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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METHODS

Purpose

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

Study Design

3 sequential groups (A n=3, B n=6 and C n=6).

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 via ex-vivo stimulation with an anti-FCεR1 monoclonal antibody.

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

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

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)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>10 mg (n=3)</th>
<th>30 mg (n=3)</th>
<th>60 mg (n=6)</th>
<th>90 mg (n=6)</th>
<th>150 mg (n=6)</th>
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<tbody>
<tr>
<td>T_max (h)</td>
<td>5.0 (5.0–6.0)</td>
<td>5.0 (5.0–6.0)</td>
<td>5.0 (5.0–6.0)</td>
<td>5.0 (3.0–6.0)</td>
<td>5.0 (3.0–6.0)</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>1.67 (86.8%)</td>
<td>3.89 (80.5%)</td>
<td>9.39 (32.2%)</td>
<td>13.6 (44.1%)</td>
<td>34.8 (55.2%)</td>
</tr>
<tr>
<td>AUC0-24h (ng*h/mL)</td>
<td>18.2 (70.6%)</td>
<td>77.3 (50.1%)</td>
<td>162 (32.6%)</td>
<td>299 (41.6%)</td>
<td>654 (61.8%)</td>
</tr>
<tr>
<td>AUC0-24h (ng*h/mL)</td>
<td>24.9 (106.8%)</td>
<td>117 (44.7%)</td>
<td>234 (21.6%)</td>
<td>466 (47.7%)</td>
<td>939 (62.2%)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>9.38 (138.8%)</td>
<td>29.29 (38.1%)</td>
<td>27.75 (36.2%)</td>
<td>27.86 (46.6%)</td>
<td>28.09 (31.1%)</td>
</tr>
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AUC: area under the concentration curve; Cmax: maximum plasma concentration; PK: pharmacokinetics; T1/2: plasma half-life; T_max: time to maximum plasma concentration

• 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

CONCLUSIONS

Reference: