EVOLVE-MS-2: Randomized, Double-Blind, Phase 3 Study of the Gastrointestinal Tolerability of ALKS 8700 Versus Dimethyl Fumarate in Relapsing-Remitting Multiple Sclerosis

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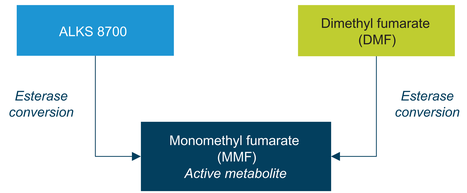
BACKGROUND

- Oral dimethyl fumarate (DMF) is approved for the treatment of relapsing forms of multiple sclerosis (MS)[1]
- In Phase 3 studies of DMF, gastrointestinal (GI) adverse events (AEs) have been among the most commonly reported AEs and were the leading cause of study discontinuation due to AEs[2–5]
  - In addition to the Phase 3 studies, subsequent DMF clinical studies using GI symptom questionnaires[6,7] as well as real-world registry studies[8] reported even higher rates of GI events and discontinuations due to GI events, perhaps reflective of real-world patient experience
  - GI events are an important concern for patients taking DMF and they can negatively impact treatment adherence, ultimately leading to treatment interruption or discontinuation
- ALKS 8700 is being developed as an oral disease-modifying treatment for relapsing forms of MS
- ALKS 8700 is a prodrug of monomethyl fumarate (MMF), which undergoes rapid pre-systemic conversion to MMF; MMF is the active metabolite of DMF (Figure 1).[9] ALKS 8700 has physicochemical properties that are distinct from DMF

Figure 1: Conversion of ALKS 8700 to Monomethyl Fumarate



- ALKS 8700 is designed to effectively treat relapsing forms of MS in a manner similar to DMF but with the potential for improved GI tolerability
- The incidence of GI AEs with ALKS 8700 was lower than with DMF in a Phase 1 crossover study in healthy subjects (N=12), indicating potentially improved GI tolerability[10]
  - Fewer subjects reported GI AEs with ALKS 8700 420 mg (8.3%) compared to DMF 240 mg (administered as commercially available Tecfidera®, Biogen Inc, Cambridge, MA) (41.7%)
- Further phase 1 evaluation determined that ALKS 8700 462 mg yields comparable MMF exposure to the maintenance dose of DMF (240 mg)[11]
- This 5-week, head-to-head, Phase 3 study (EVOLVE-MS-2) is evaluating the safety and tolerability of ALKS 8700 (462 mg twice daily) and DMF (240 mg twice daily) in patients with relapsing-remitting MS (RRMS)

METHODS

Study Design

- The Phase 3, multicenter, double-blind, active-controlled, 5-week EVOLVE-MS-2 study is designed to evaluate the GI tolerability of ALKS 8700 462 mg twice daily compared with DMF 240 mg twice daily in approximately 420 patients with RRMS (Figure 2; Table 1)
  - The study includes a 4-week screening period (including a 1-week lead-in period) followed by a 5-week double-blind treatment period with 2 blinded treatment groups
  - Patients will be randomly assigned in a 1:1 ratio to ALKS 8700 or DMF
  - Both treatment groups will include an initial 1-week dose titration period
- Registered at clinicaltrials.gov: NCT03093324
- Key GI symptoms of nausea, vomiting, upper and lower abdominal pain and diarrhea will be assessed using 2 patient-reported symptom-rating scales administered via daily electronic diaries: the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) and the Global Gastrointestinal Symptom and Impact Scale (GGISIS)

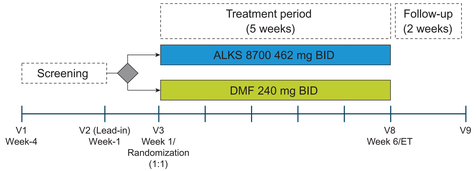
IGISIS

- The IGISIS is designed to assess the incidence, intensity, onset, duration, and functional impact of the 5 individual key GI symptoms by:
  - Asking patients to rate the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme)
  - Asking patients to indicate the start and stop times of each GI symptom
  - Asking patients how much each symptom has interfered with their ability to accomplish regular daily activity using a 5-point Likert scale

GGISIS

- The GGISIS is a global scale that assesses the overall intensity, bothersomeness, and functional impact of GI symptoms experienced by patients over the previous 24 hours while taking study drug
  - On a scale from 0 (did not have) to 10 (extreme), patients are asked to rate how intense and bothersome their GI symptoms have been in general over the past 24 hours
  - Patients are also asked questions relating to the effect of their GI symptoms on daily activities, work, and productivity
- Patients will complete both GI scales using electronic diaries daily for 7 days prior to randomization (lead-in period) to facilitate familiarity with the scales as well as to evaluate baseline GI symptomatology
- Patients completing this study will be eligible to participate in an ongoing, open-label, long-term safety study (EVOLVE-MS-1, ClinicalTrials.gov: NCT02634307)

Figure 2: Study Design



Patients completing the 5-week treatment period will either continue into the EVOLVE-MS-1 long-term safety study or enter the safety follow-up period and return for Visit 9.

BID, twice daily; DMF, dimethyl fumarate; ET, early termination; V, visit.

Study Objectives

- Compare the GI tolerability of ALKS 8700 and DMF in adult patients with RRMS using the IGISIS and GGISIS symptom scales
  - The planned primary endpoint is the number of days with IGISIS individual symptom scores relative to exposure days
  - The planned secondary endpoints are:
    - Area under the curve for the total IGISIS symptom intensity score relative to exposure days
    - Number of days with GGISIS symptom scores relative to exposure days
- Evaluate the safety and tolerability of ALKS 8700 in adult patients with RRMS

Eligibility Criteria

Main Inclusion Criteria	Main Exclusion Criteria
• Patients aged 18–65 years • Confirmed diagnosis of RRMS according to the 2010 revised McDonald criteria • Baseline Expanded Disability Status Scale (EDSS) score of 0.0-6.0 at screening and randomization • Neurologically stable with no evidence of relapse within 30 days prior to randomization	• Diagnosis of primary progressive, secondary progressive or progressive relapsing MS • Prior treatment with DMF • History of GI surgery (except appendectomy that occurred >6 months prior to screening) • History of clinically significant recurring or active GI symptoms within 3 months of screening • Chronic use (≥7 days) of medical therapy to treat GI symptoms within 1 month of screening • Lymphocyte count <0.9 x 10^3/μL

Study Treatment

- In the ALKS 8700 treatment group, study drug includes ALKS 8700 231 mg administered as 1 capsule consisting of enteric-coated, delayed-release minitablets
  - Patients will receive ALKS 8700 231 mg BID for the first week on treatment followed by 462 mg (two 231-mg capsules) BID from Day 8 onwards
- In the DMF treatment group, study drug includes commercially available DMF (Tecfidera®) administered as either one 120-mg capsule or one 240-mg capsule[1]
  - The DMF capsule is over-encapsulated to create a blinded study drug
  - Patients will receive DMF 120 mg (one 120-mg capsule) BID for the first week on treatment and 240 mg (one 240-mg capsule) BID from Day 8 onwards
- Placebo capsules will be administered to keep the number of capsules at each administration consistent between treatment groups

Table 1. Study Assessments

Safety and tolerability
Individual Gastrointestinal Symptom and Impact Scale (IGISIS)[a] Global Gastrointestinal Symptom and Impact Scale (GGISIS)[b]
Adverse events
Vital signs (temperature, respiratory rate, heart rate, and blood pressure)
Electrocardiogram (ECG) parameters
Columbia Suicide Severity Rating Scale (C-SSRS)
Clinical laboratory parameters
Clinical assessments[c]
Proportion experiencing MS relapse
Progression of disability on the Kurtzke EDSS
Timed 25-Foot Walk (T25-FW)
Quality of life[c]
EuroQoL Group health outcome measure (5 level; EQ-5D-5L)
12-item Short Form Health Survey (SF-12)
Pharmacokinetics[d]

[a]Administered twice daily and completed within 9 hours after taking each dose of study drug.
[b]Administered once daily each morning prior to taking the morning dose of study drug.
[c]Assessments will serve as pre-treatment baseline values for those patients rolling over into the ongoing safety study (EVOLVE-MS-1).
[d]Pharmacokinetic samples will be obtained in a subset of patients.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

RESULTS

- Enrollment of 420 patients is planned at multiple sites in the United States
- Patient enrollment began in March 2017 and is ongoing across the United States
  - This study is currently recruiting patients from 17 sites across 9 states (Alabama, California, Colorado, Florida, Kansas, New York, North Carolina, Tennessee, and Texas)

SUMMARY

- ALKS 8700 is a novel compound with distinct physicochemical properties that rapidly converts pre-systemically to MMF, the same active metabolite of DMF
- GI tolerability issues with DMF can negatively affect patient experience and adherence
- ALKS 8700 is designed to effectively treat relapsing forms of MS similar to DMF but with the potential for improved GI tolerability
- Results from this randomized, double-blind study will provide important information regarding the GI tolerability of ALKS 8700 compared with DMF in patients with RRMS

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DISCLOSURES

RN has consulted for Acorda, Alkermes, Bayer, Biogen, EMD Serono, Genentech, Genzyme, Mallinckrodt, Novartis, and Pfizer and was on the speakers' bureaus for Acorda, Biogen, and Genzyme.
AC, RP, YD, MH, and LVM are employees and stockholders in Alkermes, Inc.
JW has received compensation for serving as consultant or speaker from AbbVie, Actelion, Alkermes, EMD Serono, Forward Pharma, Genentech, Genzyme, Novartis, Roche, Sanofi, Takeda, Teva, and XenoPort, and has received royalties for monoclonal antibodies out-licensed to Chemicon International via The University of Texas Health Science Center at Houston.
AL has consulted for Alkermes, Ardelyx, Salix, Prometheus, Allergen, Valeant, and Ironwood.
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