Safety, Tolerability, and Pharmacokinetics of ALKS 8700, a Novel Oral Therapy for Relapsing-Remitting Multiple Sclerosis, in Healthy Subjects

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BACKGROUND

- ALKS 8700 is an aminoethyl ester of monomethyl fumarate (MMF) that undergoes hydrolysis through esterases to produce the active moiety, 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 after 7 days is 240 mg twice a day, orally.[1]
- ALKS 8700 DR 420 mg and DMF 240 mg are equimolar to 215 mg of MMF.
- DMF demonstrated robust efficacy in Phase 3 clinical studies in patients with relapsing-remitting MS. Gastrointestinal (GI) adverse events (AEs) were among the most commonly reported AEs and the reason for discontinuation in DMF-treated patients.[2,3]
- Additional studies of DMF have confirmed high rates of GI events, including nausea, abdominal pain and diarrhea.[4-5] In addition to adverse effects on tolerability, GI AEs may negatively affect adherence to DMF treatment.[5-7]
- ALKS 8700 is designed for the treatment of relapsing forms of MS with improved GI tolerability based on the chemical properties of the molecule and the drug product.

OBJECTIVES

- To evaluate the safety and tolerability of ALKS 8700 delayed-release (DR) formulation after 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

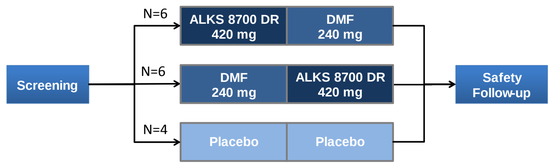
Study Design

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

Figure 1. Single-Ascending Dose of ALKS 8700 DR Study Design (Part 1)

- In Part 1, 8 subjects were randomized to each cohort in a 3:1 ratio to receive ALKS 8700 DR 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.

Figure 2. Relative Bioavailability of ALKS 8700 DR Study Design (Part 2)



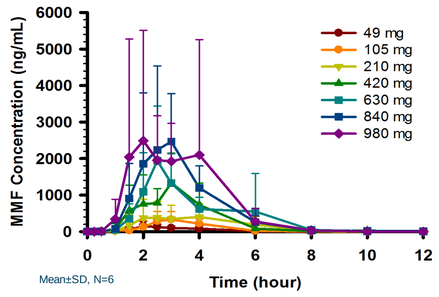
- In Part 2, 16 subjects were randomized in a 3:3:2 ratio to ALKS 8700 DR 420 mg, DMF 240 mg or placebo.
  - Sequences were run in parallel with a wash-out period of 7 days in between treatments.
  - DMF 240 mg was administered orally as a single DMF 240 mg capsule.
- Part 3 was designed to evaluate the relative bioavailability of extended-release formulations of ALKS 8700 (data not shown).

Selection of Subjects

- Key inclusion criteria
  - Healthy adults 18 to 55 years of age at screening.
  - Body mass index (BMI) between 18.0 and 32.0 kg/m^2 at screening.
- Key exclusion criteria
  - History of menopausal hot flashes, including hot flashes being controlled by treatment.
  - History of GI surgery or other chronic GI disorders.

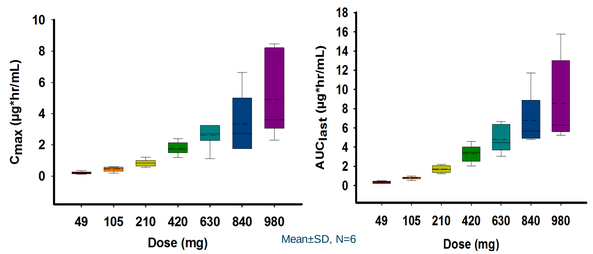
RESULTS

Figure 3. Concentrations of MMF in Plasma After Single Oral Dosing of ALKS 8700 DR (Part 1)



- Blood samples were collected at pre-dose and at specified time intervals over 24 hours post-dose. Data are presented for a 12-hour time period.
- ALKS 8700 DR was not detected in plasma as a result of being rapidly and presystemically converted to MMF.
- The median elimination half-life of MMF in plasma ranged from 0.63 to 0.83 hours across the doses investigated.
- The median T_{max} of MMF in plasma ranged from 2.25 to 3.5 hours.

Figure 4. Exposure of MMF in Plasma After Single Oral Dosing of ALKS 8700 DR (Part 1)



C_{max}: Maximum concentration; AUC_{last}: Area under the concentration-time curve from time zero to last quantifiable time interval; Boxes represent median, 25th and 75th percentiles, whiskers represent 10th and 90th percentiles.

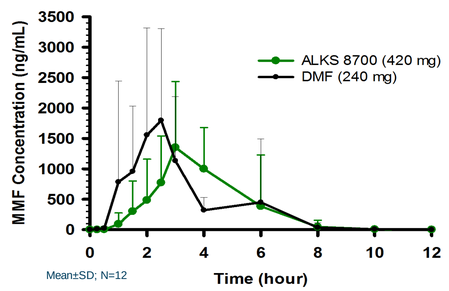
- MMF exposure increased with increasing ALKS 8700 DR dose.
- Based on the MMF exposure, the 420 mg dose was selected for further evaluation in Part 2.

Table 1. GI and Flushing AEs (Part 1)

	All	ALKS 8700 DR						
	Placebo (N=14)	49 mg (N=6)	105 mg (N=6)	210 mg (N=6)	420 mg (N=6)	630 mg (N=6)	840 mg (N=6)	980 mg (N=6)
Adverse Event	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Diarrhea	0	0	0	0	0	1 (16.7)	1 (16.7)	2 (33.3)
Flatulence	0	0	0	0	0	0	2 (33.3)	1 (16.7)
Abdominal discomfort	0	0	0	1 (16.7)	0	0	0	1 (16.7)
Nausea	0	0	0	0	0	0	0	2 (33.3)
Abdominal pain	0	0	0	0	0	0	0	1 (16.7)
Frequent bowel movements	0	1 (16.7)	0	0	0	0	0	0
Flushing	0	1 (16.7)	0	2 (33.3)	4 (66.7)	6 (100)	5 (83.3)	6 (100)

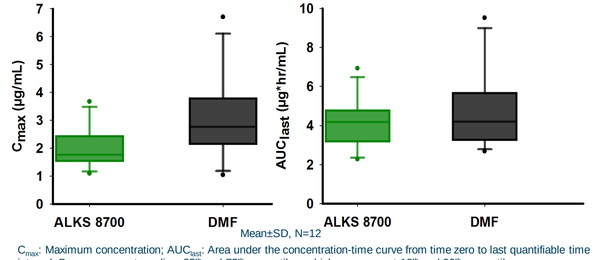
- No serious AEs or discontinuations due to AEs were reported. All AEs were mild or moderate.
- The most common AE was flushing (>50% of subjects experienced flushing at ALKS 8700 DR dose levels ≥420 mg).
- GI-related AEs were reported by >1 subject for the 2 highest ALKS 8700 DR dose levels.
- One event of orthostatic hypotension at the 840 mg dose level was reported and deemed mild by the investigator. No other clinically relevant findings were observed in the safety assessments.

Figure 5. Concentrations of MMF in Plasma After Oral Dosing of ALKS 8700 DR and DMF (Part 2)



- Blood samples were collected at pre-dose and at specified time intervals over 24 hours post-dose. Data are presented for a 12-hour time period.
- MMF C_{max} was 34% lower following ALKS 8700 DR administration as compared to DMF.
- Median lag-time (Tlag) for absorption was longer for ALKS 8700 DR compared to DMF.

Figure 6. Exposure of MMF in Plasma After Oral Dosing of 420 mg ALKS 8700 DR and 240 mg DMF (Part 2)



C_{max}: Maximum concentration; AUC_{last}: Area under the concentration-time curve from time zero to last quantifiable time interval; Boxes represent median, 25th and 75th percentiles, whiskers represent 10th and 90th percentiles.

- Total exposure of MMF (AUC) in plasma was comparable between the 2 treatments.
- The variability of MMF exposure was lower following ALKS 8700 DR administration compared to DMF (%CV of 36.5% vs. 48.9% for C_{max} and 30.8% vs 42.1% for AUC_{last}).

Table 2. GI and Flushing AEs (Part 2)

Adverse Event	Placebo (N=4) N (%)	DMF 240 mg* (N=12) N (%)	ALKS 8700 DR 420 mg (N=12) N (%)
Constipation	0	0	1 (8.3)
Diarrhea	0	1 (8.3)	0
Eructation	0	1 (8.3)	0
Flatulence	0	1 (8.3)	0
Nausea	0	3 (25.0)	0
Retching	0	1 (8.3)	0
Flushing	0	8 (66.7)	8 (66.7)

*A total of 7 GI-related AEs were reported by 5 subjects in the DMF group.

- No serious AEs or discontinuations due to AEs were reported. All AEs were mild or moderate in severity.
- Flushing was the most common AE with equal rates reported in both active treatment groups (66.7% of subjects).
- GI AEs occurred in more subjects treated with DMF (41.7%) compared to ALKS 8700 DR (8.3%).
- No clinically relevant findings were observed in the safety assessments.

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).[1]

CONCLUSIONS

- A dose proportionate increase in MMF exposure was observed over the 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.
- Less 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 chemical properties and dissolution characteristics that result in lower C_{max} and later T_{max} of ALKS 8700 DR.
- These results support further clinical investigation of ALKS 8700 DR for the treatment of relapsing forms of MS.

DISCLOSURES

This study was funded by Alkermes, Inc.
Dr. Hunt does not have a financial relationship with Alkermes.
Drs. Durairaj, Leigh-Pemberton, Jiang, Hard and Ms. Manthis are employees of Alkermes.

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