Afimetoran (BMS-986256), an oral novel toll-like receptor 7 and 8 (TLR7/8) inhibitor, is not a sensitive substrate of cytochrome P450 3A4: clinical evaluation with itraconazole

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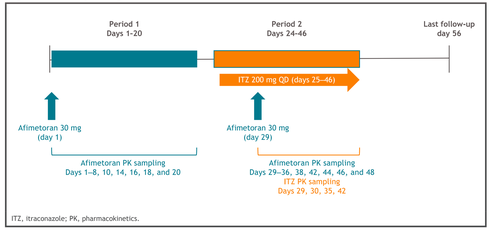
Background

- Toll-like receptor (TLR) 7 and TLR8 are inappropriately 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,[5,6] as well as favorable pharmacokinetics (PK) and acceptable safety profiles in healthy participants[7]
  - Clinical trials in patients with cutaneous lupus erythematosus and SLE are currently underway (NCT04493541 and NCT04895696)
- Based on nonclinical data, metabolism of afimetoran in human liver microsomes is primarily mediated by CYP3A4.[8] It is also a substrate of the efflux transporter P-glycoprotein (P-gp)[8]
- Itraconazole (ITZ) is a potent inhibitor of CYP3A4/P-gp and is a recommended prototypical inhibitor by the FDA in the drug–drug interaction (DDI) guidance[9]
- This study investigated the impact of CYP3A4/P-gp pathway inhibition with ITZ on afimetoran PK
- This study was designed in accordance with FDA DDI guidance

Methods

- NCT03950960 was an open-label, single-sequence crossover study in 15 healthy participants (**Figure 1**)
- Participants received a single oral dose of afimetoran 30 mg on day 1
- On day 25 through day 46, participants received oral ITZ 200 mg once daily (QD)
- On day 29, a single 30-mg dose of afimetoran was administered 1 hour following ITZ administration
- Blood samples for PK evaluation were collected after administration of ITZ and afimetoran
- Safety evaluations, including collection of adverse event (AE) data, physical examination, vital signs, electrocardiograms, and laboratory tests, were performed throughout the study

Figure 1. Study design



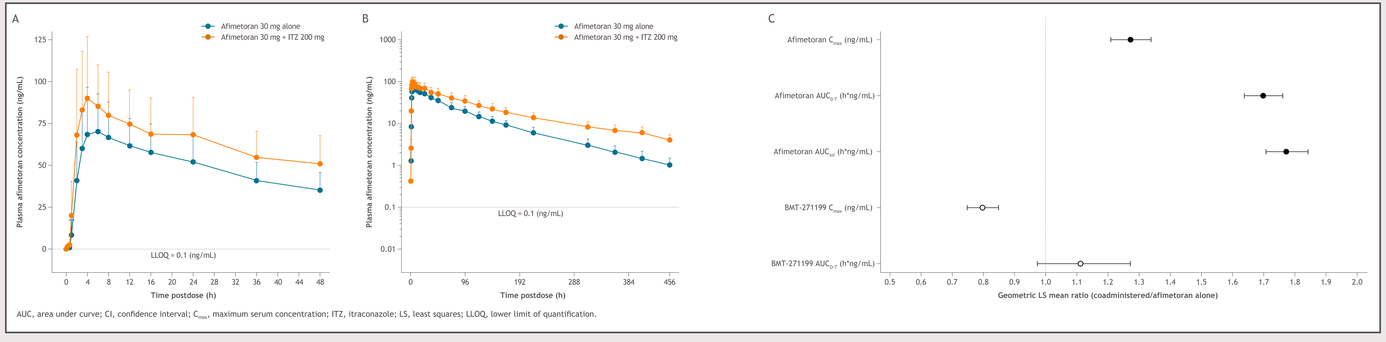
ITZ, itraconazole; PK, pharmacokinetics.

Results

- Baseline participant characteristics are presented in **Table 1**
- Concentrations of afimetoran after a single dose of 30 mg were consistent with those in participants who received afimetoran in the multiple ascending dose cohort of the first-in-human (FIH) study[7]
- Coadministration of afimetoran with ITZ resulted in increased afimetoran exposure, with afimetoran C_{max} increased by 27% and AUC_{inf} increased by 77% compared with afimetoran alone (**Figure 2** and **Table 2**)
  - Afimetoran C_{max} and AUC_{inf} were less than 2-fold higher when administered with ITZ compared with afimetoran alone
  - Afimetoran exposures following coadministration with ITZ were lower than those of the highest dose of 60 mg evaluated in the FIH study[7]
- Concentrations of the main afimetoran metabolite (BMT-271199) were consistent with those of participants who received afimetoran in the multiple ascending dose cohort of the FIH study[7] (**Figure 3**)
  - The metabolite-to-parent ratio was less than 5%, consistent with slow metabolism of afimetoran

Our study demonstrated that ITZ, a strong CYP3A4/P-gp inhibitor, resulted in less than 2-fold increase in exposures of afimetoran. This increase is not considered clinically meaningful based on the available safety data and exposure coverage in the FIH study

Figure 2. Plasma concentration–time profile of afimetoran with and without ITZ from (a) 0–48 hours and (b) 0–456 hours. (c) Geometric least-squares mean ratio of afimetoran and BMT-271199 exposure parameters following coadministration of afimetoran with ITZ vs afimetoran alone



AUC, area under curve; CI, confidence interval; C_{max}, maximum serum concentration; ITZ, itraconazole; LS, least squares; LLOQ, lower limit of quantification.

Table 1. Participant characteristics

	Cohort (N=15)
Race, n (%)	
White	5 (33.3)
Black or African American	8 (53.3)
Asian	1 (6.7)
Other	1 (6.7)
Sex	
Male/female	9/6
Body weight, mean (SD), kg	82.63 (16.1)
Age, mean (SD), years	41.5 (12.82)
Min, max	18, 54
BMI, mean (SD), kg/m²	27.45 (2.97)

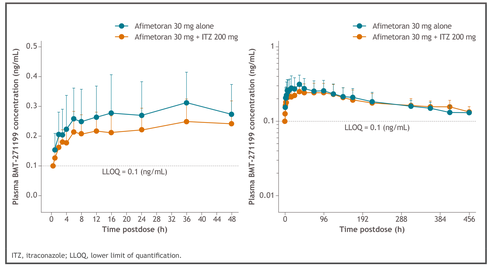
BMI, body mass index; SD, standard deviation.

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

		Geometric LS mean				Geometric LS mean ratio (test/reference)	
		Afimetoran + ITZ (test)		Afimetoran (reference)			
Analyte	Parameter (unit)	n	Result	n	Result	Estimate	90% CI
Afimetoran	C_{max} (ng/mL)	14	89.1	15	70.0	1.273	(1.211, 1.338)
	AUC_{0-T} (h*ng/mL)	14	9171.2	15	5398.1	1.699	(1.639, 1.761)
	AUC_{inf} (h*ng/mL)	12	9813.3	14	5533.4	1.773	(1.708, 1.841)

AUC, area under curve; CI, confidence interval; C_{max}, maximum serum concentration; inf, infinity; ITZ, itraconazole; LS, least square; PK, pharmacokinetics.

Figure 3. Mean plasma concentrations of afimetoran metabolite (BMT-271199) following administration of afimetoran alone or in combination with ITZ



ITZ, itraconazole; LLOQ, lower limit of quantification.

- Coadministration of afimetoran with ITZ decreased the C_{max} of BMT-271199 by approximately 20% and increased the AUC_{0-T} of BMT-271199 by approximately 11% compared with afimetoran alone (**Table 3**)
  - Decreases in the metabolite-to-parent ratios for peak and total exposures indicated that BMT-271199 exposure did not increase to the same extent as the parent drug following coadministration of afimetoran with ITZ

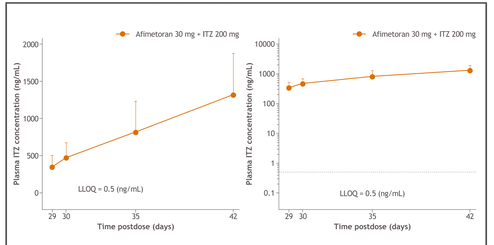
Table 3. PK of afimetoran metabolite (BMT-271199) when administered alone or in combination with ITZ

		Afimetoran + ITZ (test)		Afimetoran (reference)		Geometric LS mean ratio (test/reference)	
Analyte	Parameter (unit)	n	Result	n	Result	Estimate	90% CI
BMT-271199	C_{max} (ng/mL)	14	0.244	15	0.306	0.798	(0.750, 0.849)
	AUC_{0-T} (h*ng/mL)	14	60.6	15	54.4	1.113	(0.975, 1.272)

AUC, area under curve; CI, confidence interval; C_{max}, maximum serum concentration; ITZ, itraconazole; PK, pharmacokinetics.

- Trough plasma concentrations of ITZ were determined to be adequate to evaluate the maximum inhibitory effect on the PK of afimetoran (**Figure 4**)
  - The mean plasma trough concentrations of ITZ increased throughout the duration of the study, which is consistent with the known long half-life of ITZ
- Administration of a single 30-mg dose of afimetoran alone and in combination with ITZ 200 mg was safe and generally well tolerated in healthy volunteers (**Table 4**)
  - There were no concerning abnormal laboratory test results, including hepatic function (ie, ALT, AST, alkaline phosphatase, direct and total bilirubin), and no serious AEs (SAEs) or AEs leading to discontinuation
  - There were no deaths or other SAEs during the study
  - There were 10 treatment-emergent AEs (TEAEs) reported in 6 participants (40.0%), none of which led to discontinuation. No TEAEs were considered related to study treatments
  - The most common TEAEs were headache (30.4%), upper abdominal pain (17.4%), nausea (13.3%), and diarrhea (13.3%)

Figure 4. Plot of ITZ mean (+SD) trough plasma concentrations versus time



ITZ, itraconazole; SD, standard deviation.

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

Event	Afimetoran 30 mg (n = 15)	ITZ 200 mg (n = 14)	Afimetoran 30 mg + ITZ 200 mg (n = 14)	Overall (N = 15)
Total number of TEAEs, n	9	1	0	10
Participants with ≥1 TEAE, n (%)	5 (33.3)	1 (7.1)	0	6 (40.0)
Mild	3 (20.0)	1 (7.1)	0	4 (26.7)
Moderate	2 (13.3)	0	0	2 (13.3)
Severe	0	0	0	0
Related to ITZ/afimetoran				
Yes	0	0	0	0
No	5 (33.3)	1 (7.1)	0	6 (40.0)

ITZ, itraconazole; TEAE, treatment-emergent adverse events.

Conclusions

- In this study, afimetoran was safe and generally well tolerated alone and in combination with ITZ. There were no deaths or SAEs during the study, and no participants discontinued the study due to an AE
- Coadministration of ITZ with afimetoran resulted in less than a 2-fold increase in exposures of afimetoran, indicating that afimetoran is not a sensitive substrate of CYP3A4 or P-gp
  - ITZ had no meaningful impact on afimetoran metabolite concentrations
- In the presence of ITZ, exposures following a single dose of afimetoran 30 mg were lower than the highest dose (60 mg) evaluated in the FIH study
- The impact of changes in exposures of afimetoran in patients with SLE in the presence of CYP3A4 inhibitors will be assessed using exposure-safety modeling based on clinical data from the ongoing phase 2 SLE study

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