SUPPLEMENTAL RESULTS

Baseline characteristics part 1 and part 2

In part 1, the demographic and baseline characteristics were similar between the pooled placebo group and the pooled BIIB059 group. The mean age was 35.5 years (median 34 years), with 57% of subjects being male and 59% white. Mean weight was 75.2 kg, and mean BMI 24.7 kg/m^2 (Table 1). Baseline mean height was 174.38 cm.

For patients with SLE in part 2, baseline demographic characteristics were similar between the placebo group and the BIIB059 treatment arm. The mean age was 41.8 years (median 33.5 years), with 100% of subjects being female and 67% white. Baselinemean weight was 70.46 kg, and mean BMI 25.38 kg/m^2. Subjects in part 2 of the study were diagnosed with the following 1997 ACR classification criteria for SLE: malar rash (7 [58%] subjects), discoid rash (12 [100%] subjects), photosensitivity (9 [75%] subjects), oral ulcers (5 [42%] subjects), arthritis (11 [92%] subjects), pleuritis (1 [8%] subject), persistent proteinuria (2 [17%] subjects), hematological disorder (4 [33%] subjects), anti-dsDNA (1 [8%] subject), anti-Smith (2 [17%] subjects), and ANA (12 [100%] subjects)(Supplemental Table 3).

Based on the defined CLASI-A severity scale, with activity scores of 0–9 indicating mild disease, 10–20 indicating moderate disease, and 21–70 indicating severe disease (37), patients presented with mild to severe skin disease. Mean CLASI-A score at baseline was 16.3± 19.2 and 10.4 ± 5.4 in the placebo- and BIIB059-treated group, respectively.

Patients presented with mild to moderate active SLE manifestations, mean SLEDAI-2K score at baseline was 7.5 ±3.4 and 5.9±4.7 in the placebo- and BIIB059-treated group, respectively, with manifestations that included: rash (12 [100%] patients), alopecia (7 [58%] patients), arthritis (3 [25%] patients), vasculitis (2 [17%] patients), low complement (2 [17%] patients), anti-dsDNA Ab (1 [8%] patient), mucosal ulcer (1 [8%] patients), leukopenia (1 [8%] patient) and pleurisy (1 [8%] patient).

Of the 3 subjects who had arthritis at baseline based on SLEDAI-2 K (placebo: patient 1, BIIB059 patients 6 and 10), none improved at week 4 or week 12. Of the 2 patients who had vasculitis (placebo: patient 2 and BIIB059: patient 12), improvement occurred at week 4 but was not sustained at the subsequent time points. The number of patients with extra-cutaneous manifestations was extremely low precluding any meaningful conclusions of the global impact of BIIB059 treatment. The efficacy of BIIB059 in SLE patients with arthritis and cutaneous

manifestations is currently being evaluated in a larger phase 2 study (NCT02847598) and will inform on its potential efficacy on systemic manifestations.

Serious adverse events in patients with SLE receiving a single dose (part 2)

Listing and respective timing of the 9 SAEs that were reported in 1 patient with SLE in part 2 (single dose of 20 mg/kg BIIB059): dyspnea due to non-cardiac chest pain on day 77, gastritis secondary to prednisone used on day 78, moderate–severe anemia on day 123, intermittent leukopenia on day 123, acute respiratory distress on day 128, subarachnoid hemorrhage on day 128, fungemia on day 134, cerebral vasospasm on day 135, Clostridium difficile colitis on day 150. None of the events were considered to be related to the study treatment by the investigator.

Supplemental Materials and methods

Study design and conduct

Subjects were randomized to treatment based on a randomization list generated by an external Clinical Research Organization. Subjects were randomized and registered on Day 1, after all baseline assessments had been completed and after the Investigator had verified subject eligibility. No subject began treatment prior to randomization, registration, and assignment of a unique subject identification number. Any subject identification numbers that were assigned were not reused even if the subject did not receive treatment. A subject was considered enrolled at the time of consent. Subjects were randomized on Day 1: In Part 1, healthy volunteers were randomized to receive BIIB059 or placebo in a 2:1 (Cohorts 1 and 2) or a 3:1 (Cohorts 3 to 7) ratio; in Part 2 (Cohort 8), SLE subjects were randomized in a 2:1 ratio to BIIB059 or placebo.

Study subjects, site investigators, and study site staff were blinded to the randomized study treatment assignments with the exception of the unblinded Pharmacist or designee who was responsible for preparing the study treatments. Biogen staff or representative (e.g. clinical research organization) were also blinded to the randomized study treatment assignments, with the exception of the following individuals: the Biogen Global Safety Officer, who was unblinded

at the time of safety data review for dose escalation, and the designated representative from Clinical Pharmacology and Translational Sciences, who did not participate in the dose escalation safety data review and was only unblinded to PK and PD data.

This study was conducted from 20 February 2014 to 04 January 2016. All subjects in Part 1 were enrolled at one site in Florida. The first dose of study drug was administered on 07 April 2014. The last subject's final study visit was on 06 January 2015. Subjects in Part 2 were enrolled to 3 sites; 9 subjects to a Florida site, 2 subjects to a New York site, and 1 subject to an Alabama (Anniston) site. The first dose of study drug was administered on 03 December 2014. The last subject's final study visit was on 11 January 2016, although an Extended Follow-Up Period was conducted to monitor SAEs and AEs of interest by telephone.

Dose escalation

Dose escalation in Part 1 only occurred after review of safety data through the Week 2 Visit from subjects in the preceding cohort by the Biogen safety team. Following review of emerging safety data collected from healthy volunteers in Cohorts 1 to 6 (Part 1) through the Week 2 Visit, the Biogen safety team recommended 20 mg/kg BIIB059 be used in Part 2 of the study.

Study Stopping Rules

Dose Suspension

If 1 SAE occurred in a subject receiving BIIB059, further dosing was to be suspended pending full evaluation by the safety team. If deemed necessary based on emerging safety and potentially PK data (e.g., dose not tolerated), a lower dose could have replaced the planned dose of the current or subsequent cohort. Dosing of the cohort could not resume until Biogen completed the safety evaluation and the Investigator received written approval from Biogen to resume dosing.

Dose Termination

Further dosing at the current level and dose escalation were to be terminated, either at the determination of the SST or if the following was observed: a single life-threatening SAE or 2 or more SAEs occurring in subjects receiving BIIB059 in the same cohort, unless clearly unrelated to BIIB059 (e.g., motor vehicle accident).

Interferon Response Gene (IRG) Score:

The arithmetic mean of the final normalized ΔCt for a given set of IFN inducible genes was calculated and designated as the IRG score. In order to further minimize missing values in the IRG scores, any genes that had missing values for >20% of samples were not included in IRG score calculations. To categorize the SLE patients' samples into IFN-high and IFN-low groups, each sample was compared with the average IRG scores of the control samples from 52 healthy volunteers with similar distribution of age, gender, and ethnicity to the patients with SLE. Specifically, when the IFN gene signature score for a given sample was 2 SD above the average of the control samples (≥ mean + 2 SD), the samples were categorized as IFN high; if IFN gene signature score was within 2 SD of the control samples or lower (< mean + 2 SD), as IFN low. Pearson's correlation was calculated between the IFN gene signature score on the basis of 9 genes (IFN.9) and other versions of IFN signature scores.

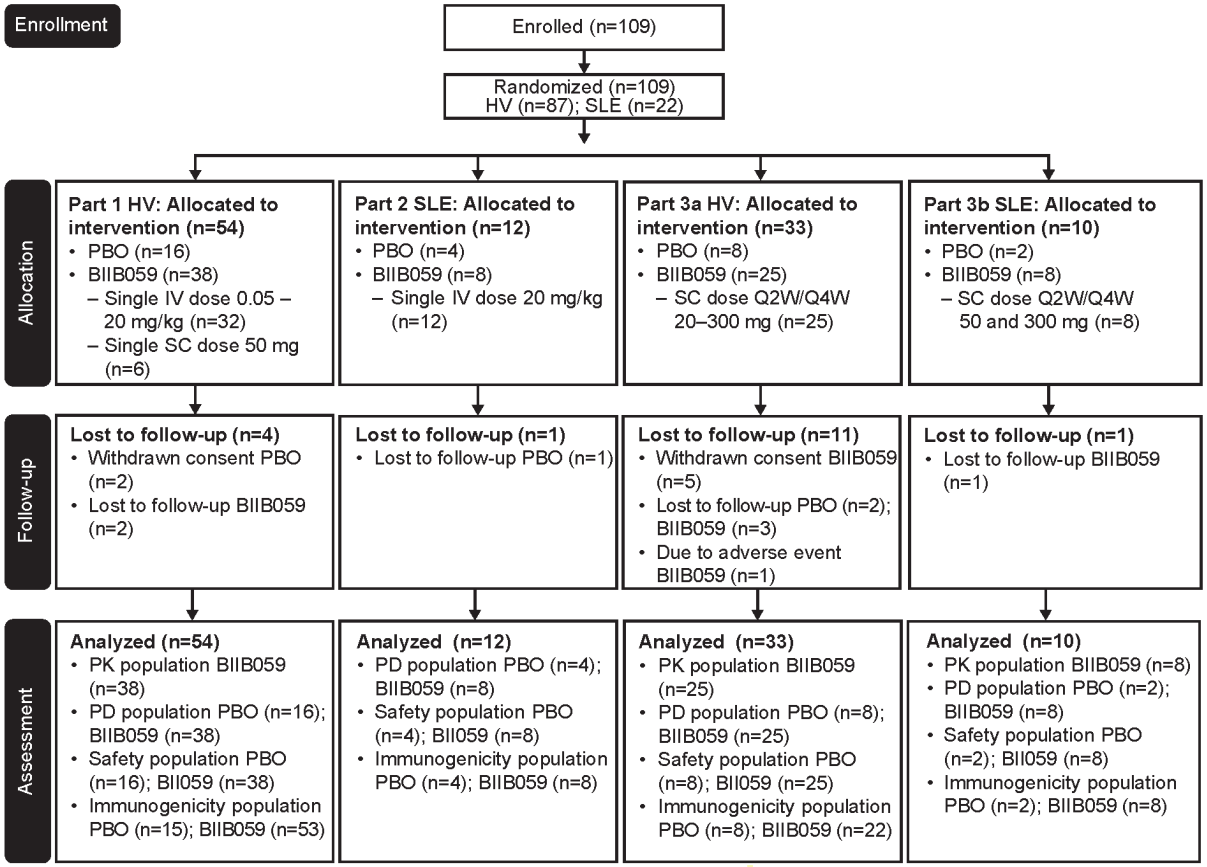
PBMC and pDC isolation and stimulation:

Whole human blood was collected in sodium heparin tubes. PBMCs were isolated using a ficoll plaque plus gradient, washed twice with PBS. PDCs were isolated from PBMC preparation using the Diamond pDC Isolation Kit II (Miltenyi) according to the manufacturer's protocol. In brief, isolation of pDCs was performed in a two-step procedure. First, all non-pDC cells were magnetically labeled with a cocktail of biotin-conjugated antibodies and anti-biotin MicroBeads for depletion. In the subsequent positive selection step, the enriched pDC fraction was directly magnetically labeled with CD304 (BDCA-4/Neuropilin-1) MicroBeads.

PBMC and pDCs were both suspended in RPMI 1640 media containing 10% FBS, HEPES, penicillin, streptomycin, L-glutamine and non-essential amino acids and stimulated with 1 μM of CpG-A (Invivogen) with or without 10 μg/mL of BIIB059 or isotype control. Supernatants were collected after 18 hours and evaluated by ELISA for IL-6 (R+D), IFNα (PBL Interferon source), IFNλ1 (LEGEND MAX™, Biolegend). The concentration of TNFα, CCL2, CCL3, CCL4 and CCL5 was measured using a human cytokine/chemokine multiplex magnetic panel (Luminex; EMD Millipore) according to the manufacturer's instruction.

SUPPLEMENTAL FIGURES

Supplemental Figure 1. CONSORT diagram for the 230LE101 phase I randomized clinical trial. A total of 109 eligible patients were randomized, and none were excluded; 87 healthy volunteers (HV) and 22 patients with systemic lupus erythematosus (SLE) were enrolled into the study, with 79 subjects receiving BIIB059 and 30 subjects receiving placebo (PBO). PK, pharmacokinetic, PD, pharmacodynamic; Q2W, every 2 weeks; Q4W, every 4 weeks

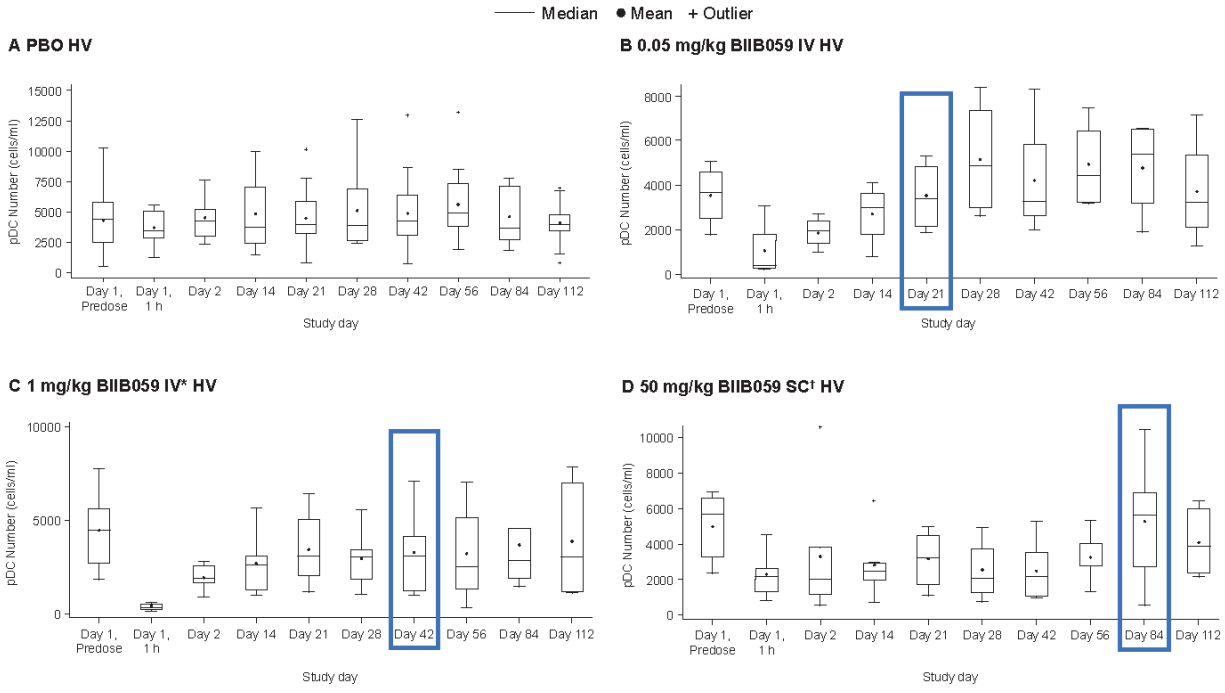


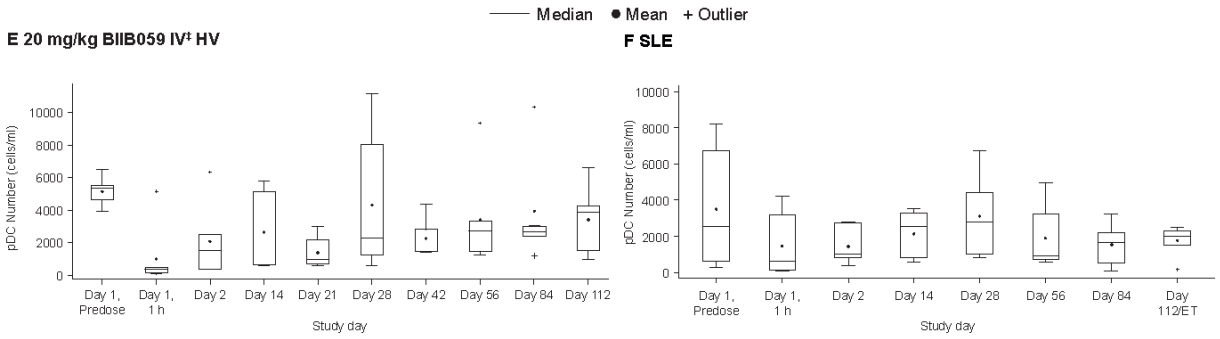
Supplemental Figure 2. BIIB059 treatment leads to transient decrease in circulating plasmacytoid dendritic cells (pDCs). The pDC population ($CD123^+$ $HLA\text{-}DR^+$) was identified in whole blood of HV (panels A-E) or SLE cohort (panel F) using Trucount™ beads. The horizontal line inside each box indicates the median pDC number. The bottom and top edges of the box indicate the interquartile range (IQR) of the pDC number and the filled circle inside indicates the mean pDC value. The whiskers of the box are drawn from the box to the most extreme points less than or equal to 1.5 times the IQR. Blue lines indicate the time of loss of pharmacodynamic effect (loss of target engagement and BDCA2 internalization). Panel G depicts the average pDC number and PK in HV and SLE cohort pre-dose and after treatment with a single dose of 20 mg/ kg BIIB059.

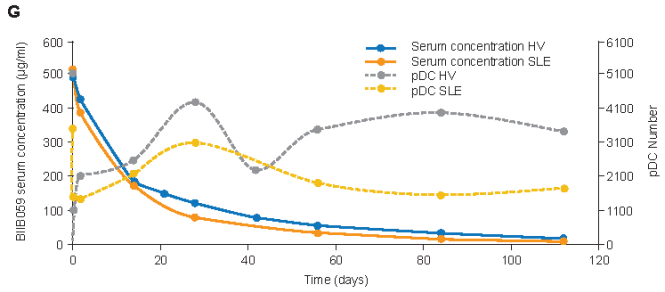
*One extreme value was recorded on day 84; the value was 12909 cells/ml.

†One extreme value was recorded on day 1, pre-dose; the value was 23,657 cells/ml. One extreme value was recorded on day 1, 1 h; the value was 26,338 cells/ml.

‡One extreme value was recorded on day 1, pre-dose; the value was 12,925 cells/ml. §Two extreme values were recorded on day 21; the values were 15,797 cells/ml and 27,487 cells/ml. One extreme value was recorded on day 42; the value was 14,311 cells/ml. All the extreme values were excluded from the analysis



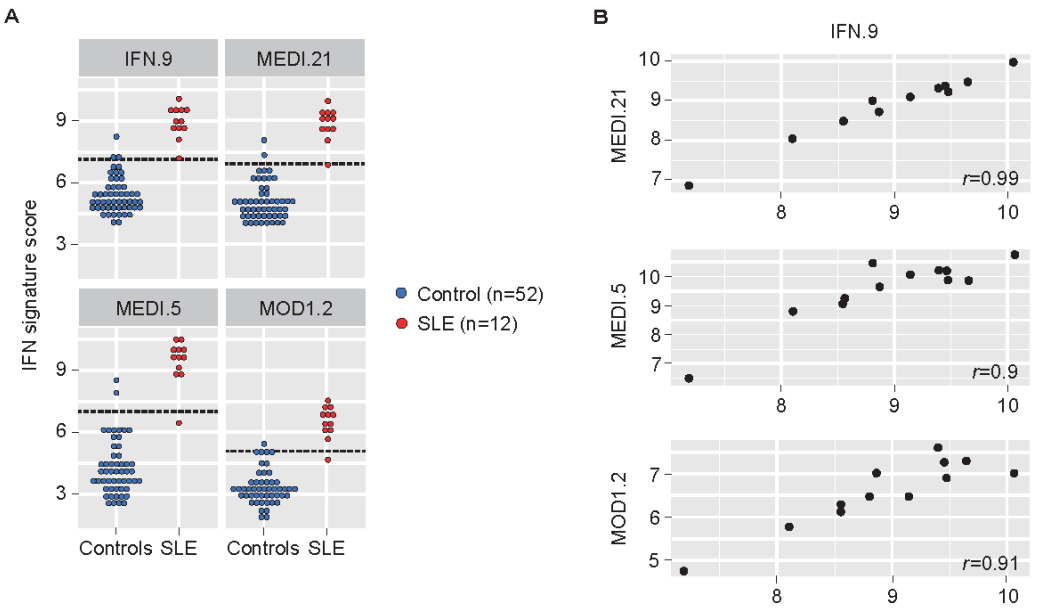

Median
Mean
+ Outlier
E 20 mg/kg BIIB059 IV‡ HV
F SLE
pDC Number (cells/ml)
Study day
Day 1, Predose
Day 1, 1 h
Day 2
Day 14
Day 21
Day 28
Day 42
Day 56
Day 84
Day 112
Day 112/ET


G
Serum concentration HV
Serum concentration SLE
pDC HV
pDC SLE
BIIB059 serum concentration (µg/ml)
pDC Number
Time (days)

Supplemental Figure 3. Selection of IFN response gene (IRG) signature and determination of cutpoint of IFN-high group. (**A**) Baseline IRG scores for patients with systemic lupus erythematosus (SLE) compared with HV for different versions of IRG scores (dotted lines are the threshold for IFN high and are determined as 2 SD above the mean of the IRG scores for the 52 healthy controls). (**B**) Correlation between IFN scores based on the 9 selected IRGs compared with other versions of IRG scores for patients with SLE at baseline (*r* is the Pearson's correlation). (**C**) Gene lists for different versions of IRG scores.

†Indicates genes with missing data in >20% of samples that were removed from the gene signature score calculation.

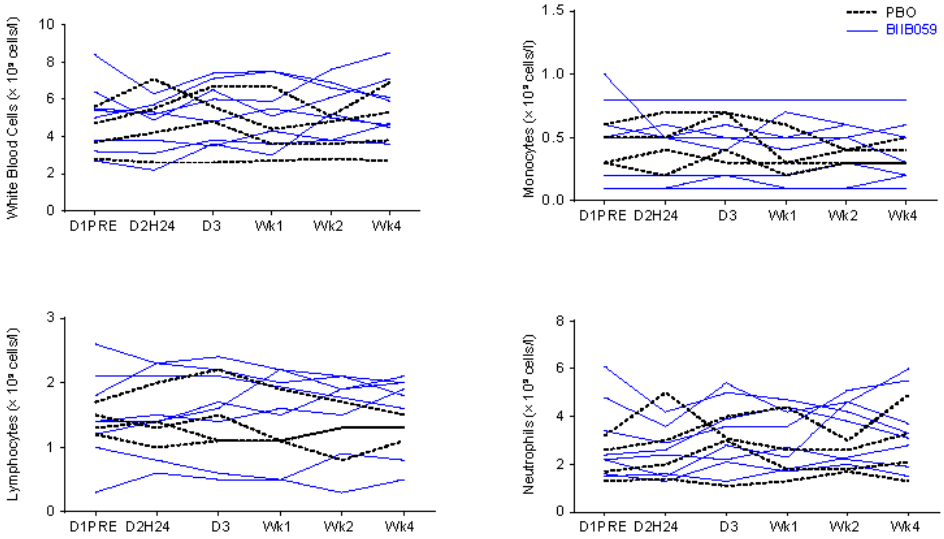
Chaussabel D et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity* 2008; 29(1):150–164.



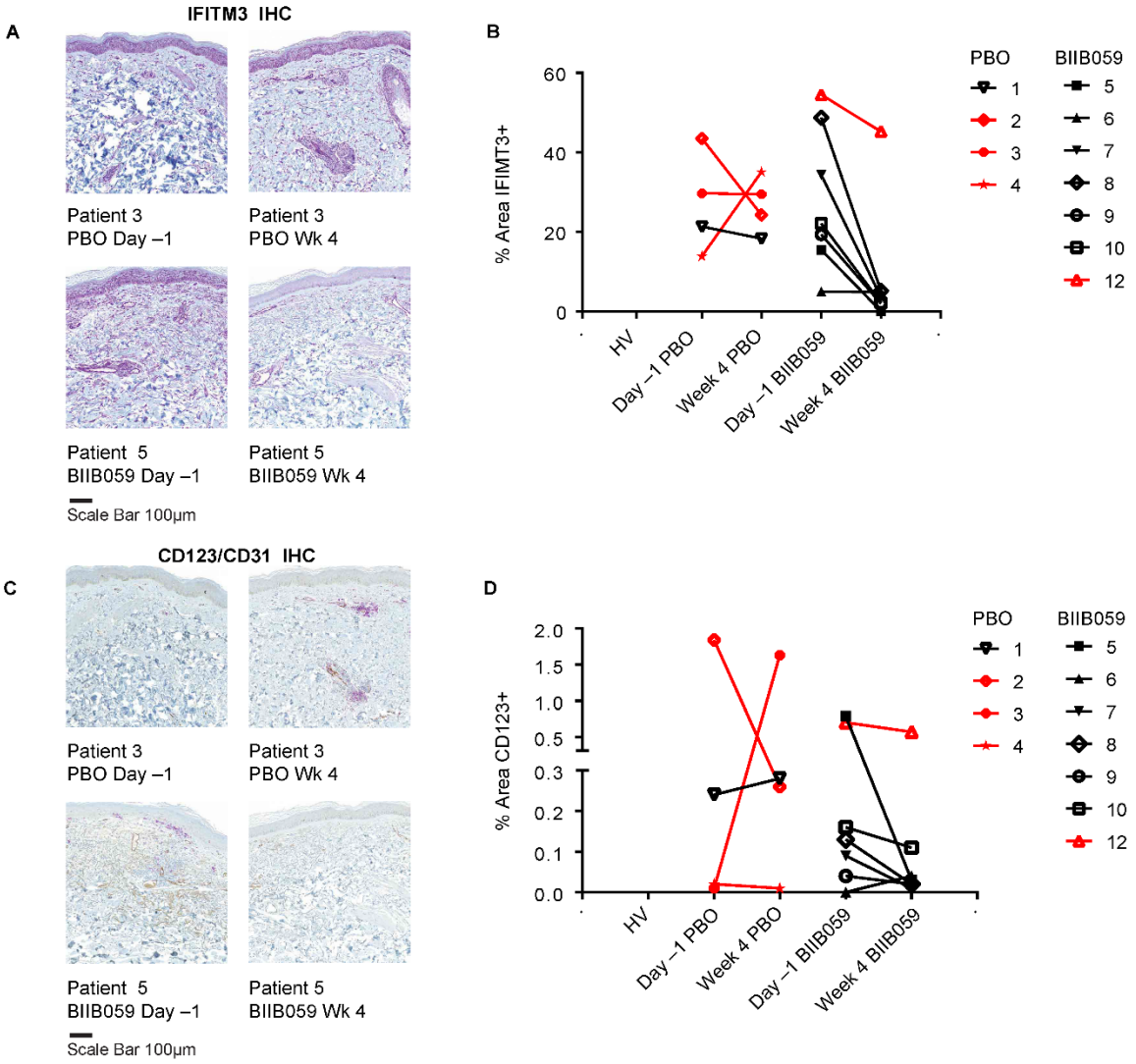
C

IRG scores	IFN-responsive genes
IFN.9	*IFI44*†, *IFI44L*, *IFIT1*, *IFIT3*, *MX1*, *OAS1*, *OAS2*, *OAS3*, *PLSCR1*
MEDI.21	*EPSTI1*, *G1P2*, *HERC5*, *IFI27*, *IFI44*†, *IFI44L*, *IFI6*, *IFIT1*, *IFIT3*, *LY6E*, *MX1*, *OAS1*, *OAS2*, *OAS3*, *PLSCR1*, *RSAD2_415*, *RTP4*, *SIGLEC1*†, *USP18*
MEDI.5	*IFI27*, *IFI44*†, *IFI44L*, *IFI6*, *RSAD2_415*
Selected genes from Chaussabel et al. MOD1.2	*IFI44*†, *XAF1*, *SPATS2L*†

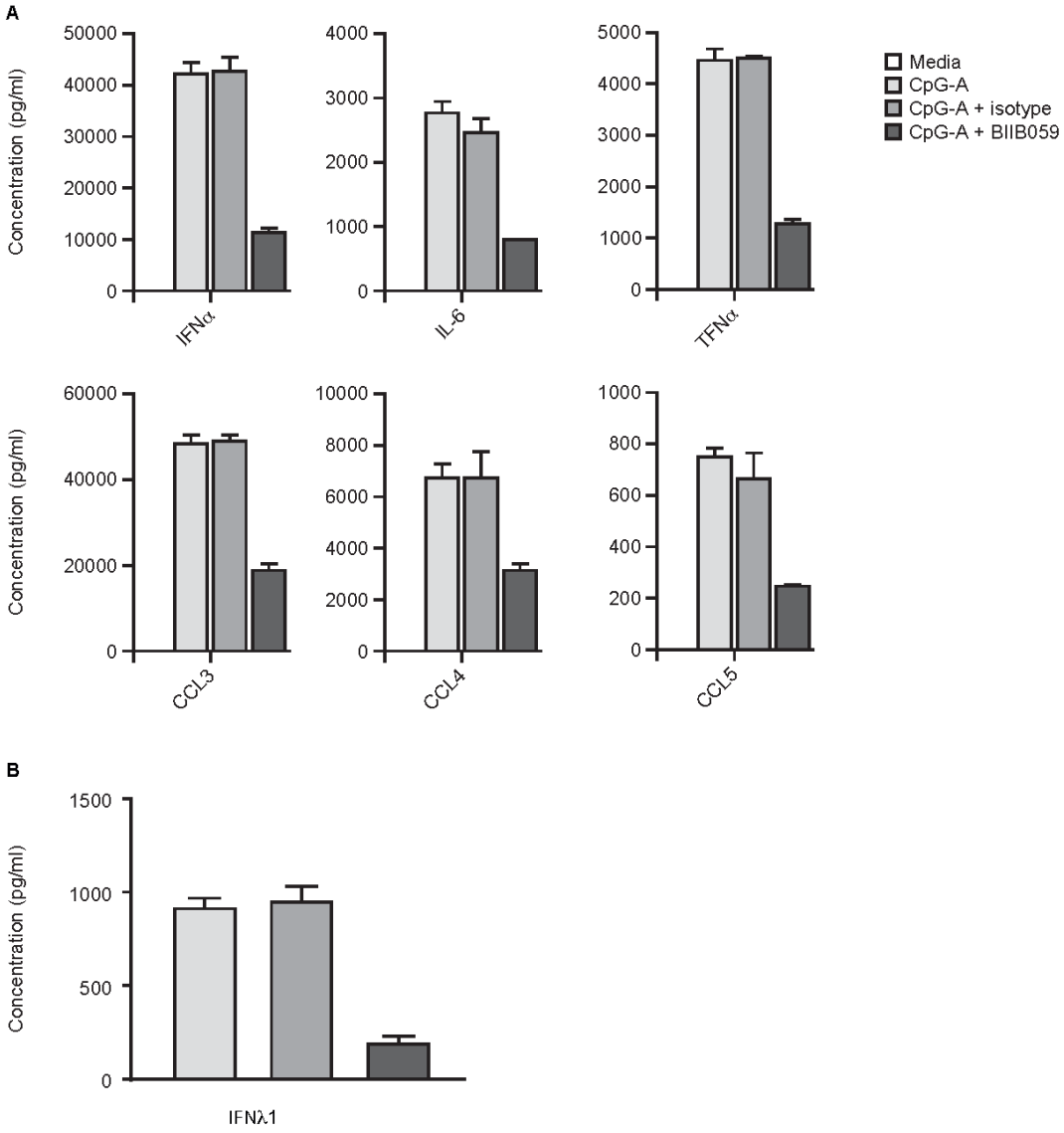
Supplemental Figure 4. BIIB059 treatment does not impact the immune cell counts in patients with SLE. Whole blood was collected on different time points (Pre-dose, 24 hours, 3 days, and weeks 1, 2, and 4 post-dose). White blood cells (WBC) count (top left panel), and differential cell count of monocytes (top right panel), lymphocytes (lower left panel) and neutrophils (lower right panel) were performed using an automated cell counter. Placebo (PBO); dotted black lines; BIIB059 treated (BIIB059) (the solid blue lines).



Supplemental Figure 5. BIIB059 reduces IFN responsive protein, IFITM3, and pDC numbers in skin lesions of patients with SLE. Representative photomicrographs of IHC of (A) IFITM3 and (C) CD123. CD123 immunoreactivity was quantified by first excluding pixels immunopositive with CD31 to differentiate capillaries from pDCs. Patient 3 pre-dose (top left panel), week 4 post-placebo (PBO) (right top panel), pre-dose patient 5 (lower left panel), week 4 post-BIIB059 (lower right panel). Percent area of immunoreactivity of IFITM3 protein (B) and CD123 (D) in PBO and BIIB059-treated patients pre-dose (day -1) and 4 weeks post-dose. For CD123 immunopositive area, values below 0.1% are approaching the sensitivity threshold with fewer than ~20 pDCs in the papillary dermis in the single plane of section quantified. CLASI-A responders are depicted with a black line, non-responders with a red line.



Supplemental Figure 6. BIIB059 inhibits plasmacytoid dendritic cell (pDC)-derived cytokines, and chemokines and IFNλ1. A, pDCs from human healthy donors were isolated using a 2-step magnetic bead separation procedure (MACS kit, Miltenyi Biotech). 5×10^4 purified human pDCs/well were left untreated (Media) or were stimulated with 1 µM TLR9 ligand (CPG-A) in the presence of either 10 µg/ml of BIIB059 mAb (CpG-A + BIIB059) or isotype control antibody (CpG-A + isotype). The plates containing pDCs were incubated for 18 hours at 37°C and 5% CO_2, and supernatants were collected for use in ELISA or multiplex assays to measure concentrations of inflammatory cytokines and chemokines. Each bar represents the mean for duplicate wells from a representative healthy human donor out of 5 tested. **B:** PBMC from human healthy donors were isolated and $1X10^6$ cells were plated in triplicate and stimulated with 1µM TLR9 ligand (CpG-A) in the presence of either 10 µg/mL of BIIB059 mAb (CpG-A + BIIB059) or isotype control antibody (CpG-A + isotype). Following 18 hours at 37°C and 5% CO2 supernatants were collected and IFNλ1 (IL-29) was measured by ELISA (Biolegend). Shown is a representative healthy human donor out of 3 tested. Vertical lines depict the standard deviation (SD).


A
Concentration (pg/ml)
50000
40000
30000
20000
10000
0
IFNα
4000
3000
2000
1000
0
IL-6
5000
4000
3000
2000
1000
0
TFNα
Media
CpG-A
CpG-A + isotype
CpG-A + BIIB059
60000
40000
20000
0
CCL3
10000
8000
6000
4000
2000
0
CCL4
1000
800
600
400
200
0
CCL5
B
1500
1000
500
0
IFNλ1

SUPPLEMENTAL TABLES

Supplemental Table 1. Study design

Part	Cohort	Dose (route)	Planned subjects, N (BIIB059:placebo)	Enrolled subjects, N (BIIB059:placebo)	Study population
1	1	0.05 mg/kg (i.v.)	6 (4:2)	7 (4:3)	HV
	2	0.3 mg/kg (i.v.)	6 (4:2)	6 (4:2)	
	3	1 mg/kg (i.v.)	8 (6:2)	8 (6:2)	
	4	3 mg/kg (i.v.)	8 (6:2)	8 (6:2)	
	5	10 mg/kg (i.v.)	8 (6:2)	8 (6:2)	
	6	20 mg/kg (i.v.)	8 (6:2)	8 (6:2)	
	7	50 mg (s.c.)	8 (6:2)	9 (6:3)	
2	8	20 mg/kg (i.v.)	12 (8:4)	12 (8:4)	SLE

HV, healthy volunteers; SLE, patients with systemic lupus erythematosus.

Supplemental Table 2. Summary of Safety of Single Dose in HV (Part 1) and Single Dose in SLE (Part 2)

Event, n (%)	Part 1: Single dose in HV		Part 2: Single Dose in SLE	
	Placebo	≤20 mg/kg	Placebo	20 mg/kg
Dosed	16	38	4	8
With any AE	4 (25)	16 (42)	3 (75)	7 (88)
Upper respiratory tract infection	0	3 (8)	0	3 (38)
Headache	1 (6)	2 (5)	0	0
Nausea	1 (6)	2 (5)	0	0
Laceration	0	2 (5)	0	0
Streptococcal pharyngitis	0	2 (5)	0	0
Viral upper respiratory tract infection	0	2 (5)	0	0
Diarrhea	0	0	0	2 (25)
Gastritis	0	0	0	2 (25)
Non-cardiac pain	0	0	0	2 (25)

Preferred term of most frequent AE reported in Placebo and BIIB059-treated subject from part 1 (HV) and part 2 (patients with SLE).
AE, adverse event; HV, healthy volunteer; SLE, systemic lupus erythematosus

Supplemental Table 3: SLE patients in Part 2- Summary of 1997 ACR classification criteria for SLE at diagnosis

	Placebo	BIIB059 IV 20 mg/kg	Total
Number of patients dosed	4	8	12
ACR Criteria n (%)			
Malar Rash	2 (50)	5 (63)	7 (58)
Discoid Rash	4 (100)	8 (100)	12 (100)
Photosensitivity	4 (100)	5 (63)	9 (75)
Oral Ulcers	2 (50)	3 (38)	5 (42)
Arthritis	4 (100)	7 (88)	11 (92)
Serositis	0	1 (13)	1 (8)
Pleuritis	0	1 (13)	1 (8)
Pericarditis	0	0	0
Renal disorders	0	2 (25)	2 (17)
Persistent proteinuria	0	2(25)	2(17)
Cellular casts	0	0	0
Neurologic disorders	0	0	0
Seizures	0	0	0
Psychosis	0	0	0
Hematologic disorder	1 (25)	3 (38)	4 (33)
Hemolytic anemia	1 (25)	2 (25)	3 (25)
Leukopenia	0	1 (13)	1 (8)
Lymphopenia	0	1 (13	1 (8)
Thrombocytopenia	0	0	0
Immunologic disorder	0	2 (25)	2 (17)
Anti-dsDNA	0	1 (13)	1 (8)
Anti-Smith	0	2 (25)	2 (17)
Antiphospholipid antibodies	0	0	0
Antinuclear antibody (ANA)	4 (100)	8 (100)	12 (100)