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A pharmacokinetic study of delayed-release dimethyl fumarate to evaluate cerebrospinal fluid penetration in patients with secondary progressive multiple sclerosis

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Background

Delayed-release dimethyl fumarate (DMF) has been approved for the treatment of patients with relapsing multiple sclerosis (MS) or relapsing remitting MS. Evidence suggests that the pathogenesis of MS involves inflammation-driven oxidative injury in the central nervous system (CNS). Studies in rodents suggest that monomethyl fumarate (MMF), the primary and measurable metabolite of DMF, penetrates into the brain and cerebrospinal fluid (CSF). The CSF levels of MMF in humans after DMF treatment have not been evaluated.

Methods

Sixteen SPMS patients with no prior DMF exposure were recruited to take oral DMF 120 mg twice daily (BID) for 4 weeks, followed by DMF 240 mg BID for 24 weeks. During Week 6 (the second week on DMF 240 mg), plasma samples were collected before the morning dose and then at 2, 3, 5, 6, 7, 8 and 10 hours post morning dose. On the day of PK sampling, the patients took a morning dose after a low fat meal at the clinic. CSF samples were collected at pre-dose or 3, 5, 7 or 10 hours post-dose (3-4 patients at each time point (Table 1). Baseline demographics are described in Table 2. MMF concentrations in plasma and CSF samples were determined by LC-MS.

Results

After oral administration, DMF is rapidly converted to its active metabolite MMF, and DMF is not quantifiable in plasma. Therefore, all pharmacokinetic analyses were performed using MMF concentrations. In this study, MMF showed variable concentration-time profiles as illustrated in Figure 1A , which is consistent with historical data. MMF levels in CSF for all patients are presented in Figure 1B. The steady-state PK parameters for MMF are shown in Table 3. At a dose of 240 mg taken after a meal, the mean maximum plasma concentrations (C_{max}) was 1750 ng/mL, and the mean time to maximum concentration (T_{max}) was 4.6 hours. The PK parameters were similar to previously observed in MS patients[4]. Highest CSF level of MMF was at 7 hours post-dose, lagging behind plasma Tmax, with maximal CSF concentration of 39–79 ng/mL. Mean plasma and CSF MMF concentration – time profiles are shown in Figure 2. Mean MMF CSF C_{max} to plasma C_{max} ratio is 5.5%. As shown in Table 4, the mean CSF-to-plasma exposure ratio for MMF is 11%. For additional information on CNS penetration of DMF, please, refer to poster A-777-0030-01044.

Conclusion

This study demonstrates that MMF penetrates into CNS as evidenced by its CSF levels in SPMS patients.

Objective

To investigate the pharmacokinetics of MMF in plasma and CSF after oral administration of DMF in subjects with SPMS

Table 1: CSF Collection at Week 6

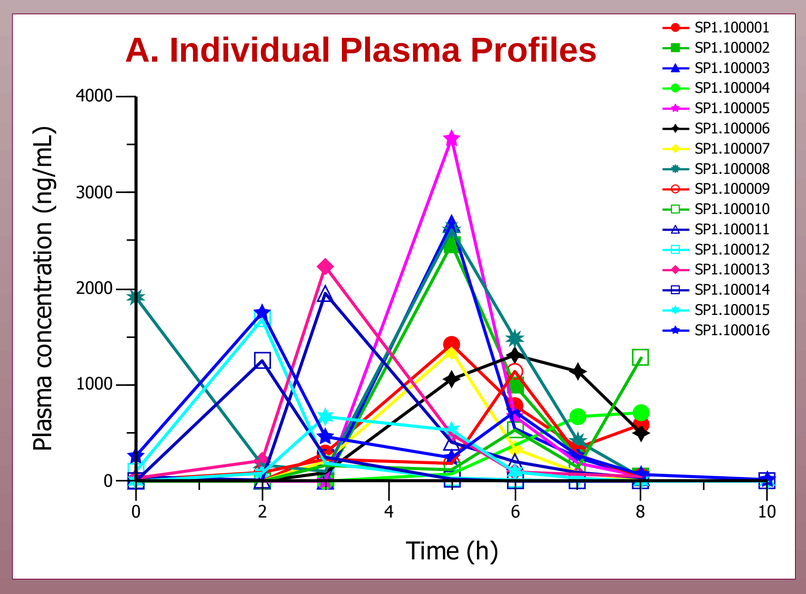
Subject	CSF Collection at Week 6				
	Post-dose				Pre-morning dose
	3 h	5 h	7 h	10 h	
1-4		x			
5-8			x		
9-12	x				
13					x
14-16				x	x

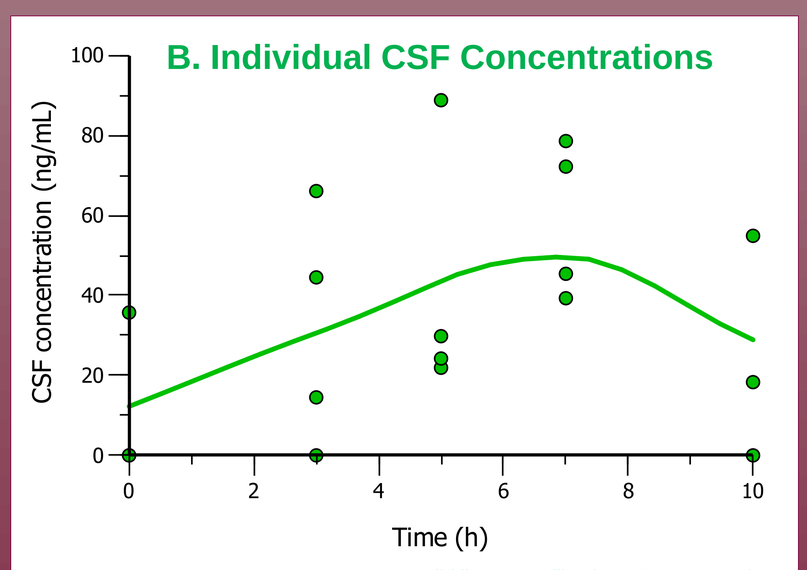
Table 2 : Baseline demographics

SPMS Patients (n=16)	Percentage	Mean (SD)	Range
Female	87.5 %	n/a	n/a
Race - Caucasian	100 %	n/a	n/a
Age	n/a	55.4 (8.93)	37-65
EDSS	n/a	4.44 (1.56)	3-6.5
Disease duration (in years)	n/a	22.5 (11.69)	3-39
MS Relapses (past 12 months)	n/a	0.19 (0.40)	0-1
Gad+ lesions	n/a	0 (0)	n/a

Data are mean (SD), n(%), unless otherwise stated. MS = multiple sclerosis. EDSS= expanded disability status scale.

Figure 1: Individual Plasma (A) and CSF (B) MMF Profiles after 240 mg DMF dose taken after meal





Solid line = trendline in CSF concentrations

Table 3: Pharmacokinetic Parameters of MMF in plasma after 240 mg DMF dose

Parameter	Mean	Min	Max	CV%
AUC_{last}, h*ng/ml	3850	1520	8150	47
C_{max}, ng/ml	1750	669	3560	45
T_{max}, h	4.6	2.0	8.0	42

Figure 2. Mean (± SE) MMF Plasma and CSF Concentration After Administration of 240 mg BID doses of DMF

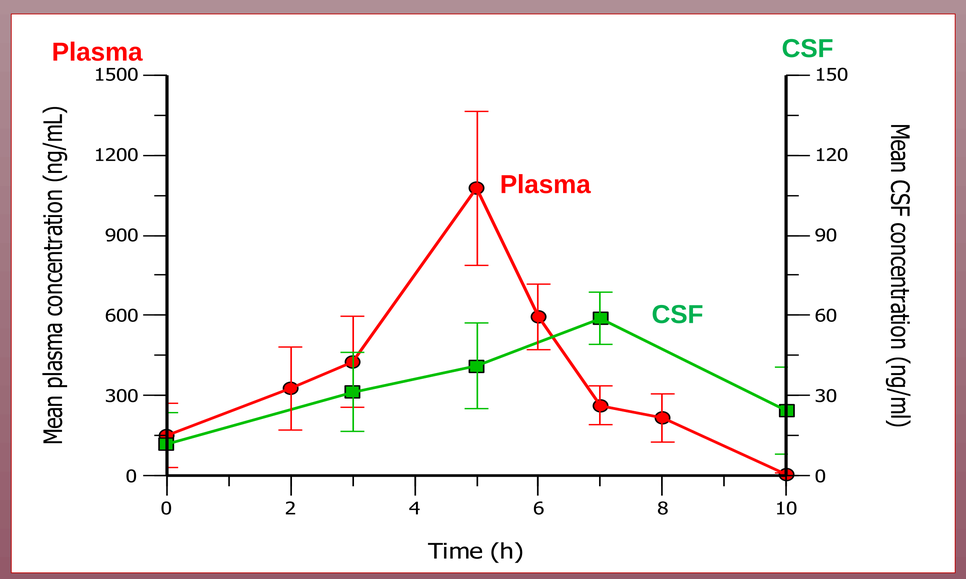


Table 4: Pharmacokinetic Parameters of MMF in Plasma and CSF

Parameter	Plasma	CSF	CSF/Plasma ratio
AUC_{inf}, h*ng/ml	4090	455	11%
T_{max}, h	5	7	

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Natasha Penner: employee of and holds stock/stock options in Biogen
Mark Rogge: holds stock/stock options in Biogen
Sarah Sheikh: employee of and holds stock/stock options in Biogen
Bing Zhu: employee of and holds stock/stock options in Biogen

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