Potent and Selective Inhibitor of Phosphatidylinositol 3-Kinase P110δ, 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.

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