Afimetoran (BMS-986256), an oral novel toll-like receptor 7 and 8 (TLR7/8) inhibitor, does not affect the pharmacokinetics of mycophenolate mofetil in healthy subjects

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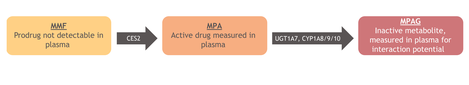
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*At the time this study was conducted

Introduction

- Toll-like receptor (TLR) 7 and TLR8 may be activated as part of the disease pathophysiology of systemic lupus erythematosus (SLE), including lupus nephritis (LN) and related autoimmune diseases[1-4]
- Afimetoran (BMS-986256), an orally administered, potent, and selective inhibitor of TLR7/8, has demonstrated efficacy in animal models of lupus,[5-8] as well as favorable pharmacokinetics (PK), pharmacodynamics, and acceptable safety profiles in healthy participants[9]
  - Clinical trials in patients with cutaneous lupus erythematosus and SLE are currently underway (NCT04493541 and NCT04895696)
- Mycophenolate mofetil (MMF) is an immunosuppressive agent that is widely used in immune-mediated diseases and is often utilized in the treatment of patients with more serious presentations of active SLE[10,11]
  - MMF becomes converted to its active metabolite, mycophenolic acid (MPA), and its inactive metabolite (mycophenolic acid glucuronide [MPAG]), following oral administration (**Figure 1**)[11]

Figure 1. Metabolism of MMF to its active and inactive metabolites



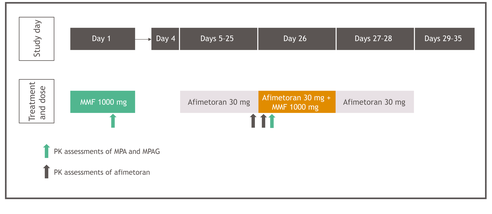
CES, carboxylesterase; CYP, cytochrome; UGT, uridine diphosphate glucuronosyltransferase.

- Therapeutic drug monitoring of MPA can be utilized in patients with SLE and LN to ensure a favorable treatment outcome and reduce adverse events (AEs)[12]
- Given that MMF is often used in the treatment of SLE, it is possible that afimetoran will be administered concomitantly with MMF in phase 2 studies
- In the current study, we evaluated the effect of afimetoran on the exposures of the active (MPA) and inactive (MPAG) metabolites of MMF

Methods

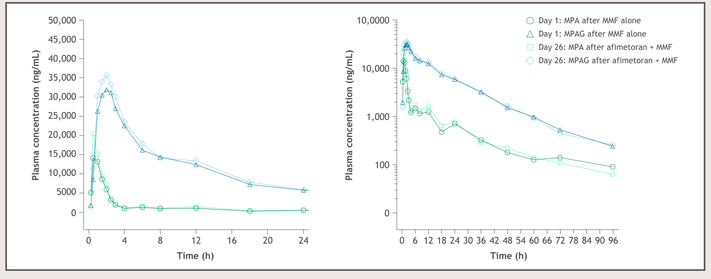
- This was an open-label, single-sequence crossover study in which 24 healthy participants received a single oral dose of MMF 1000 mg on day 1 (**Figure 2**)
  - Starting on day 5 through day 28, participants received 30 mg of afimetoran once daily orally
  - On day 26, participants received a second oral dose of MMF 1000 mg (in addition to afimetoran 30 mg once daily)
- Blood samples for PK evaluation were collected after administration of MMF and afimetoran
- Safety evaluations, including collection of AE data, physical examination, vital signs, electrocardiograms, and laboratory tests, were performed during the course of the study

Figure 2. Study design

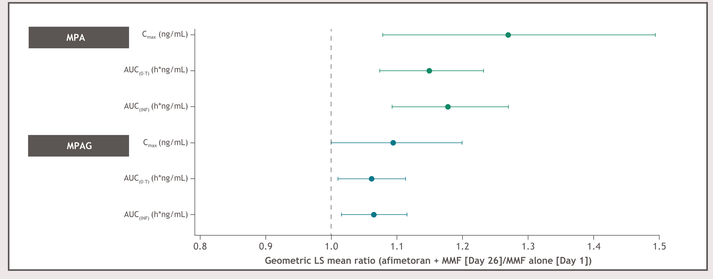


Our study demonstrated that afimetoran (BMS-986256) can be safely coadministered with MMF without requiring dose adjustment

Mean plasma concentrations of MPA and MPAG alone and in combination with afimetoran



Effects of afimetoran on PK of MPA and MPAG



$AUC_{(0-T)}$, area under the concentration-time curve from time of dosing to the time of the last quantifiable concentration observed; $AUC_{(INF)}$, area under the concentration-time curve from time of dosing to extrapolated infinity; C_{max}, maximum plasma concentrations; LS, least squares.

Results

Table 1. Participant characteristics

Characteristic	Cohort (N = 24)
Mean age, years (SD)	31 (10.4)
Min, max	19, 51
Sex, n (%)	
Male	24 (100)
Race, n (%)	
White	19 (79.2)
Black or African American	1 (4.2)
Native American or Alaska Native	3 (12.5)
Native Hawaiian or Other Pacific Islander	1 (4.2)
Mean body weight, kg (SD)	84 (14.5)
Mean BMI, kg/m² (SD)	26 (3.6)

BMI, body mass index; SD, standard deviation.

- Baseline participant characteristics are presented in **Table 1**
- At the 30 mg once daily dose, concentrations of afimetoran were consistent with those of participants who received afimetoran in the multiple ascending dose cohort of the first-in-human study[9]
- C_{max} and area under the concentration-time curve (AUC) of MPA were higher when MMF was coadministered with afimetoran than when MMF was administered alone (**Key Message** and **Table 2**)
  - C_{max} and total exposure ($AUC_{(INF)}$) increased by 27% and 17.8%, respectively, compared with MMF alone
  - Based on reported safety data of MMF in patients with SLE or LN, the 17% increase in AUC of MPA was below that associated with safety outcomes and not considered clinically relevant[12,13]

Table 2. PK of MPA following administration of MMF alone or in combination with afimetoran

PK parameter	Geometric LS mean: MMF 1000 mg alone (n = 24)[a]	Geometric LS mean: Afimetoran 30 mg + MMF 1000 mg (n = 22)[b]	Geometric LS mean ratio: Estimate (90% CI)
C_{max} (ng/mL)	18,451.1	23,423.8	1.3 (1.1-1.5)
$AUC_{(0-T)}$ (h*ng/mL)	51,337.7	59,045.4	1.2 (1.1-1.2)
$AUC_{(INF)}$ (h*ng/mL)	52,688.9	62,069.2	1.2 (1.1-1.3)

[a]$AUC_{(INF)}$, n = 23. [b]$AUC_{(INF)}$, n = 19.

- Exposures of the MPA metabolite MPAG were comparable in participants who were administered afimetoran alone or in combination with MMF, with C_{max} and total exposure ($AUC_{(INF)}$) increased by 9.5% and 6.5%, respectively, indicating no impact on metabolism of MPA by afimetoran (**Key Message** and **Table 3**)
- A single oral dose of MMF did not alter steady-state concentrations of afimetoran (**Figure 3** and **Figure 4**)
- Afimetoran had an acceptable safety profile and was well tolerated alone or in combination with MMF in healthy volunteers (**Table 4**)
- There were no concerning abnormal laboratory test results, including tests of hepatic function (ALT, AST, alkaline phosphatase, direct and total bilirubin), and no serious AEs, deaths, or AEs leading to discontinuation
- All treatment-emergent AEs (TEAEs) were mild and resolved spontaneously
  - Most common TEAEs included headache (30.4%), upper abdominal pain (17.4%), nausea (13%), and diarrhea (13%)

Table 3. PK of MPAG following administration of MMF alone or in combination with afimetoran

PK parameter	Geometric LS mean: MMF 1000 mg alone (n = 24)	Geometric LS mean: Afimetoran 30 mg + MMF 1000 mg (n = 22)	Geometric LS mean ratio: Estimate (90% CI)
C_{max} (ng/mL)	34,626.1	37,920.5	1.1 (1.0-1.2)
$AUC_{(0-T)}$ (h*ng/mL)	412,924.6	437,942.6	1.1 (1.0-1.1)
$AUC_{(INF)}$ (h*ng/mL)	417,648.3	444,630.9	1.1 (1.0-1.1)

Figure 3. Mean plasma concentrations of afimetoran when administered alone or in combination with MMF

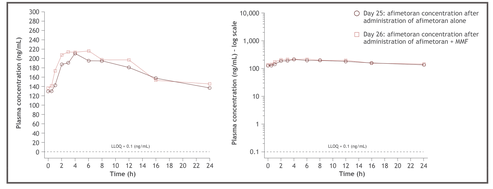


Figure 4. Effect of administration of MMF on PK of afimetoran

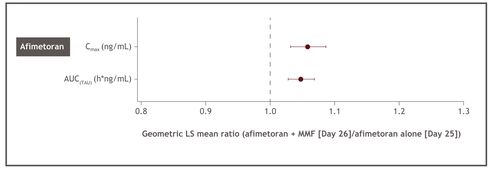


Table 4. TEAEs in participants who received MMF, afimetoran, or afimetoran in combination with MMF

Event	Cohort: MMF 1000 mg (n = 24)	Afimetoran 30 mg (n = 23)	Afimetoran 30 mg + MMF 1000 mg (n = 22)	Overall (N = 23)[a]
Total TEAEs, n	12	38	14	52
Participants with ≥1 TEAE, n (%)	4 (16.7)	14 (60.9)	10 (45.5)	18 (78.3)
Severity				
Mild	4 (16.7)	14 (60.9)	9 (40.9)	17 (73.9)
Moderate	0	0	1 (4.5)	1 (4.3)
Severe	0	0	0	0
Related to MMF				
Yes	1 (4.2)	-	2 (9.1)	2 (8.7)
No	3 (12.5)	-	8 (36.4)	16 (69.6)
Related to afimetoran				
Yes	-	6 (26.1)	4 (18.2)	8 (34.8)
No	-	8 (34.8)	6 (27.3)	10 (43.5)

[a]Number of patients who received at least one dose of afimetoran.

Conclusions

- Administration of afimetoran alone or in combination with MMF 1000 mg was generally safe and well tolerated
- Co-administration of MMF with afimetoran resulted in a minor increase in exposures of MPA, while there was no impact on MPAG exposures
  - MPA C_{max} and $AUC_{(INF)}$ increased by 27% and 17.8%, respectively
  - Based on previous studies, the increased exposures of MPA observed in this study were not considered clinically relevant
- Administration of a single dose of MMF had no impact on afimetoran exposure
- The lack of clinically relevant interactions observed between MMF and afimetoran suggests that both can be safely coadministered
- Our results support clinical application of afimetoran in patients with SLE who are also being treated with MMF

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