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

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BACKGROUND

- Phosphatidylinositol 3 kinase (PI3K) is a lipid kinase having a catalytic subunit that exists in 4 different isoforms: α, β, γ, and δ
- In B lymphocytes, the δ isoform (PI3Kδ) plays a central role in normal B-cell development and function, transducing signals from the B-cell receptor as well as from receptors for various cytokines, chemokines, and integrins
- PI3Kδ signaling pathways are commonly hyperactive in B-cell malignancies
- PI3Kδ inhibition is important in the treatment of lymphoid malignancies by inhibiting growth and survival of lymphoid malignancies, particularly in response to chemokines[1]
- This approach has been validated by an approved therapy; however, the approved therapeutic has significant toxicity complications[2]
- This presents an opportunity for a drug with an improved therapeutic window
- ME-401 is a potent and selective inhibitor of PI3Kδ[3]
- Preclinical toxicology and safety pharmacology data supported initial clinical assessment of oral ME-401 in healthy volunteers

METHODS

Study Design

Study Objectives

- To assess the safety and tolerability of ME-401 after single ascending oral doses in healthy subjects
- To assess the pharmacokinetics (PK) of ME-401
- To assess the pharmacodynamics (PD) of ME-401

Study Population

- Healthy males, 18-65 years of age

Methodology

- Open label, single dose
- Enrolled 3 sequential groups: A (n=3), B (n=6), C (n=6)
- Dose levels of 10, 30, 60, 90, and 150 mg
- Blood samples collected to measure:
  - Plasma concentrations of ME-401 over a 48-hour period
  - Effect of treatment on a PD marker for PI3Kδ inhibition: basophil activation assessed via measurement of CD63 expression by flow cytometry, following *ex vivo* stimulation with an anti-FCεR1 monoclonal antibody
- The clinical study was conducted using the Translational Pharmaceutics® platform
  - Collected PK/PD data immediately after each dose
  - Real-time decision making and manufacturing between dose groups

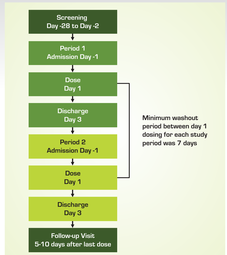
Assessment of CD63 as an Activation Marker

- The cell surface marker CD63 is a basophil activation marker directly linked to basophil degranulation[4]
- Inhibition of PI3Kδ is reported to inhibit FcεR1 signaling in peripheral blood basophils, measured by reduction in CD63 expression after stimulation by anti-FcεR1 antibody
- Effect of ME-401 treatment was assessed using the Flow CAST® Basophil Activation Test, which measures CD63 expression after *ex vivo* stimulation of basophils with anti-FCεR1 antibody
- Basophil activation was defined as the difference between [% positive cells after stimulation with anti-FcεR1 antibody] and [% positive cells without stimulation], from a given blood sample

Inhibition (%) = 100 x (1 – basophil activation post-dose/basophil activation pre-dose)

Study Sequence

- Subjects were:
  - Screened for eligibility between day -28 and day -2
  - Admitted to the clinical unit before dose administration (day -1) for both periods 1 and 2
  - Single daily doses were administered on day 1 in periods 1 and 2, and subjects were discharged after completion of study procedures (day 3)
- Follow-up was conducted 5 to 10 days after last dose administered
- Safety parameters evaluated included adverse events, vital signs, electrocardiogram, and physical examination findings



RESULTS

- A total of 15 volunteers were enrolled
- All planned dose levels were completed
- 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

Pharmacokinetic Analysis

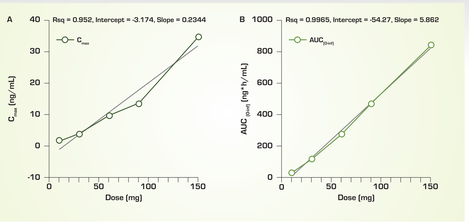
- The mean PK parameters for subjects receiving each of the tested doses are included in Table 1
  - ME-401 demonstrated linear pharmacokinetics over the dose range evaluated (Figure 1)
  - A shorter half-life was observed in subjects administered the 10 mg single dose in Group A. This is likely due to plasma levels that were below the limit of quantification (BQL) and were obtained from the terminal time points utilized in the half-life estimation

Table 1. Geometric Mean (Geometric CV%) PK Parameters for All Groups and Doses Tested

PK Parameter	10 mg (n=3)	30 mg (n=3)	60 mg (n=6)	90 mg (n=6)	150 mg (n=6)
T_{max}[a] 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%)
$AUC_{0-tlast}$, 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	9.352 (138.8%)	29.229 (38.1%)	27.775 (36.2%)	27.560 (46.6%)	28.034 (31.1%)

AUC: area under the concentration-time curve; C_{max}: maximum plasma concentration; $T_{1/2}$: plasma half-life; T_{max}: time to maximum plasma concentration.
[a]Median [range].

Figure 1. PK Parameters as a Function of Dose: a) C_{max} and b) $AUC_{(0\text{-}Inf)}$



Pharmacodynamic Analysis

- Pre-dose samples were used as negative controls for each post-dose time point to obtain percent inhibition of basophil stimulation
- Following single oral doses of ME-401, inhibition of basophil activation was observed for all dose levels with the exception of the 10 mg dose at 0.5 hours post-dose. Inhibition approaching 90% was achieved at the 60 mg dose level at 4 and 6 hours post-dose (Table 2)
- Figure 2 depicts inhibition of basophil activation as a function of drug plasma concentration across all samples. Based on the E_{max} model that was fitted to the data, the 90% effective concentration (EC_{90}) was determined to be 5 ng/mL (9 nM)

Figure 2. % Inhibition of Basophil Activation as a Function of ME-401 Plasma Concentration

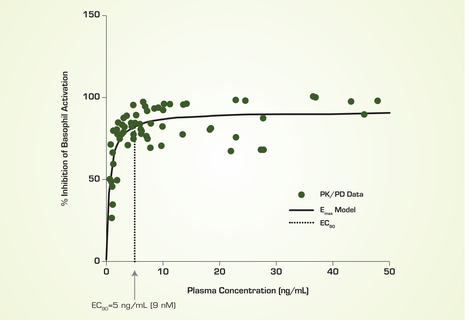


Table 2. Percent Inhibition of Basophil Activation as a Function of Time and Dose: Pharmacodynamic Population

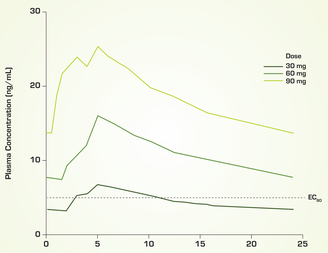
Dose Level[a]	Time Point	Mean Percent Inhibition (SD)	Range
10 mg (n=3)	Pre-dose	0 (0)	0
	0.5 h post-dose[b]	0.41 (2.55)	-2.45-2.44
	1.5 h post-dose	13.58 (3.68)	9.98-17.33
	4 h post-dose	45.12 (16.82)	26.65-59.56
30 mg (n=3)	Pre-dose	0 (0)	0
	1.5 h post-dose	51.46 (34.13)	12.35-75.12
	4 h post-dose	69.32 (20.15)	46.14-82.68
	6 h post-dose	68.68 (17.50)	49.91-84.55
60 mg (n=6)	Pre-dose	0 (0)	0
	1.5 h post-dose	46.63 (33.31)	11.45-89.33
	4 h post-dose	87.17 (7.93)	77.11-97.49
	6 h post-dose	89.97 (7.17)	78.04-96.13
150 mg (n=6)	Pre-dose	0 (0)	0
	1.5 h post-dose	84.79 (n=5) (14.19)	67.49-100.45
	4 h post-dose	86.74 (n=5) (12.46)	68.25-98.75
	6 h post-dose	86.56 (n=5) (14.05)	68.31-100.69

SD: standard deviation
Values are presented to 2 decimal places.
[a]Samples from patients receiving the 90 mg dose were compromised during shipment for analysis and therefore the data are not included in this analysis.
[b]This timepoint was eliminated and replaced with a 6-hour evaluation for all future dosing.

Extrapolation of PK to Daily Dosing

- Data from the phase 1 PK analysis were modeled using non-parametric superposition (Figure 3) to predict the steady-state PK estimates following dosing of the intended therapeutic regimen of daily oral dosing
- The modeling and simulation predicted that daily dosing of 60 mg would maintain plasma levels above the established EC_{90}

Figure 3. Simulated Steady-State Plasma Concentration-Time Profiles for ME-401 Following Daily Oral Administration of 30, 60, and 90 mg Capsules



Simulation of 60 mg Dosed Daily to Larger Population

- PK models were fitted to the individual data observed from the 60 mg dose level (Group B, phase 1 study). 1-, 2-, and 3-compartment models were tested and all underestimated maximal plasma concentrations. The 1-compartment PK model, however, fitted the terminal phase well enough to estimate trough levels from daily dosing
- The 1-compartment PK model was used to generate steady-state trough plasma concentrations (C_{trough}) from daily dosing of a simulated population of 250 individuals. Based on the simulated data the median, mean, geometric mean, and lower end of the 95% confidence interval were all above the EC_{90} (Table 3)

Table 3. Simulated Trough Concentrations of ME-401 (ng/mL) Following a Single 60 mg Oral Dose (Day 7)

Parameter	Day 1 C_{trough}	Day 7 C_{trough}
N	250	250
Mean	3.635	6.534
Standard deviation	0.967	2.542
Median	3.58	6.32
Geometric mean	3.498	6.016
CV% geometric mean	29.41	45.13
CI 95% lower geometric mean	3.38	5.7
CI 95% upper geometric mean	3.63	6.35

CI: confidence interval; C_{trough}: steady-state trough plasma concentration; CV: coefficient of variation

CONCLUSIONS

- ME-401 is an orally bioavailable molecule that exhibits a linear increase in exposure, over the tested 10-150 mg dose range
- The half-life supports once-daily dosing
- ME-401 is well tolerated when administered to healthy volunteers as a single oral dose up to 150 mg
- Daily dosing of ME-401 ≥60 mg is expected to afford trough plasma levels that lie above the EC_{90}, on the plateau of the effectiveness/dose-response curve

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

- ME-401 is expected to enter a phase 1b study for the treatment of B-cell malignancies in the first half of 2016, with a starting dose of 60 mg. The 60 mg dose was chosen based on PK/PD measurements and models, which demonstrate trough plasma values above the EC_{90}
  - Preclinical toxicology data support a maximum recommended starting dose of 150 mg per day in cancer patient trials
- The trial will include patients with relapsed/refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, or follicular lymphoma
- The trial is anticipated to include 42-84 patients at approximately 10 sites

References

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http://goo.gl/sSzjx7

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