First-in-human safety, pharmacokinetic, and pharmacodynamic study of escalating single- and multiple-doses of afimetoran (BMS-986256), a novel, potent, oral inhibitor of TLR7 and TLR8

Melanie Harrison, Manoj Chiney, Diane Shevell*, Ihab G. Girgis

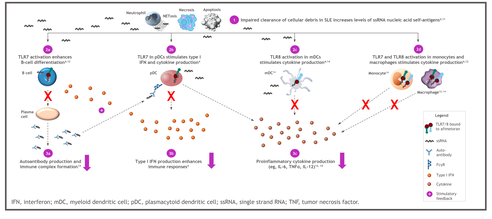
Bristol Myers Squibb, Princeton, NJ, USA

*At the time this study was conducted

Introduction

- Toll-like receptors (TLRs) are a class of cell surface and endogenous receptors that initiate early response of the innate immune system to an unknown pathogen[1]
- Endogenous TLRs, such as TLR7 and TLR8, can be activated by self-RNA as part of the pathophysiology of autoimmune conditions such as systemic lupus erythematous (SLE)[2,3]
- TLR signaling has been shown to induce a pro-inflammatory response, including the production of interleukin (IL)-6 by B cells, which is increased in patients with active SLE[4]
- In mouse models, overexpression of TLR7 induces autoimmunity and lupus-like disease[5,6]
  - In a similar model, it was demonstrated that TLR8 is involved in the regulation of myeloid cells and prevention of autoimmunity by regulating TLR7 expression[7]
- Afimetoran (BMS-986256) is an oral, potent, and selective inhibitor of TLR7 and TLR8 with potential for therapeutic effect in SLE (**Figure 1**)
- Preclinical studies have demonstrated robust pharmacodynamic (PD) activity and efficacy in multiple murine lupus models and in vitro studies[8-10]
- The objective of this work is to present safety, pharmacokinetic (PK), and PD results from a first-in-human study investigating afimetoran administered to healthy volunteers as single ascending doses (SAD) and as multiple ascending doses in participants of non-Japanese (MAD) and of Japanese descent (J-MAD) (NCT03634995)

Figure 1. Mechanism of action of afimetoran

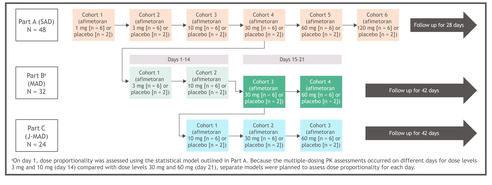


IFN, interferon; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; ssRNA, single strand RNA; TNF, tumor necrosis factor.

Study design

- Each of the SAD, MAD, and J-MAD parts of the study were randomized, double-blind, placebo-controlled trials in which healthy adults were randomized 3:1 (afimetoran:placebo) within each dose cohort (**Figure 2**)

Figure 2. Study design



[a]On day 1, dose proportionality was assessed using the statistical model outlined in Part A. Because the multiple-dosing PK assessments occurred on different days for dose levels 3 mg and 10 mg (day 14) compared with dose levels 30 mg and 60 mg (day 21), separate models were planned to assess dose proportionality for each day.

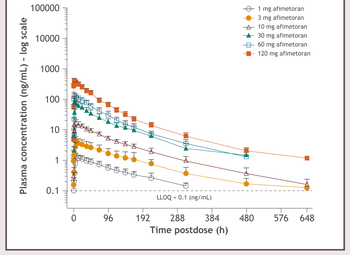
- In Part A (SAD), 48 healthy adults were enrolled across 6 cohorts of 8 participants each to receive placebo (n = 12) or afimetoran (n = 36) at doses of 1, 3, 10, 30, 60, and 120 mg and were followed for up to 28 days
- In Part B (MAD), 32 healthy adults of non-Japanese descent were enrolled across 4 cohorts to receive placebo (n = 8) or afimetoran (n = 24) once daily at doses of 3 and 10 mg for 14 days and 30 and 60 mg for 21 days and were followed for up to 42 days
- In Part C (J-MAD), 24 healthy adults of Japanese descent were enrolled across 3 dose cohorts to receive placebo (n = 6) or afimetoran (n = 18) once daily at doses of 10, 30, and 60 mg for up to 21 days and followed for up to 42 days

Methods

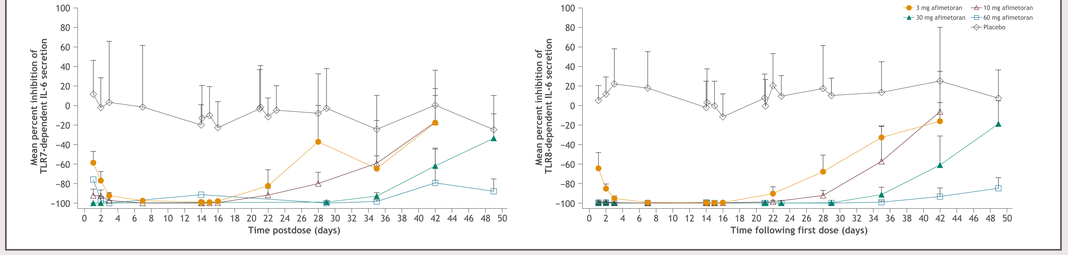
- Safety assessments
  - Safety and tolerability were assessed as rates and by severity of all treatment-emergent adverse events (TEAEs)
- PK and PD assessments
  - PK parameters were estimated from plasma concentration versus time data using Phoenix WinNonlin™ software (Certara, Princeton, NJ, USA)
  - To assess target engagement of afimetoran with TLR7/8, ex vivo assays (TruCulture) that measure IL-6 production in response to ex vivo stimulation with a TLR7 (gardiquimod)- or TLR8 (TL8-506)-specific agonist were performed

Afimetoran (BMS-986256) displayed favorable safety, PK, and PD profiles with single and multiple dosing in healthy volunteers and is currently in a Phase II clinical trial in patients with SLE (NCT04895696)

Mean (+ SD) plasma concentration-time profiles of single doses of afimetoran



Rapid and durable suppression of TLR 7/8 pathway as measured in a whole blood assay following multiple doses of afimetoran



LLOQ, lowest limit of quantification; SD, standard deviation.

- Statistical methods
  - In Part A, PK parameters C_{max} (maximum observed plasma concentration) and $AUC_{INF,}$ (area under the concentration-time curve from time of dosing to extrapolated infinity) for afimetoran were compared across all dose levels to assess dose proportionality
    - Estimate of the slope was reported along with 90% CIs for each parameter; dose was proportionality established if CIs were contained within accepted Hummel-adjusted critical region
  - In Part B, statistical evaluation of steady state was made by dose level using the trough afimetoran plasma concentrations
    - Trough concentrations were analyzed using an analysis of variance model with study days as a fixed effect and plotted graphically
  - In Part C, dose proportionality was examined for the PK parameters C_{max} and AUC_{TAU} (area under the concentration-time curve in one dosing interval), using similar methods outlined in Part B
    - Body-weight adjusted, dose-normalized C_{max} and AUC_{TAU} were also analyzed

Results

Table 1. Baseline participant characteristics

Characteristic	SAD (n = 48)	MAD (n = 32)	J-MAD (n = 24)
Race, n (%)			
White	27 (56.3)	17 (53.1)	-
Black or African American	20 (41.7)	13 (40.6)	-
Asian	1 (2.1)	1 (3.1)	24 (100)
Native American or Alaska Native	-	1 (3.1)	-
Sex, n (%)			
Male	26 (54.2)	26 (81.3)	16 (66.7)
Female	22 (45.8)	6 (18.8)	8 (33.3)
Mean body weight, kg (SD)	77.09 (12.68)	78.63 (11.923)	66.4 (11.584)
Mean age, years (SD)	33.9 (9.69)	35.9 (10.32)	39.5 (9.06)

- Baseline participant characteristics are shown in **Table 1**
- Across all cohorts, the frequency of TEAEs was low, and the majority were unrelated to afimetoran (**Tables 2-4**)
  - The most common TEAEs were headache, followed by upper respiratory infection and gastrointestinal symptoms (dyspepsia, constipation, and vomiting)
  - All TEAEs were classified as mild, except for 2 that were classified as moderate (viral upper respiratory infection and tooth fracture)
  - Reversible, elevated ALT levels were identified in a subset of participants
    - Eleven (14%) of those who received afimetoran and 4 (15%) of those who received placebo
    - Only 4 participants (2 who had received afimetoran 60 mg and 2 who received placebo) had elevations > 2 × upper limit of normal (ULN; 4.3 × ULN and 6.1 × ULN)
    - No consistent or recognizable pattern was detected for the presentation of the ALT abnormalities that suggested a single or specific etiology
  - One participant in the J-MAD 60-mg cohort discontinued afimetoran for asymptomatic, elevated ALT, which then resolved
- No serious adverse events were reported

Table 2. TEAEs in participants who received afimetoran or placebo in Part A (SAD)

Characteristic	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 6)	30 mg (n = 6)	60 mg (n = 6)	120 mg (n = 6)	Overall (n = 36)	Placebo (n = 12)
Total TEAEs, n	8	1	0	0	0	3	12	7
Participants with ≥ 1 TEAE, n (%)	4 (66.7)	1 (16.7)	0	0	0	3 (50.0)	8 (22.2)	4 (33.3)
Severity								
Mild	3 (50.0)	1 (16.7)	0	0	0	3 (50.0)	7 (19.4)	4 (33.3)
Moderate	1 (16.7)	0	0	0	0	0	1 (2.8)	0
Severe	0	0	0	0	0	0	0	0
Related to afimetoran or placebo								
Yes	0	1 (16.7)	0	0	0	0	1 (2.8)	0
No	4 (66.7)	0	0	0	0	3 (50.0)	7 (19.4)	4 (33.3)

Table 3. TEAEs in participants who received afimetoran or placebo in Part B (MAD)

Characteristic	3 mg (n = 6)	10 mg (n = 6)	30 mg (n = 6)	60 mg (n = 6)	Overall (n = 24)	Placebo (n = 8)
Total TEAEs, n	6	0	2	3	11	2
Participants with ≥ 1 TEAE, n (%)	3 (50.0)	0	1 (16.7)	2 (33.3)	6 (25.0)	2 (25.0)
Severity						
Mild	3 (50.0)	0	0	2 (33.3)	5 (20.8)	2 (25.0)
Moderate	3 (50.0)	0	1 (16.7)	0	1 (4.2)	0
Severe	0	0	0	0	0	0
Related to afimetoran or placebo						
Yes	1 (16.7)	0	0	0	1 (4.2)	0
No	2 (33.3)	0	1 (16.7)	2 (33.3)	5 (20.8)	2 (25.0)

Table 4. TEAEs in participants who received afimetoran or placebo in Part C (J-MAD)

Characteristic	10 mg (n = 6)	30 mg (n = 6)	60 mg (n = 6)	Overall (n = 18)	Placebo (n = 6)
Total TEAEs, n	6	5	10	21	1
Participants with ≥ 1 TEAE, n (%)	3 (50.0)	3 (50.0)	5 (83.3)	11 (61.1)	1 (16.7)
Severity					
Mild	3 (50.0)	3 (50.0)	5 (83.3)	11 (61.1)	1 (16.7)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
Related to afimetoran or placebo					
Yes	3 (50.0)	0	2 (33.3)	5 (27.8)	1 (16.7)
No	0	3 (50.0)	3 (50.0)	6 (33.3)	0

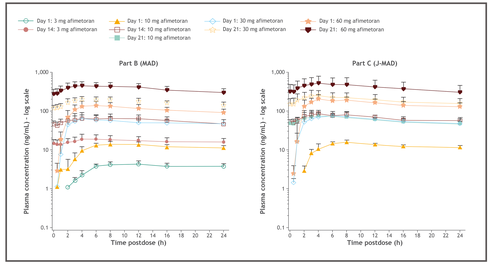
Table 5. Summary of SAD PK

PK parameter	Afimetoran cohorts					
	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 6)	30 mg (n = 6)	60 mg (n = 6)	120 mg (n = 6)
C_{max},* ng/mL	1.26 (16.4)	3.98 (26.2)	17.5 (19.5)	77.3 (22.4)	128 (20.0)	414 (14.8)
$AUC_{INF,}$* h*ng/mL	160 (24.1)	475 (41.7)	1605 (17.5)	5766 (21.1)	8774 (23.7)	22267 (11.2)
Median T_{max}, h (min, max)	12.0 (8.0, 24.0)	8.0 (8.0, 12.0)	6.3 (4.0, 12.0)	8.0 (4.0, 8.1)	4.0 (4.0, 8.0)	4.0 (4.0, 12.0)

*Determined using geometric mean (% coefficient of variation).
T_{max}, time of maximum observed concentration.

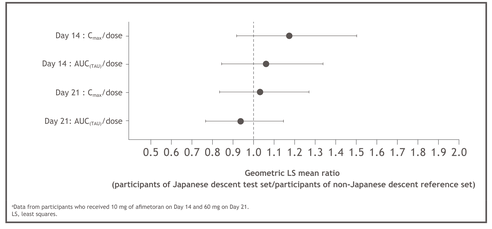
- In the SAD (Part A) cohort, afimetoran displayed linear PK with dose-dependent increase in exposures (**Table 5**)
- Afimetoran demonstrated a long half-life (~ 80 h) across the doses evaluated, which is consistent with its predicted low clearance
- Consistent with an observed low clearance, the level of active circulating minor active metabolite in plasma was low (< 2% of AUC); this ratio was similar across all doses evaluated
- Low inter-individual exposure variability was also observed among participants across cohorts (% coefficient of variation ~ 30%)
- The PK profile of participants who received multiple doses (Part B) was consistent with the known PK properties assessed based on Part A
- Exposures in Japanese subjects (Part C) were slightly higher than those estimated in Part B; however, the overall PK properties of afimetoran across Part B and Part C were similar (**Figure 3**)

Figure 3. Mean (+ SD) afimetoran plasma concentration-time profiles in participants in Part B (MAD) and Part C (J-MAD)



- When PK parameters of participants of Japanese descent were adjusted for body weight and compared with participants not of Japanese descent, exposures of afimetoran were found to be equivalent (**Figure 4**)
- An ex vivo PD assay that measured afimetoran inhibition of TLR7-dependent or TLR8-dependent IL-6 production showed rapid PD inhibition at all doses tested (Part B shown in **Key Message** box)
  - The effect was dose-dependent and was maintained for the duration of treatment, reaching > 90% inhibition

Figure 4. Comparison of body-weight adjusted, dose-normalized C_{max} and AUC at days 14 and 21 between participants of Japanese (n = 24) and non-Japanese descent (n = 18)[a]



[a]Data from participants who received 10 mg of afimetoran on Day 14 and 60 mg on Day 21.
LS, least squares.

Conclusions

- Afimetoran was generally well tolerated following single and multiple doses administered across the dose range studied
- PK properties were consistent and favorable, with the long half-life supporting once daily dosing
- Response of biomarkers was robust, dose-dependent, and demonstrated PD inhibition consistent with a high degree of target engagement starting from a 10-mg single dose of afimetoran
- These findings support further clinical development of afimetoran, with phase 1 and phase 2 clinical trials in patients with cutaneous lupus erythematosus and SLE, respectively, currently underway (NCT04493541 and NCT04895696)

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Email: Melanie.Harrison@bms.com