A phase 2b study of afimetoran (BMS-986256) in patients with active systemic lupus erythematosus: optimization of a lupus clinical trial design

PO6:132

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Background

- Activation of toll-like receptor (TLR) 7/8 may contribute to the pathophysiology of systemic lupus erythematosus (SLE) and other related autoimmune diseases by inducing the production of proinflammatory cytokines, such as type 1 interferon[1-5]
  - TLR 7/8 can be activated by self-RNA,[1-5] and a gain-of-function mutation in TLR7 has been identified that causes SLE[6]
- Afimetoran, a potent, selective, oral, small-molecule inhibitor of TLR 7/8, has been developed as a potential treatment for autoimmune diseases
- Afimetoran has shown robust efficacy and improved survival in animal models of established and advanced lupus and has demonstrated favorable pharmacologic and safety profiles in healthy volunteers[7,8]
- Together, these data indicate that afimetoran may offer a novel therapeutic approach for the treatment of patients with SLE
- To determine whether TLR 7/8 inhibition using afimetoran leads to clinical improvement in SLE disease activity, we are conducting a phase 2b clinical trial of afimetoran in patients with active SLE; this clinical trial employs an optimized design that leverages lessons learned from previous clinical studies

Study design

- IM026-024 (EudraCT 2019-004021-25; NCT04895696) is a phase 2b, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of afimetoran compared with placebo for the treatment of patients with active SLE
- Select eligibility criteria are shown in **Table 1**
- Approximately 344 patients on standard medications will be randomized 1:1:1:1 to receive one of three different dose levels of oral afimetoran or placebo once daily for ~48 weeks (**Figure 1**)
  - Patients may continue blinded treatment for an additional 52 weeks during an optional long-term extension period

Lessons learned from failed clinical trials in patients with SLE and best practices from recent successful trials are being adopted in this study, including:

- Modified eligibility criteria requiring adequate disease severity, to ensure observed improvements are clinically meaningful (**Figure 1**)
- Tapering of corticosteroid therapy to reduce placebo responses
  - Patients receiving corticosteroids > 7.5 mg/day will be required to attempt to taper their dose during the study
- Ongoing review by a panel of lupus trial experts to ensure accuracy and consistency of patient diagnosis and data

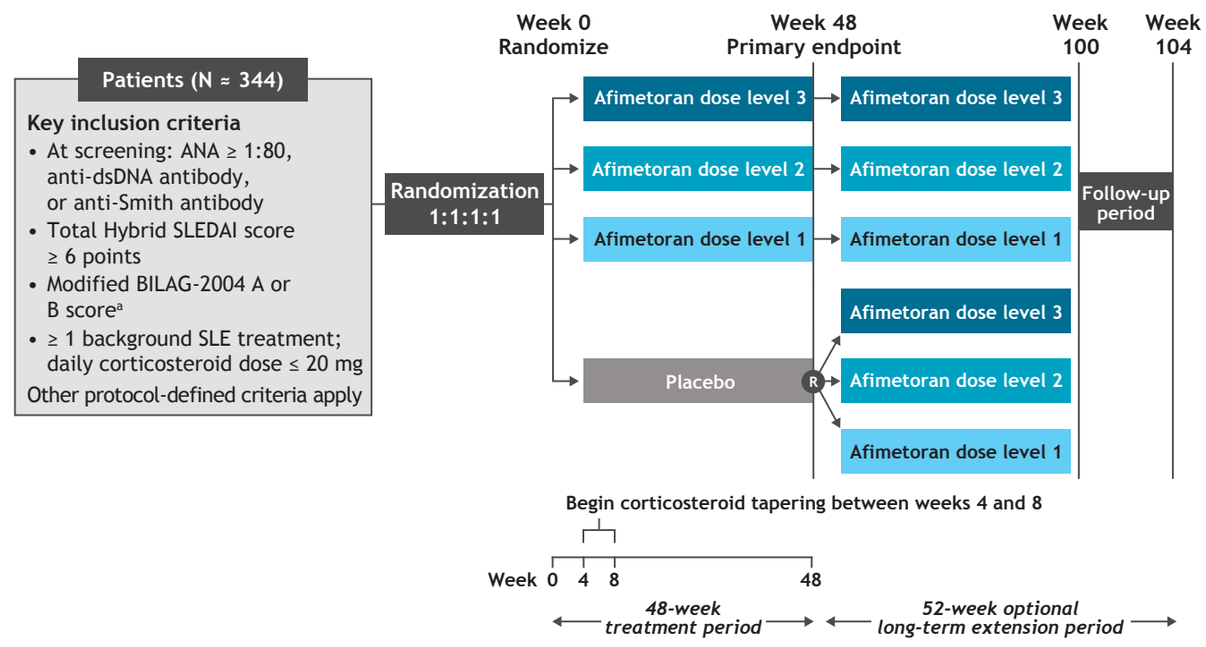
- Endpoints are shown in **Table 2**

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
Qualify as having SLE, according to SLICC Classification Criteria ≥ 12 weeks before the screening visit	Active severe lupus nephritis as assessed by the investigator
Test positive, as determined by a central laboratory, for at least 1 of the following lupus-related autoantibodies at the time of screening: ANA ≥ 1:80, anti-dsDNA antibody, or anti-Smith antibody	Active or unstable neuropsychiatric lupus manifestations defined by the Hybrid SLEDAI
Have a total Hybrid SLEDAI[9,10] score ≥ 6 points and clinical Hybrid SLEDAI score ≥ 4 points with joint involvement and/or rash	Diagnosis of Mixed Connective Tissue Disease for which the predominant diagnosis is not SLE
Have a modified BILAG-2004 A or B score; impairment of activities of daily living	Antiphospholipid syndrome (APS), or history of probable or definite catastrophic APS
Have ≥ 1 background SLE treatment, which can include an oral corticosteroid (daily dose ≤ 20 mg)	Taking > 1 immunosuppressant or oral corticosteroid > 20 mg once daily
Doses for SLE treatments must be stable for ≥ 2 weeks (corticosteroids) or ≥ 4 weeks (non-corticosteroid treatments)	

Other protocol-defined inclusion/exclusion criteria apply.
ANA, antinuclear antibody; BILAG A or B, British Isles Lupus Assessment Group A severe arthritis (active synovitis in ≥ 6 joints) or B moderate arthritis (active synovitis in ≥ 3 joints); dsDNA, double-stranded DNA; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, SLE International Collaborating Clinics.

Figure 1. Study design



[a]Modified BILAG A severe arthritis (active synovitis in ≥ 6 joints) or BILAG B moderate arthritis (active synovitis in ≥ 3 joints); impairment of activities of daily living.

Table 2. Study endpoints

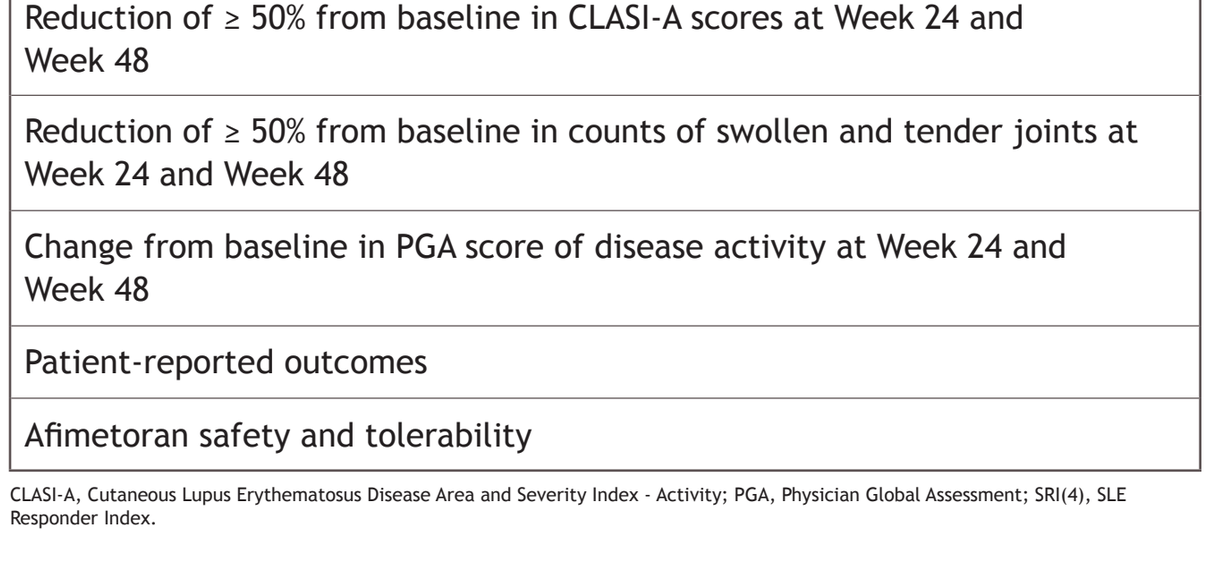
Primary endpoint
Response rate per the SRI(4) at Week 48
Secondary endpoints
SRI(4) response with corticosteroid reduction and maintenance to ≤ 7.5 mg per day at Week 48
BILAG-based Composite Lupus Assessment response at Week 24 and Week 48
Reduction of ≥ 50% from baseline in CLASI-A scores at Week 24 and Week 48
Reduction of ≥ 50% from baseline in counts of swollen and tender joints at Week 24 and Week 48
Change from baseline in PGA score of disease activity at Week 24 and Week 48
Patient-reported outcomes
Afimetoran safety and tolerability

CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index - Activity; PGA, Physician Global Assessment; SRI(4), SLE Responder Index.

Enrollment

- Enrollment is ongoing or is planned in 131 sites across 17 countries (**Figure 2**)

Figure 2. Participating countries



Accurate as of 2 September, 2022.

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