**BACKGROUND**

- ALKS 8700 is an anti-malarial agent of monomethyl fumarate (MMF) that undergoes hydrolysis through esterases to produce the active moieties, MMF.
- MMF is the active metabolite of dimethyl fumarate (DMF; Tecfidera®) that is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). The DMF maintenance dose range was established at 7.2 mg/kg/day in two divided doses.
- ALKS 8700 420 mg and DMF 240 mg were equianalgesic to 215 mg of MMF.
- DMF demonstrated robust efficacy in Phase 3 clinical studies in patients with relapsing-remitting MS. Gastrointestinal (GI) adverse events were among the most commonly reported AEs and the reason for discontinuation in DMF-treated patients.4
- Additional adverse events in DMF included gastrointestinal side effects, such as nausea, abdominal pain, and diarrhea. GI adverse events were among the most common AEs reported following oral administration of MMF.

**OBJECTIVES**

- To evaluate the safety and tolerability of ALKS 8700 delayed-release (DR) formulation following a single oral administration in healthy subjects.
- To determine the pharmacokinetics (PK) of ALKS 8700 following a single dose of a DR formulation.
- To compare the PK of ALKS 8700 DR to the currently marketed DMF drug.

**METHODS**

**Study Design**

- This was a Phase 1, single-center study conducted in 3 parts.

**RESULTS**

**Part 1**

- In Part 1, 8 subjects were randomized to each cohort in a 3:1 ratio to receive ALKS 8700 240 mg or placebo.
- ALKS 8700 dose levels assessed were 49 mg, 105 mg, 210 mg, 420 mg, 630 mg, 840 mg, and 980 mg.
- Results from Part 1 were used to determine dose selection for Part 2.

**Part 2**

- In Part 2, 16 subjects were randomized in a 3:2:2 ratio to receive ALKS 8700 240 mg or placebo.
- Sequences were run in parallel with a wash-out period of 7 days in between sequences.
- DMF 240 mg was administered orally as a single DR 240 mg capsule.
- Part 3 was designed to evaluate the relative bioavailability of extended-release formulations of ALKS 8700 (data not shown).

**Selection of Subjects**

- **Inclusion Criteria**
  - Healthy adults 18 to 55 years of age at screening.
  - Body mass index (BMI) between 18.0 and 32.0 kg/m² at screening.
  - Male or non-pregnant females.

**RESULTS**

**Part 3**

- Blood samples were collected at pre-dose and at specified time intervals over 24 hours post-dose. Data were presented for a 24-hour time period.
- ALKS 8700 DR was not detected in plasma as a result of being rapidly and prematurely converted to MMF by the body. The median elimination half-life of MMF in plasma ranged from 0.53 to 0.83 hours across the doses investigated.
- The median Tmax of MMF in plasma ranged from 2.25 to 3.5 hours.

**DISCUSSIONS**

**LIMITATIONS**

- This was a single dose study conducted in healthy volunteers, and requires further evaluation following repeated administration.
- This study did not include the recommended initial starting dose of DMF (120 mg).

**CONCLUSIONS**

- A dose proportionate increase in MMF exposure was observed following ALKS 8700 DR dose range investigated.
- ALKS 8700 DR 420 mg provided MMF plasma exposure comparable to DMF 240 mg, within the expected therapeutic range.
- Loss variability in MMF exposure was observed following ALKS 8700 DR administration compared to DMF.
- ALKS 8700 DR was generally well tolerated following single oral administration of doses up to 980 mg.
- Fewer GI AEs were observed with ALKS 8700 DR 420 mg compared to DMF 240 mg. This may be due to differences in the properties of the molecule and the drug product. Further studies are required following repeated administration of ALKS 8700 DR for the treatment of relapsing forms of MS.

**REFERENCES**