Pharmacodynamic effects and exploratory efficacy of afimetoran, a TLR7/8 inhibitor, in patients with cutaneous lupus erythematosus

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Introduction

- Cutaneous lupus erythematosus (CLE) is a chronic inflammatory skin condition that occurs in isolation or with systemic lupus erythematosus (SLE)
- With the lack of approved treatments for CLE,[1] there is an unmet need for new, safe, and effective treatments
- Type I interferons (IFNs) are major drivers of disease[2]
  - Toll-like receptor 7 (TLR7) and 8 (TLR8) are endosomal RNA sensors that stimulate Type I IFN production in lupus[3]
- Afimetoran is an investigational, first-in-class, orally bioavailable, potent, selective small molecule inhibitor of TLR7/8
- Afimetoran may have therapeutic potential for CLE, given the involvement of TLR7/8 in disease pathobiology of the closely related SLE[3]
- A phase 1b, randomized, double-blind, placebo-controlled study (NCT04493541) demonstrated the preliminary safety, tolerability, and efficacy of afimetoran in patients with active CLE[4]

Objective

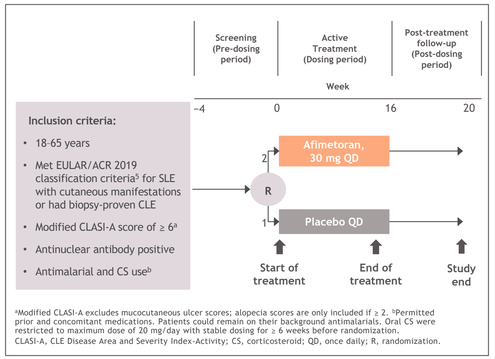
- To assess the pharmacodynamic (PD) effects of afimetoran, its impact on CLE pathobiology, and exploratory endpoints of clinical efficacy

Methods

Study design and patients

- This was an exploratory, post hoc analysis of the phase 1 study
- Patients were screened for up to 4 weeks and then randomized 2:1 to 30 mg once-daily oral afimetoran (BMS-986256) or placebo for 16 weeks with a 4-week post-treatment follow-up **(Figure 1)**

Figure 1. Clinical study design



[a]Modified CLASI-A excludes mucocutaneous ulcer scores; alopecia scores are only included if ≥ 2. [b]Permitted prior and concomitant medications. Patients could remain on their background antimalarials. Oral CS were restricted to maximum dose of 20 mg/day with stable dosing for ≥ 6 weeks before randomization.
CLASI-A, CLE Disease Area and Severity Index-Activity; CS, corticosteroid; QD, once daily; R, randomization.

Endpoints and assessments

- The primary endpoints of safety and tolerability were measured by assessing adverse events, clinical laboratory values, physical examination findings, vital signs, and electrocardiography parameters
- Exploratory efficacy was assessed via change in CLE Disease Area and Severity Index-Activity (CLASI-A) scores from baseline to weeks 4, 8, 12, 16, and 20
- Exploratory disease profile and PD biomarkers were assessed using whole blood transcriptomics and target engagement–related changes in cytokine levels
  - Biomarkers associated with the TLR7/8 pathway activation were measured, including mRNA signatures of IFN pathways, TLR7 signaling, TLR8 signaling, and immune cell populations such as immature and activated dendritic cells (DCs)
  - Transcriptomics and cytokine analyses were performed using peripheral whole blood and serum, respectively, at weeks 0 (baseline), 1, 2, 4, 8, 12, 16, and 20
  - For cytokine analysis, whole blood was stimulated ex vivo with a TLR7 agonist (Gardiquimod™, InvivoGen, San Diego, CA) or a TLR8 agonist (TL8-506, InvivoGen, San Diego, CA)
- The differential of gene set variation analysis (GSVA) enrichment scores (ES) between patients with CLE and healthy volunteers (HVs), defined as the CLE disease profile, were calculated at each time point

Statistical analysis

- Statistical analyses were performed to pool and compare data from 13 patients and 13 age-, ethnicity-, and gender-matched HVs
- Treatment responses were evaluated longitudinally in each treatment arm
- The dataset was analyzed using a linear regression model (limma package in R)
- GSVA was performed for pathway enrichment
- Statistical significance was assessed using *t*-tests comparing means of normalized GSVA scores with standard deviations in groups

Results

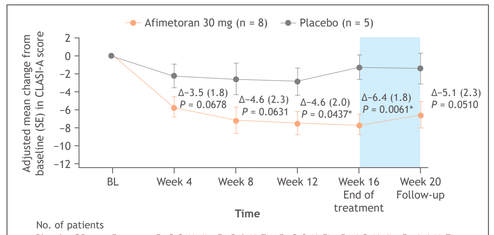
Patients

- A total of 13 patients were randomized (afimetoran, n = 8; placebo, n = 5) and 12 patients completed 16 weeks of treatment
  - One patient discontinued afimetoran due to COVID-19

Safety and efficacy

- Afimetoran demonstrated a favorable safety profile and was well tolerated compared with placebo in patients with CLE, with no serious adverse events (data not shown)
- A greater reduction in CLASI-A scores was observed with afimetoran than placebo over time **(Figure 2)**
  - At weeks 12 and 16, the reduction in CLASI-A scores from baseline was significantly greater for the afimetoran arm than the placebo arm ($P < 0.05$)
  - The CLASI-A scores also showed a trend toward greater reductions with afimetoran than placebo at weeks 4, 8, and 20

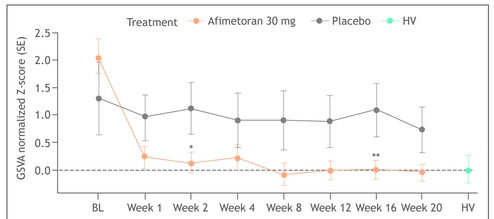
Figure 2. Mean change in CLASI-A scores from baseline for afimetoran versus placebo over 20 weeks



No. of patients						
Placebo QD	5	5	−2.2 (1.4)	5	−2.6 (1.7)	5	−2.8 (1.5)	5	−1.2 (1.4)	5	−1.4 (1.7)
Afimetoran 30 mg QD	8	8	−5.8 (1.1)	7	−7.2 (1.4)	7	−7.4 (1.3)	7	−7.6 (1.2)	5	−6.6 (1.5)

*$P < 0.05$.
The shaded blue area indicates the 4-week follow-up period. Values shown on the figure represent the difference in adjusted mean change from baseline (SE) between afimetoran vs placebo, and values next to number of patients represent adjusted mean change from baseline (SE) for afimetoran or placebo, from mixed-effect model of repeated measures. *P*-values are from ad hoc analysis of two-sample *t*-test.
BL, baseline.

Figure 3. CLE disease gene scores for afimetoran versus placebo over 20 weeks



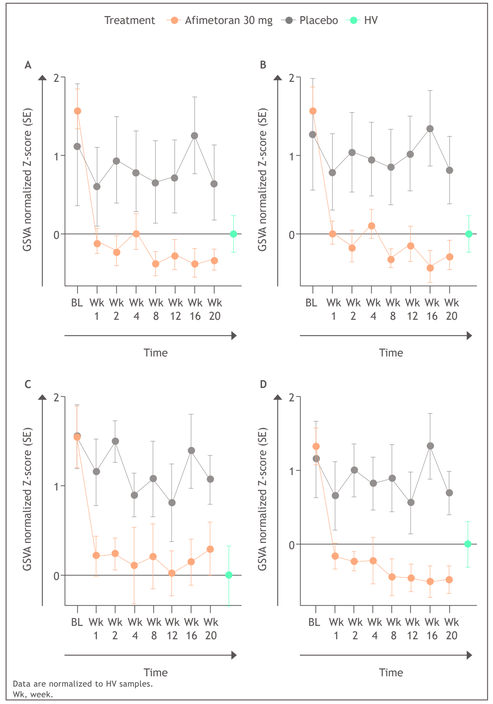
Afimetoran	N/A	−1.85	−1.95	−1.84	−2.16	−2.09	−2.08	−2.12
Placebo	N/A	−0.34	−0.18	−0.40	−0.39	−0.42	−0.20	−0.57

Data are normalized to HV samples.
$P < 0.005$ for change from baseline at all timepoints in the afimetoran arm. None were significant in the placebo arm.
*$P = 0.045$ for afimetoran versus placebo at week 2.
**$P = 0.028$ for afimetoran versus placebo at week 16.

Disease profile impact and pharmacodynamics

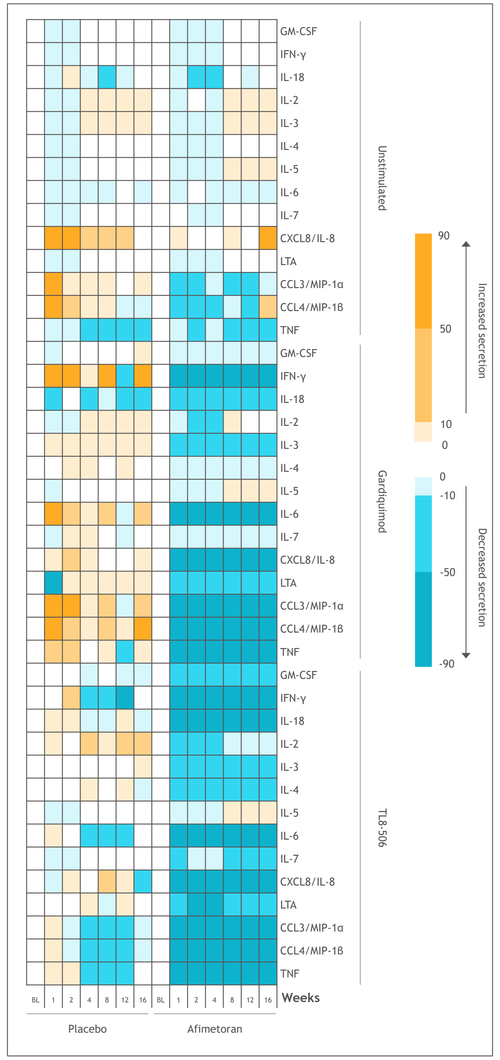
- The disease profile is defined by the comparison between patient and HV samples at baseline. The change in disease profile, assessed by the change in GSVA ES over time, showed the rapid impact of afimetoran treatment (week 1), which was sustained throughout the treatment period (up to week 16), and maintained up to 4 weeks post-treatment **(Figure 3)**
  - GSVA ES were significantly reduced from baseline at all time points for afimetoran ($P < 0.005$); no significant changes in ES were observed in the placebo arm
  - Compared with placebo, afimetoran showed significant reduction in ES at week 2 (ΔGSVA ES = −0.99, $P = 0.045$) and week 16 (ΔGSVA ES = −1.10, $P = 0.028$) **(Figure 3)**
- GSVA ES analysis showed robust PD activity of afimetoran on the expression of the drug target TLR7/8 pathway genes involved in TLR7/8 signaling **(Figure 4A, B)** and in immune cell populations including both immature and activated DCs **(Figure 4C, D)** compared with placebo. Similar PD activity was noted in macrophages and with IFN and inflammatory pathway signatures (data not shown)
  - In the afimetoran arm, GSVA ES at all time points were significantly reduced from baseline ($P < 0.05$). No significant reduction in ES was observed in the placebo arm
  - The afimetoran arm showed significant reduction in GSVA ES compared with the placebo arm at weeks 2 and 16 for all pathways and at weeks 8, 12, and 20 for TLR7 signaling, TLR8 signaling, and activated DCs ($P < 0.05$)

Figure 4. Pharmacodynamics of afimetoran versus placebo: gene expression of gene sets associated with (A) TLR7 signaling,(B) TLR8 signaling, (C) immature DCs, and (D) activated DCs over 16 weeks of treatment and 4 weeks of follow-up



Data are normalized to HV samples.
Wk, week.

Figure 5. Heat map of mean percentage change from baseline in cytokine secretion for unstimulated, TLR7-stimulated, and TLR8-stimulated whole blood samples from afimetoran and placebo groups over 20 weeks



- Expression of IFN pathway genes in whole blood was also significantly reduced as early as week 1 compared with baseline in the afimetoran arm (ΔGSVA ES = 1.57, $P < 0.0001$) and the placebo arm (ΔGSVA ES = 0.56, $P < 0.01$), and maintained for 16 weeks of treatment and at least 4 weeks post-treatment (up to week 20; data not shown)
- In the afimetoran arm, TLR7/8-stimulated samples showed >50% decreased secretion for most cytokines (including IFN-γ, TNF-α, IL-family cytokines) and chemokines (eg, CCL3/MIP1α and CCL4/MIP1β), which was not seen in the placebo arm **(Figure 5)**
  - No notable changes were observed in the unstimulated samples
  - Decreased secretion occurred as early as week 1 of treatment and was sustained throughout the treatment period (week 16)

Conclusions

- In patients with CLE, afimetoran was safe and well tolerated compared with placebo, and showed clinical efficacy, molecular disease impact, and potent PD effects early, throughout, and beyond the treatment period
- The effects measured on the disease profile support the clinical impact of afimetoran observed with CLASI-A scores
- The positive impact of afimetoran on the disease profile and accompanying potent PD and clinical effects suggest potentially substantial therapeutic benefit for patients with CLE
- These results support the continued clinical investigation of afimetoran in lupus, including the ongoing phase 2b study in SLE (NCT04895696)

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Disclosures

JS: employee and shareholder: Bristol Myers Squibb. **SI:** nothing to disclose. **KC:** employee and shareholder: Bristol Myers Squibb. **LZ:** employee and shareholder: Bristol Myers Squibb. **HYTB:** employee and shareholder: Bristol Myers Squibb. **HK:** employee and shareholder: Bristol Myers Squibb. **MD:** employee and shareholder: Bristol Myers Squibb. **MH:** employee: Bristol Myers Squibb; shareholder: Bristol Myers Squibb and Pfizer. **LC:** employee and shareholder: Bristol Myers Squibb. **GK:** employee and shareholder: Bristol Myers Squibb. **FH:** employee and shareholder: Bristol Myers Squibb. **FB:** employee: Bristol Myers Squibb; shareholder: Bristol Myers Squibb and Janssen Pharmaceuticals.

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