**COVER PAGE**

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| **Official Title:** | An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis |
| **NCT number:** | NCT05083923 |
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| **Name of Sponsor/Company:** | Biogen MA Inc./Biogen Idec Research Limited |
| **Name of Finish Product:** | Diroximel Fumarate (BIIB098) |
| **Name of Active Ingredient:** | Diroximel Fumarate |
| **Study Indication:** | Relapsing Forms of Multiple Sclerosis (RMS) |

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# 2. STUDY SYNOPSIS

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**Title of Study:**

An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region with Relapsing Forms of Multiple Sclerosis.

**Principal Investigator/Coordinating Investigator:**

Not applicable

| **Study Period:** | **Phase of Development:** 3 |
|---|---|
| Date of first treatment: 09 December 2021<br>End of Study Date: 11 September 2024 | |

**Study Objectives:**

**Part 1**

Primary Objective:

To determine the safety and tolerability of diroximel fumarate (DRF) administered for up to 24 weeks in adult East Asian participants with RMS.

Of note, safety and tolerability results for Part 1 (i.e., up to Week 24) of the study were presented in an interim analysis. Cumulative results up to Week 48 for safety and tolerability are presented in this final clinical study report (CSR).

Secondary Objective:

To evaluate the pharmacokinetics (PK) of DRF metabolites (monomethyl fumarate [MMF] and 2-hydroxyethyl succinimide [HES]) following multiple doses of DRF in a subset of adult East Asian participants with RMS.

[redacted]

**Part 2**

Primary Objective:

To determine the safety and tolerability of DRF administered for up to 48 weeks in adult East Asian participants with RMS.

[redacted]

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**Study Design:**

This was an open-label, single-arm study to evaluate the safety, tolerability, and PK of DRF administered orally to East Asian participants with RMS. This study had 2 cohorts: 1 with Japanese participants and 1 with Chinese participants. This study was conducted in 2 parts: Part 1 evaluated the safety, tolerability, and PK from Week 1 to Week 24 and Part 2 was a safety extension period from Week 24 to Week 48.

An interim analysis of the Part 1 data was performed after all the participants in the Japanese cohort completed the first 24-week Treatment Period (i.e., completed the Week 24 visit or withdrew from the study before the Week 24 assessment). This interim analysis evaluated the primary and secondary endpoints [redacted] defined by Week 24. Results of the interim analysis were reported separately.

The final analysis was performed after all participants in the Japanese and Chinese cohorts completed the 48-week Treatment Period along with the 2-week Safety Follow-up Period (or withdrew from the study before the Week 48 assessment). If at least 1 participant entered the Lymphocyte Monitoring Period after the 2-week Safety Follow-up Period, the final analysis was to be performed upon having completed all required assessments for participants in the Lymphocyte Monitoring Period. The final analysis evaluated the primary, secondary, [redacted] endpoints defined by End of the Study. Note that, although PK data were collected and analyzed in Part 1 only, they are also presented in this final CSR. There was no change in PK data between the interim and the final analysis. [redacted] The Week 24 safety endpoints were analyzed only as part of the interim analysis (reported separately); this final CSR presents cumulative safety data up to Week 48 in the final dataset.

Forty-eight sites screened participants, and 43 sites (23 sites in China and 20 sites in Japan) dosed participants.

**Number of Participants (Planned and Analyzed):**

Planned:

Approximately 50 Japanese participants and 50 Chinese participants were planned to be enrolled.

Analyzed:

Overall, 102 participants received the study treatment: 52 participants in the Japanese cohort and 50 participants in the Chinese cohort.

**Study Population:**

Main Inclusion Criteria:

- RMS diagnosis as defined by revised 2017 McDonald's criteria
- Age between 18 and 65 years (both inclusive)
- Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0, inclusive, at Screening and Baseline Visit (Day 1)
- Neurologically stable with no evidence of multiple sclerosis (MS) relapse within 30 days prior to Baseline Visit (Day 1)

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- Participants born either in Japan or China and their biological parents and grandparents were of Japanese or Chinese origin, respectively

Main Exclusion Criteria:

- Participants with history of gastrointestinal (GI) surgery, clinically significant recurring or active GI symptoms, or any clinically significant conditions that could preclude participation in a clinical trial, as determined by the Investigator

**Study Treatment, Dose, Mode of Administration:**

DRF, a white to off-white powder, is formulated as enteric coated minitablets in hydroxypropyl methylcellulose capsules for oral administration. Each capsule consists of [redacted] minitablets and contains 231 mg DRF. A total of 9 lots of DRF were used as of Week 48.

DRF 231 mg was administered twice daily from Day 1 through Day 7, followed by 462 mg twice daily from Day 8 onwards. The study treatment was administered orally with a gap of at least 6 hours between the doses. Dose reduction was allowed for tolerability from Day 8 onwards.

**Duration of Treatment and Follow-Up:**

Study duration was up to 54 weeks:

- 4-week Screening Period
- 24-week Treatment Period in Part 1
- 24-week Treatment Period in Part 2
- 2-week Safety Follow-Up Period

During Part 1, the participants had up to 8 visits during the Treatment Period (i.e., Baseline Visit [Day 1], Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24) and were contacted via telephone twice.

During Part 2, the participants had a total of 7 study visits, every 4 weeks up to Week 48 during the Treatment Period. A Safety Follow-Up Visit occurred 2 weeks later (Week 50) after the end of the Treatment Period.

**Criteria for Evaluation:**

Following is a description of all safety, PK, [redacted] assessments that were originally planned for Part 1 of this study.

Safety:

*Clinical Safety Assessments*

The following clinical assessments were performed to evaluate the safety profile of DRF:

- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Medical history

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- Physical examinations
- Vital sign measurements
- Electrocardiograms (ECGs)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Concomitant therapy and procedures

*Laboratory Safety Assessments*

The following laboratory assessments were performed to evaluate the safety profile of DRF by determining clinical laboratory abnormalities:

- Hematology
- Blood chemistry
- Urinalysis

Pharmacokinetics:

- Plasma concentrations of MMF and HES
- Noncompartmental plasma PK parameters of MMF and HES, including the following:
  - maximum observed concentration ($C_{max}$)
  - area under the concentration-time curve from time 0 to time of the last measurable concentration ($AUC_{last}$)
  - time to reach maximum observed concentration ($T_{max}$)
  - terminal elimination half-life (MMF only)

[redacted]

**Statistical Methods:**

Planned Analyses:

Analysis populations were defined as follows:

- [redacted]
- Safety Analysis Set (SAS): All participants who received at least 1 dose of study treatment.
- PK Analysis Set: All participants who received at least 1 dose of study treatment and had at least 1 postdose plasma concentration for MMF and HES.

Demographics and Baseline Disease Characteristics:

Participant demographic data, including age, age categories in years (e.g., ≤ 40, > 40), gender, race, ethnicity, height, weight, weight categories in kilograms (e.g., ≤ 40, > 40), and body mass index (BMI), are summarized descriptively by cohort and overall in the SAS.

The following baseline disease characteristics are summarized using descriptive summary statistics by cohort and overall for the SAS: [redacted]

Medical history is summarized using system organ class (SOC) and preferred term (PT) by cohort and overall in the SAS.

Demographics, baseline disease characteristics, and medical history data are presented in listings.

Pharmacokinetics:

The PK Analysis Set with intensive blood sample collection consisted of a subset of 7 participants in the Japanese cohort. The PK Analysis Set with sparse blood sample collection consisted of 49 Japanese participants and 48 Chinese participants.

Blood samples for PK analysis of metabolites MMF and HES were collected at the following timepoints on any day (from Day 29 to Day 169) for intensive blood samples and on Day 29 and Day 57 for sparse blood samples:

- Intensive blood sample collection on any day (from Day 29 to Day 169): predose (within 30 min), 0.5 (± 5 min), 1 (± 5 min), 2 (± 15 min), 3 (± 15 min), 4 (± 15 min), 6 (± 15 min), and 8 (± 15 min) hours postdose. Intensive PK samples were collected in a subset of the PK population (N = 7 of the 49 Japanese participants). Data are presented with data from the non-Asian population (N = 45) with intensive PK concentrations at nominal Day 29 from Study ALK8700-A301 as a comparison.
- Sparse blood sample collection on Day 29 and Day 57: predose and 2 to 3 hours postdose, in participants who did not have intensive PK collected and in participants in both the Intensive and Sparse PK Analysis Sets (excluding the intensive PK sampling day for applicable participants). Data are presented for both cohorts (N = 49 Japanese participants, N = 48 Chinese participants), with data from the non-Asian population (N = 45) with sparse PK concentrations at nominal Day 15 from Study ALK8700-A301 as a comparison.

In addition, a previous joint population PK model for MMF and HES using data from 11 global clinical studies was modified and updated with data from the present study and the ethnic bridging study 272HV111 in [redacted] healthy volunteers to further characterize the PK of MMF and HES.

MMF and HES plasma concentrations were analyzed using the PK Analysis Set. The plasma concentrations are presented separately for intensive and sparse subsets of data. The plasma concentrations for sparse subsets of data are summarized using population PK analysis and are presented by cohort. Additionally, the descriptive summary statistics and box plots were constructed to descriptively compare MMF (postdose) and HES (predose and postdose) plasma concentrations between Japanese and Chinese participants of this study and all participants with sparse PK concentrations from Study ALK8700-A301.

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The descriptive summary statistics are provided by nominal sampling times of PK Study Day. Plots of individual concentrations over actual sampling time and mean concentrations (with standard deviation [SD]/standard error [SE] as error bars) over nominal sampling time are presented on both a linear and a semilogarithmic scale for the intensive subset of participants only. In addition, geometric mean concentrations (with 95% confidence interval [CI] as error bars) over nominal sampling time are presented on both a linear and a semilogarithmic scale for the intensive subset of participants only.

Lower limit of quantitation for plasma concentration of MMF and HES was 25 ng/mL and 50 ng/mL, respectively.

PK parameters and/or timepoints with PK concentrations excluded from the PK analysis and summary statistics are flagged and presented in listings.

MMF and HES plasma concentrations for all study participants are listed.

[redacted]

[redacted]

Safety:

All AEs, medical history, and nondrug therapy were coded with the Medical Dictionary for Regulatory Activities using version 27.0. Concomitant medications were coded using the WHO-DD based on the March 2024 version.

An overview table and incidences of the treatment-emergent AEs (TEAEs) including deaths, SAEs, AEs of special interest (AESIs), events leading to drug dose reductions or interruptions, and events leading to withdrawal from the study and discontinuation from the study treatment are summarized for each cohort and overall.

Incidence of TEAEs is summarized by SOC, PT, maximum severity, and relatedness, as appropriate. All AEs are included in the participant-level listings.

Descriptive summary statistics for actual values, change from baseline, and percent change from baseline are provided for all quantitative laboratory parameters and are presented by cohort and overall.

Mean plots with the corresponding SE for selected hematology and chemistry laboratory parameters are presented for each cohort overlaid on the same plot.

Shift tables are presented for hematology, blood chemistry, and urinalysis data. The number and percentage of participants with shifts from baseline to high, low, or abnormal status are presented by cohort. In addition, the number and percentage of participants with values considered potentially clinically significant (PCS) occurring at any postbaseline visit for selected parameters are summarized using criteria prespecified in the statistical analysis plan (SAP).

All abnormal data for laboratory tests, vital signs, and ECGs are included in the participant-level listings, along with a listing of participants who required additional lymphocyte count monitoring visits.

For vital sign and physical examination assessments, abnormal new or worsening findings that occurred during or after administration of study treatment and were deemed by the Investigator as clinically significant are reported as AEs and included in the AE analysis. Findings that occurred prior to administration of the study treatment are reported under medical history and included in the medical history analysis.

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Participants meeting one of the C-SSRS criteria at postbaseline are included in the listings, and incidences meeting criteria for suicidal behavior, suicidal ideation, and nonsuicidal self-injurious behavior are summarized by each cohort and overall using criteria prespecified in the SAP.

Sample Size Calculations:

A sample size of approximately 50 participants per cohort was based on feasibility considerations and was deemed sufficient to characterize the safety and tolerability profile of the study treatment.

Based on the observed DRF PK parameters in fasted participants from Study ALK8700-A103, the coefficient of variation of $AUC_{last}$ was estimated to be 30.9; therefore, a sample size of 7 Japanese participants would be needed to evaluate the MMF PK parameters with sufficient precision, which was defined as an evaluation of the PK parameters of MMF with at least 80% power to achieve a 95% CI within 60% to 140% of the geometric mean. Since the variability of HES parameters is significantly lower, the data from 7 participants was expected to provide a robust assessment of $AUC_{last}$ and $C_{max}$ of HES in Japanese MS participants.

**Results:**

**Participant Accountability:**

A total of 136 participants were enrolled, and 102 participants (52 participants in the Japanese cohort and 50 participants in the Chinese cohort) received at least 1 dose of study treatment and were included in the SAS.

[redacted]

There were 97 participants (95.1%; 49 participants [94.2%] in the Japanese cohort and 48 participants [96.0%] in the Chinese cohort) who had at least 1 postdose plasma concentration for MMF and HES and who were included in the PK Analysis Set.

Overall, 85 participants (46 participants [88.5%] in the Japanese cohort and 39 participants [78.0%] in the Chinese cohort) completed the study treatment. There were 17 participants (16.7%) who discontinued study treatment. The most common reasons for discontinuation of study treatment were withdrawal by participant (7 participants [6.9%]), lack of efficacy (5 participants [4.9%]), and AE and other (2 participants [2.0%] each).

Overall, 87 participants (85.3%; 47 participants [90.4%] in the Japanese cohort and 40 participants [80.0%] in the Chinese cohort) completed the Week 48 Visit. There were 15 participants (14.7%) who withdrew from the study. The most common reasons for study withdrawal were withdrawal by participant (8 participants [7.8%]), lack of efficacy (4 participants [3.9%]), and AE (2 participants [2.0%]). No participants discontinued study treatment or withdrew from the study due to coronavirus disease 2019 (COVID-19).

**Demographics and Baseline Disease Characteristics:**

The majority of participants were female (82 participants [80.4%]). Overall, the mean (SD) age was 37.9 (10.23) years, with 67 participants (65.7%) ≤ 40 years of age and 35 participants (34.3%) > 40 years of age. The mean (SD) weight was 60.28 (11.467) kg, and all the participants weighed > 40 kg with mean (SD) BMI of 23.057 (3.8505) $kg/m^2$.

**Baseline Disease Characteristics**

[redacted]

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Mean (SD) time since the onset of MS symptoms for all participants was 7.79 (6.920) years, and the mean (SD) time since MS diagnosis was 5.8 (5.77) years. [redacted] A total of 51 participants (50.0%) did not use prior DMTs, 35 participants (34.3%) used 1 DMT, 11 participants (10.8%) used 2 DMTs, and 5 participants (4.9%) used ≥ 3 DMTs.

[redacted]

**Baseline Medical History**

A total of 95 participants (93.1%) had a medical history of at least 1 other medical condition in addition to MS, of whom 34 participants (33.3%) had a medical history of nervous system disorders.

**Prior and Concomitant Treatments**

A total of 51 participants (50.0%) reported at least 1 prior DMT at Baseline. Overall, the most commonly (> 10% of participants) reported prior DMTs were DMF (27 participants [26.5%]) and interferon beta-1a (12 participants [11.8%]).

A total of 91 participants (89.2%) reported at least 1 concomitant medication during the study. A total of 41 participants (40.2%) received concomitant nondrug therapy during the study, of which 28 participants (27.5%) underwent investigational procedures and 22 participants (21.6%) had surgical and medical procedures.

**Protocol Deviations**

Overall, major protocol deviations were reported in 26 participants (25.5%) in the SAS during the study. The most commonly (> 3% of participants) reported major deviations were related to administration of study treatment and visit schedule (8 participants [7.8%] each), concomitant medication (5 participants [4.9%]), and safety and participant study treatment compliance (4 participants [3.9%] each). None of these deviations affected the safety of the participants, nor were they considered to have a significant impact on the study results or the overall analysis of the data.

**Exposure and Compliance**

Over all participants (n = 102), the mean (SD) duration of exposure to study treatment was 303.5 (85.11) days (approximately 43 weeks). Overall, 62 participants (60.8%) had ≥ 48 weeks (≥ 12 months) of exposure to study treatment, where one month was defined as 28 days.

Overall, the mean (SD) study treatment compliance rate was 98.25% (6.827), with most participants having treatment compliance rates ranging from ≥ 70% (102 participants [100%]) to ≥ 90% (94 participants [92.2%]).

**Pharmacokinetics:**

Plasma concentrations of MMF and HES were comparable between Japanese participants (this study) and non-Asian participants (Study ALK8700-A301). Similarly, plasma concentrations of MMF and HES in Chinese participants were in line with those in non-Asian participants. [redacted] The PK results from this study were generally consistent with those of previous DRF studies.

[redacted]

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[redacted]

**Safety:**

Ninety-nine participants (97.1%) experienced at least 1 AE. Fifty-one participants (50.0% of SAS) had AEs that were considered mild, 39 participants (38.2%) had moderate AEs, and 9 participants (8.8%) had severe AEs. Seventy-two participants (70.6%) experienced AEs that were considered study treatment related, and 2 participants (2.0%) had AEs that led to discontinuation of study treatment and withdrawal from the study.

The most common SOCs (> 20% of participants) were Infections and infestations (61 participants [59.8%]), Gastrointestinal disorders (51 participants [50.0%]), Investigations (35 participants [34.3%]), Nervous system disorders (33 participants [32.4%]), Vascular disorders (32 participants [31.4%]), and Skin and subcutaneous tissue disorders (25 participants [24.5%]).

By PT, the most common AEs (> 10% of participants) were flushing (26 participants [25.5%]), upper respiratory tract infection (24 participants [23.5%]), diarrhoea (23 participants [22.5%]), COVID-19 (14 participants [13.7%]), nasopharyngitis (13 participants [12.7%]), multiple sclerosis relapse and pyrexia (12 participants [11.8%] each), and alanine aminotransferase increased, lymphocyte count decreased, and headache (11 participants [10.8%] each).

Twelve participants (11.8%) experienced SAEs, of whom 8 participants (7.8%) experienced SAEs that were neurological in nature: multiple sclerosis relapse or relapsing-remitting multiple sclerosis and demyelination. These 12 participants experienced 16 SAEs, of which 14 were treatment emergent. Eight of the treatment-emergent SAEs (fall, humerus fracture, foot deformity, staphylococcal bacteraemia, multiple sclerosis relapse, iron deficiency anaemia, demyelination, and relapsing-remitting multiple sclerosis) were considered severe by the Investigator, and 1 SAE (iron deficiency anaemia) was considered related to study treatment. None of the SAEs led to discontinuation of study treatment or withdrawal from the study. One treatment-emergent SAE (iron deficiency anemia [not resolved]) led to temporary dose interruptions. None of the SAEs led to dose reductions.

Overall, 9 participants (8.8%) experienced treatment-emergent AESIs in the category of cardiac disorders, including 1 participant (1.0%) reporting an AESI of dizziness that led to discontinuation of study treatment and

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withdrawal from the study. Thirty-eight participants (37.3%) experienced AESIs in the category of flushing and related events. One participant (1.0%) experienced a severe AESI of staphylococcal bacteraemia in the category of infections and the category of serious and opportunistic infections. No AESIs of malignancies were reported.

There were no GI AEs that were severe or serious or that led to study treatment discontinuation. The most common GI-related AE was diarrhoea in 23 participants (22.5%).

The most common shift from baseline to low in hematology was in the category of lymphocytes (50 participants [51.5%]). Among all 102 participants, a PCS decrease of lymphocyte count of $< 0.5 \times 10^9$/L, $< 0.8 \times 10^9$/L, and $< 0.91 \times 10^9$/L occurred in 6 participants (5.9%), 31 participants (30.4%), and 44 participants (43.1%), respectively. Additionally, 11 participants (10.8%) experienced AEs of lymphocyte count decreased, and 5 participants (4.9%) experienced AEs of lymphopenia.

The most common shifts from baseline to high in hematology were in the category of neutrophils/leukocytes (33 participants [33.7%]) and eosinophils/leukocytes (27 participants [31.0%]). Additionally, 7 participants (6.9%) had a PCS change in eosinophil count of $> 1.0 \times 10^9$/L, and 3 participants (2.9%) each experienced AEs of eosinophil count increased and eosinophilia.

The most common shift from baseline to low in blood chemistry parameters was creatinine (37 participants [38.9%]). The most common shift from baseline to high was ALT (38 participants [40.4%]).

The only shift from baseline to low in urinalysis parameters was creatinine (25 participants [25.3%]). The most common shift from baseline to high was albumin/creatinine (46 participants [56.1%]).

AEs related to vital signs included pyrexia in 12 participants (11.8%), and AEs related to ECG abnormalities included abnormal electrocardiogram T wave and supraventricular extrasystoles in 1 participant (1.0%) each. Two participants from the Chinese cohort exhibited suicidal ideation, and no suicidal behavior was observed.

**Conclusions:**

DRF was well tolerated in both cohorts. Twelve participants (11.8%) experienced SAEs, 9 participants (8.8%) experienced severe AEs, and 2 participants (2.0%) experienced AEs leading to study treatment discontinuation.

The most frequent AE overall was flushing (25.5%); there were no flushing or related events that were severe or serious or that led to study treatment discontinuation. The next most commonly reported AEs were upper respiratory tract infection (23.5%) and diarrhoea (22.5%).

With regard to GI events, while the incidence of diarrhea was higher in the Japanese cohort (36.5%) than in previous studies, the events were predominantly nonserious, mild, and self-limiting, and they did not lead to study treatment discontinuation. These observations align with the known safety profile of DRF and the classification of diarrhea as a very common adverse drug reaction.

Overall, the safety profile of DRF was generally consistent with the known safety profile of DRF and with previous DRF studies.

Plasma concentrations of MMF and HES were comparable between Japanese participants (this study) and non-Asian participants (Study ALK8700-A301). Similarly, plasma concentrations of MMF and HES in Chinese participants were in line with those in non-Asian participants. There were no major differences in the key PK parameters including $C_{max}$, $T_{max}$, and $AUC_{last}$ between Japanese and non-Asian participants. This suggests that the PK of MMF and HES in Japanese and Chinese participants are generally similar to those in non-Asian participants. The PK results from this study were generally consistent with those of previous DRF studies.

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| [redacted] | | |
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