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APPLICATION NUMBER:

761123Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761123
Priority or Standard	Standard
Submit Date(s)	July 22, 2020
Received Date(s)	July 31, 2020
PDUFA Goal Date	July 31, 2021
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)
Review Completion Date	See electronic stamp
Established/Proper Name	anifrolumab-fnia
(Proposed) Trade Name	Saphnelo
Pharmacologic Class	Type I interferon (IFN) receptor antagonist
Code name	MEDI-546
Applicant	AstraZeneca AB, c/o AstraZeneca Pharmaceuticals, L.P.
Dosage form	Injection
Applicant proposed Dosing Regimen	300 mg IV every 4 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with moderate to severe systemic lupus erythematosus (SLE) (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	55464009 – Systemic Lupus Erythematosus (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	55464009 – Systemic Lupus Erythematosus (disorder)
Recommended Dosing Regimen	300 mg IV every 4 weeks

Table of Contents

Table of Tables	v
Table of Figures	viii
Reviewers of Multi-Disciplinary Review and Evaluation	1
Glossary	6
1. Executive Summary	8
1.1. Product Introduction	8
1.2. Conclusions on the Substantial Evidence of Effectiveness	8
1.3. Benefit-Risk Assessment	13
1.4. Patient Experience Data	21
2. Therapeutic Context	22
2.1. Analysis of Condition	22
2.2. Analysis of Current Treatment Options	23
3. Regulatory Background	25
3.1. U.S. Regulatory Actions and Marketing History	25
3.2. Summary of Presubmission/Submission Regulatory Activity	25
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	29
4.1. Office of Scientific Investigations (OSI)	29
4.2. Product Quality	30
4.3. Clinical Microbiology	30
4.4. Devices and Companion Diagnostic Issues	30
5. Nonclinical Pharmacology/Toxicology	31
5.1. Executive Summary	31
5.2. Referenced NDAs, BLAs, DMFs	32
5.3. Pharmacology	32
5.4. ADME/PK	34
5.5. Toxicology	35
5.5.1. General Toxicology	35
5.5.2. Genetic Toxicology	37
5.5.3. Carcinogenicity	37
5.5.4. Reproductive and Developmental Toxicology	37
5.5.5. Other Toxicology Studies	39
6. Clinical Pharmacology	40
6.1. Executive Summary	40
6.2. Summary of Clinical Pharmacology Assessment	41
6.2.1. Pharmacology and Clinical Pharmacokinetics	41
6.2.2. General Dosing and Therapeutic Individualization	41
6.3. Comprehensive Clinical Pharmacology Review	41
6.3.1. General Pharmacology and Pharmacokinetic Characteristics	41
6.3.2. Clinical Pharmacology Questions	44
7. Sources of Clinical Data and Review Strategy	53
7.1. Table of Clinical Studies	53

7.2. Review Strategy	56
8. Statistical and Clinical and Evaluation	57
8.1. Review of Relevant Individual Trials Used to Support Efficacy	57
8.1.1. CD-IA-MEDI-546-1013 (Phase 2), D3461C00004 (Phase 3), and D3461C00005 (Phase 3).....	57
8.1.2. Study Results	73
8.1.3. Assessment of Efficacy Across Trials	108
8.1.4. Integrated Assessment of Effectiveness	109
8.2. Review of Safety.....	110
8.2.1. Safety Review Approach	110
8.2.2. Review of the Safety Database	114
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments	118
8.2.4. Safety Results.....	118
8.2.5. Analysis of Submission-Specific Safety Issues	136
8.2.6. Infections	136
8.2.7. Non-opportunistic serious infections.....	137
8.2.8. Opportunistic infections	138
8.2.9. Herpes Zoster	139
8.2.10. Tuberculosis (TB) including latent TB.....	141
8.2.11. Influenza	142
8.2.12. Anaphylaxis, hypersensitivity, and infusion-related reactions	142
8.2.13. Anaphylaxis.....	142
8.2.14. Hypersensitivity	143
8.2.15. Infusion-related reactions.....	144
8.2.16. Malignancies.....	145
8.2.17. MACE	146
8.2.18. Vasculitis (non-SLE).....	146
8.2.19. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	147
8.2.20. Safety Analyses by Demographic Subgroups	147
8.2.21. Specific Safety Studies/Clinical Trials	151
8.2.22. Additional Safety Explorations.....	151
8.2.23. Safety in the Postmarket Setting	153
8.2.24. Integrated Assessment of Safety	153
8.3. Statistical Issues	154
8.4. Conclusions and Recommendations.....	156
9. Advisory Committee Meeting and Other External Consultations.....	159
10. Pediatrics.....	160
11. Labeling Recommendations	162
11.1. Prescription Drug Labeling	162
12. Risk Evaluation and Mitigation Strategies (REMS).....	166
13. Postmarketing Requirements and Commitment.....	168
14. Division Director (Clinical) Comments.....	170
15. Office Director (Signatory authority) Comments.....	172

16. Appendices.....	173
16.1. References	173
16.2. Financial Disclosure.....	173
16.3. Nonclinical Pharmacology/Toxicology.....	176
16.4. OCP Appendices (Technical documents supporting OCP recommendations)	179
16.4.1. Summary of Bioanalytical Assays.....	179
16.4.2. Population Pharmacokinetics	182
16.4.2.1. Structural Model.....	182
16.4.2.2. Covariate Effect.....	182
16.4.2.3. Conclusion.....	194
16.4.3. Exposure Response Relationship	194
16.4.3.1. Baseline demographics and disease characteristics.....	194
16.4.3.2. BICLA.....	197
16.4.3.3. SLE Responder Index.....	200
16.4.3.4. OCS Reduction and annualized flare rate.....	204
16.5. Additional Clinical Outcome Assessment Analyses	207

Table of Tables

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication	23
Table 2. Key activities leading to the changes to the primary endpoint and key secondary endpoints for study 04	26
Table 3. Summary of anifrolumab serum concentrations in SLE patients (Study 1013)	43
Table 4. Overview of anifrolumab clinical studies	45
Table 5. Summary of ADA responses in phase 3 studies 04 and 05	52
Table 6. Listing of Clinical Trials Relevant to this NDA/BLA	54
Table 7. Patient disposition (all randomized patients) in study 1013	74
Table 8. Patient disposition in studies 04 and 05	75
Table 9. Summary of study 1013 protocol deviations (10 total)	76
Table 10. Summary of study 04 protocol deviations	77
Table 11. Summary of study 05 protocol deviations	77
Table 12. Demographic characteristics for efficacy and safety analysis in the 3 studies submitted to support approval (studies 04, 05, and 1013)	78
Table 13. Baseline SLE disease characteristics in the 3 studies submitted to support approval (studies 04, 05, and 1013)	79
Table 14. Baseline SLEDAI-2K organ system involvement in Studies 04, 05 and 1013	81
Table 15. SLE-related SOC treatments at baseline in study 1013	82
Table 16. SLE-related SOC treatments at baseline in studies 04 and 05	82
Table 17. Data capture at week 24 and week 52 for study 1013	84
Table 18. Data capture at week 52 for study 05	84
Table 19. Data capture at week 52 for study 04	85
Table 20. Study 1013: SRI-4 + OCS tapering response at week 24 in whole population and type I IFN test high patients	85
Table 21. Study 1013: SRI-4 response at week 24 in whole population	86
Table 22. Study 1013: SRI-4 response at week 24 in type I IFN test high patients	87
Table 23. Study 1013: SRI-4 response at week 52 in whole population	87
Table 24. Study 1013: BICLA response at week 52 in whole population	88
Table 25. Study 05: SRI-4 response at week 52: Primary and post-hoc analyses	88
Table 26. Study 05: BICLA response at week 52	89
Table 27. Study 04: BICLA response at week 52: Primary analyses	90
Table 28. Study 04: SRI-4 response at week 52	90
Table 29. Study 04: BICLA response at week 52 excluding sites 7815 and 7834	91
Table 30. Study 1013: Tipping point scenarios for SRI-4 + OCS tapering response at week 24 ..	92
Table 31. Study 1013: Tipping point scenarios for BICLA response without tapering at week 52	93
Table 32. Study 05: Tipping point scenarios for BICLA response at week 52	95
Table 33. Study 04: Tipping point scenarios for BICLA response at week 52	96
Table 34. Study 1013: Exploratory Secondary Endpoints	97
Table 35. Study 1013: Annual flare rate through Day 365	98

Table 36. Study 05: Pre-specified key secondary endpoints	99
Table 37. Study 05: Annual flare rate through week 52	99
Table 38. Study 05: Post-hoc analysis of secondary endpoints under study 04 rules.....	101
Table 39. Study 04: Pre-specified key secondary endpoints	102
Table 40. Study 04: Annual flare rate through week 52	102
Table 41. Individual Studies Contributing to Safety Review	110
Table 42. Summary of Safety Pools for Integrated Assessment of Safety	111
Table 43. Identification and definition of adverse events of special interest (AESIs)	112
Table 44. Safety Population, Size and Denominators for anifrolumab (any dose) in SLE	114
Table 45. Safety, Population, Size and Denominators for anifrolumab 300 mg in SLE	115
Table 46. Duration of exposure in Primary (studies 04 & 05) and Supportive (1013, 04 & 05) pools	116
Table 47. Phase 3 PC Long-Term Safety Duration of Exposure (with 120-day safety update)...	117
Table 48. Summary of all deaths occurring during the anifrolumab SLE development program	120
Table 49. Summary of Deaths by Cause and AE contributing to death	121
Table 50. Serious Adverse Events during the 52-week treatment period by PT in ≥2 patients in the anifrolumab 300 mg group--Studies 1013, 04, & 05	122
Table 51. Phase 3 Long-Term Extension—Serious Adverse Events During Treatment by Time Interval.....	123
Table 52. Adverse Events leading to discontinuation of IP during treatment by SOC and PT—52- week safety (studies 1013, 04, and 05)	124
Table 53. Phase 3 LTE (including 120-day safety update) for DAE Nervous system disorders...	126
Table 54. Severe AEs by SOC/PT for common AEs (>5%) reported during 52-week study period (studies 1013, 04 and 05).....	127
Table 55. Severe AEs by SOC/PT for common AEs (>5%) reported during phase 3 LTE (including 120-day safety update)	128
Table 56. Adverse events reported in > 2% of patients during treatment, by PT—52 week safety period (studies 1013, 04, and 05).....	129
Table 57. Hematology variables, potentially clinically meaningful treatment-emergent laboratory changes in phase 3 52-week data and phase 3 long-term safety (including 120-day safety update)	130
Table 58. Clinical Chemistry variables, potentially clinically meaningful treatment-emergent laboratory changes in phase 3 52-week data and phase 3 long-term safety (including 120-day safety update)	132
Table 59. Study 05 (compare 150 mg to 300 mg dose) Potentially Clinically Important Changes in Laboratory Parameters--Hematology	133
Table 60. Study 05 (compare 150 mg to 300 mg dose) Potentially Clinically Important Changes in Laboratory Parameters—Chemistry.....	134
Table 61. Infections and infestations during treatment, overall and by intensity—52-week data for studies 1013, 04 and 05.....	136
Table 62. Non-opportunistic serious infections during treatment during 52-week study period (studies 1013, 04 and 05).....	137

Table 63. Herpes zoster events during the 52-week study period (studies 1013, 04 and 05) ...	139
Table 64. Herpes zoster events during the phase 3 long-term study period	140
Table 65. Hypersensitivity events during the 52-week study period (studies 1013, 04 and 05)	143
Table 66. Infusion related reactions during the 52-week study period (studies 1013, 04 and 05)	144
Table 67. Malignancy by type during the 52-week study period (studies 1013, 04 and 05).....	145
Table 68. Comparison for infectious SAE and AESI in the phase 3 52-week safety pool for different baseline use of OCS and anifrolumab treatment	149
Table 69. Comparison for infectious SAE and AESI in the phase 3 52-week safety pool for different baseline use of Immunosuppressant and anifrolumab treatment	150
Table 70. Phase 3 (studies 04 and 05) 52-week treatment period data on depression SMQ (narrow)	152
Table 71. Calculated maximum human exposure of process-related impurities in drug substance for the MRHD of 300 mg anifrolumab/50 kg/28 days	176
Table 72. Bioanalytical methods for determination of anifrolumab concentrations in human serum	179
Table 73. Summary of the bioanalytical validation report CTVR-0059	180
Table 74. Summary of the bioanalytical validation reports REWL2 and REWL5	181
Table 75. Summary statistics of baseline patient characteristics by study and for the pooled dataset	183
Table 76. Summary statistics of baseline laboratory values by study and for the pooled dataset	184
Table 77. Baseline SLE disease characteristics by study and for the pooled dataset.....	185
Table 78. SLE-related treatment at baseline by study and dose group	185
Table 79. Summary of parameters from the final PK model with time-varying linear clearance	186
Table 80. Baseline demographics and disease characteristics in ITT	194
Table 81. Baseline demographics and disease characteristics in patients who completed treatment.....	195
Table 82. Baseline demographics and disease characteristics in Completer with type I IFN gene signature high	196
Table 83. Logistics regression of BICLA response at week 52 parameter estimates in type I IFN gene signature test high patients who completed treatment (full exposure-response analysis set)	198
Table 84. Logistics regression of SRI(4) response at week 52 parameter estimates in all patients who completed treatment (full exposure-response analysis set)	201
Table 85. Logistics regression of SRI(4) response at week 52 parameter estimates type I IFN test high patients who completed treatment (full exposure response analysis set)	203

Table of Figures

Figure 1. Model-predicted concentration-time profiles of anifrolumab 100, 150, 300, and 1000 mg after a single dose IV administration by type I IFN test status (typical weight of 70 kg)	42
Figure 2. Mean predose anifrolumab serum concentration-time profiles by baseline type I IFN gene signature test and by treatment group (Study 1013)	43
Figure 3. Type I IFN gene signature as percent of baseline in SLE patients with high type I IFN gene signature at baseline (studies 1013, 04, and 05)	47
Figure 4. BICLA and SRI(4) response rates at week 52 vs. median neutralization of the type I IFN gene signature in type I IFN test high patients from anifrolumab 150 and 300 mg in studies 04 and 05	47
Figure 5. SRI(4) response rate without OCS tapering requirement (study 1013)	49
Figure 6. Exposure response (BICLA) relationship in patients with type I IFN gene signature test high who completed treatment	49
Figure 7. Exposure response (SRI(4)) relationship in patients who completed treatment	50
Figure 8. Design for study 1013.....	59
Figure 9. Design for study 05.....	61
Figure 10. Design for Study 04	62
Figure 11. Study 05 Alpha Recycling for Weighted Holm Procedure.....	65
Figure 12. Study 04 Alpha recycling for Weighted Holm procedure.....	66
Figure 13. Pooled Studies 04 and 05: Cumulative distribution function of FACIT-F score change from baseline at Week 52, by treatment arm	73
Figure 14. Forest plot of subgroup analyses for study 1013.....	104
Figure 15. Forest plot of subgroup analyses for study 05.....	105
Figure 16. Forest plot of subgroup analyses for study 04.....	106
Figure 17. SLEDAI-2K over time in study 05	107
Figure 18. SLEDAI-2K over time in study 04	107
Figure 19. SLEDAI-2K over time in study 1013.....	107
Figure 20. Anifrolumab PK Model	182
Figure 21. Individual clearance by weight categories.....	187
Figure 22. Body weight-adjusted CL stratified by sex and baseline type I IFN status	187
Figure 23. CL stratified by region and ethnicity and baseline type I IFN status	188
Figure 24. Body weight-adjusted CL stratified by race, by Japanese and South Korean patient populations, and baseline type I IFN status.....	188
Figure 25. Effect of renal function (eGFR and CLcr) on clearance	189
Figure 26. Effect of hepatic function (AST, ALT, total bilirubin, albumin) on clearance.....	189
Figure 27. Individual CL versus ADA status in SLE patients from studies 1013, 02, 04, and 05..	190
Figure 28. Standardized random effects plots of background medications on CL.....	191
Figure 29. Individual weight-adjusted CL to 69.1 kg versus mizoribine in studies 1013, 02, 04, 05, and 06 (post-hoc analysis).....	192

Figure 30. Individual CL versus NSAIDs, ACE inhibitors, and HMG-CoA reductase inhibitors in studies 1013, 04, and 05 (post-hoc analysis).....	193
Figure 31. Percent of patients completed the study by treatment and exposure quartiles	197
Figure 32. Predicted BICLA response rate at week 52 in patients with type I IFN gene signature test high who completed treatment (full exposure response analysis set)	198
Figure 33. Reviewer’s assessment of exposure response (BICLA) in patients with type I IFN gene signature test high who completed treatment	199
Figure 34. Reviewer’s assessment of exposure response (BICLA) in all the patients.....	199
Figure 35. Reviewer’s assessment of exposure response (BICLA) in all the patients who completed treatment.....	200
Figure 36. Predicted SRI(4) response rate at week 52 in patients who completed treatment (full exposure-response analysis set)	201
Figure 37. Reviewer’s assessment of exposure response (SRI(4)) relationship in patients who completed treatment.....	202
Figure 38. Predicted SRI(4) response rate at week 52 in patients with type I IFN gene signature test high who completed treatment (full exposure response analysis set)	202
Figure 39. Reviewer’s assessment of exposure response (SRI(4)) relationship in patients with type I IFN gene signature test high who completed treatment.....	203
Figure 40. Oral corticosteroid (OCS) reduction	204
Figure 41. BICLA response with oral corticosteroid reduction	205
Figure 42. SRI(4) response with oral corticosteroid reduction	205
Figure 43. Annualized flare rate	206

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OPQ=Office of Pharmaceutical Quality

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

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Saphnelo (anifrolumab-fnia) for adults with SLE

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Saphnelo (anifrolumab-fnia) for adults with SLE

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
Alpha-gal	galactose-alpha-1,3-galactose
AR	adverse reaction
AWC	adequate and well-controlled
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-suicide severity rating scale
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FACIT-F	Functional Assessment of Chronic Illness Therapy – FATIGUE
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IFNAR1	Type I interferon receptor
IND	Investigational New Drug
IRR	Infusion-related reaction

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
LTE	long-term extension
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MPPRC	Medical Policy and Program Review Council
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAIDs	non-steroidal anti-inflammatory drugs
OCS	Office of Computational Science
OCSs	oral corticosteroids
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase chain reaction
PD	pharmacodynamics
PHQ-8	Patient health questionnaire scale
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE disease activity index (updated in 2000)
SOC	standard of care
SRI-4	SLE Responder Index
TEAE	treatment emergent adverse event
UPCR	Urine protein/creatinine ratio

1. Executive Summary

1.1. Product Introduction

Anifrolumab (Saphnelo), a monoclonal antibody (mAb) that inhibits subunit 1 of the type I interferon receptor (IFNAR1), is a new biological product. The proposed indication is treatment of adults with moderate to severe systemic lupus erythematosus (SLE) (b) (4). The proposed dosing regimen is 300 mg every 4 weeks administered as an intravenous (IV) infusion.

1.2. Conclusions on the Substantial Evidence of Effectiveness

A 351 (a) biologics license application (BLA) is submitted by AstraZeneca AB for IV administration of anifrolumab for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4). SLE is a serious and potentially life-threatening disease that can impact any organ system. This disease can cause significant morbidity and mortality as well as impact patients' function and quality of life. The toxicities associated with both the approved drugs for SLE as well as off-label treatments commonly used to treat SLE contribute to the long-term morbidity and mortality observed in patients with SLE. Only one targeted therapy, belimumab, has been approved for SLE in the last 60 years.

To support the SLE indication, the Applicant provided results from two phase 3 studies, D3461C00004 (04) and D3461C00005 (05) and one phase 2 study, CD-IA-MEDI-546-1013 (1013). These studies evaluated anifrolumab IV 300 mg as well as two additional IV doses (150 mg and 1000 mg) in a total of 1,123 adults with active SLE on stable immunosuppressive background medications. From one phase 2 study (1013) and two phase 3 studies (04 & 05), 459 subjects were treated with the proposed dose of 300 mg IV compared to 468 subjects treated with placebo. Patients with severe active lupus nephritis or severe active central nervous system (CNS) lupus were excluded. In addition, cyclophosphamide and the use of other biologic agents were not permitted during the studies.

In all three studies, the SLE Responder Index (SRI-4) was originally selected as the primary endpoint, to establish efficacy. SRI-4 was included as the primary endpoint at week 24 in study 1013 and proposed as the primary endpoint at week 52 in study 05 and study 04. SRI-4 is a composite clinical endpoint to assess clinical response in SLE and has been successfully used to support the approval of belimumab. All three studies included the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) endpoint. The review team notes that BICLA and SRI-4 are both considered clinically meaningful endpoints for evaluating a treatment effect on clinical response in SLE.¹

¹ Guidance for Industry: Systemic Lupus Erythematosus—Developing Medical Products for Treatment (June 2010); <https://www.fda.gov/media/71150/download>

In study 1013, a higher proportion of anifrolumab 300 mg IV subjects (34%) achieved the primary endpoint, SRI-4 response with oral corticosteroid tapering at week 24, as compared to the placebo group (18%) [odds ratio (90% CI): 2.4 (1.3, 4.3)]. Because study 1013 was designed as a proof-of-concept and dose-ranging study and did not appropriately control for multiplicity (see section 8.1), the primary endpoint of SRI-4 is viewed as only having achieved nominal significance for benefit of anifrolumab 300 mg IV compared to placebo. However, study 1013 shared many of the features of the design and conduct of the phase 3 trials—it was randomized, placebo-controlled, 52 weeks in duration, and assessed the proposed dosing regimen in an appropriate patient population with respect to clinically relevant primary and secondary efficacy endpoints—and estimated effects were consistent with meaningful benefit. In addition to the results for the primary week 24 SRI-4 response endpoint, there was supportive evidence for SRI-4 and BICLA endpoints at week 52 (without oral corticosteroid tapering). At week 52, a higher proportion of anifrolumab 300 mg IV subjects (63%) achieved SRI-4 response (without oral corticosteroid tapering) as compared to the placebo group (40%) [risk difference (95% CI): 24.0 (10.9, 37.2)], and a higher proportion of anifrolumab 300 mg IV subjects (54%) achieved the BICLA response (without oral corticosteroid tapering) at week 52 as compared to the placebo group (26%) [risk difference (95% CI): 28.4 (15.3, 41.5)].

The first phase 3 study completed, study 05, did not show a statistically significant difference in SRI-4 response rate between anifrolumab 300 mg IV and placebo groups at week 52 [anifrolumab 36% compared to placebo 40%; risk difference (95% CI): -4.2 (-14.2, 5.8)]. Upon further review of the data, the Applicant indicated that some of the protocol-specified restrictions on medication were not implemented as intended per protocol and were not appropriate based on clinical practice. As a result, a number of subjects who would be considered responders in clinical practice were deemed non-responders due to these overly restrictive medication rules. These rules included restricted use of non-steroidal anti-inflammatory drugs (NSAIDs) and limited oral corticosteroids (OCSs) used for mild SLE flares. When restricted medication rules were revised in a post-hoc analysis of study 05, there was a numerically higher SRI-4 response rate observed in the anifrolumab treatment groups when compared to placebo, though not reaching nominal significance. While study 05 did not show statistically significant improvement in the prespecified primary endpoint (SRI-4), it did show nominally significant changes in the key secondary BICLA endpoint in favor of anifrolumab 300 mg IV dose. Specifically, under the revised restricted medication rules, at week 52, a higher proportion of anifrolumab 300 mg IV subjects (47%) achieved BICLA response as compared to the placebo group (30%) [risk difference (95% CI): 17.0 (7.2, 26.8)]. Also, disease activity measured by the SLE disease activity index (updated in 2000), (SLEDAI-2K), showed a dose-dependent separation in favor of anifrolumab in study 05.

Noting the treatment effects in BICLA response rate in studies 05 and 1013, the Applicant proposed changing the primary endpoint to BICLA response rate at week 52 for the second phase 3 study (study 04) prior to database lock and unblinding. In May 2019, with agreement from the Division, the Applicant amended the protocol and statistical analysis plan for the

ongoing second phase 3 trial, study 04, to change the primary endpoint from SRI-4 to BICLA response as well as to modify the restricted medication rules.

Study 04 showed favorable, clinically meaningful, and statistically significant changes on the primary (BICLA) and secondary endpoints (including SRI-4) when comparing anifrolumab 300 mg IV versus placebo. Specifically, at week 52, a higher proportion of anifrolumab 300 mg IV subjects (48%) achieved BICLA response as compared to the placebo group (31%) [risk difference (95% CI): 16.3 (6.4, 26.3)]. Further, at week 52, a higher proportion of anifrolumab 300 mg IV subjects (56%) achieved SRI-4 response as compared to the placebo group (37%) [risk difference (95% CI): 18.2 (8.10, 28.3)]. The results for BICLA and SRI-4 in study 04 were consistent regardless of which medication restriction rules were applied, i.e., original versus amended.

A drug's effectiveness must be established by substantial evidence². While this has often been interpreted as requiring two adequate and well-controlled trials, there are other circumstances where substantial evidence of effectiveness can be provided outside of this setting. For example, there are situations when FDA finds one adequate and well-controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness³. In particular, when the disease is life-threatening or severely debilitating with an unmet need, additional flexibility may be warranted. The team notes that a significant unmet medical need exists for safe and efficacious treatment for patients with SLE, which was a consideration in the assessment of effectiveness in the anifrolumab application.

In this case, 04 represents an adequate and well-controlled trial showing favorable and statistically significant changes on the pre-specified, clinically meaningful primary and secondary endpoints when comparing anifrolumab 300 mg IV versus placebo. Because the phase 2 trial (1013) was designed only as a proof of concept and dose-ranging study with inadequate multiplicity control and study 05, the first phase 3 trial, failed on its primary endpoint, these cannot be considered additional successful adequate and well-controlled trials when considered independently. However, the review team feels that when these trials are considered in combination, the consistent results observed in studies 1013 and 05 do provide confirmatory evidence that support the effectiveness of anifrolumab 300 mg IV.

Across the three studies, there are three randomized comparisons, each with adequate duration (52 weeks), that support the claim that anifrolumab 300 mg IV yields higher BICLA response rates compared to placebo. Further, two of the three studies provide support that anifrolumab 300 mg IV yields higher SRI-4 response rates compared to placebo at week 52. While study 05 failed to show an effect on SRI-4, the study showed a numerically dose-dependent trend that is not statistically significant in SLEDAI-2K, a measure of disease activity

² The FD&C Act section 505(d) (21 U.S.C. § 355(d))

³ <https://www.fda.gov/media/133660/download>

that is used to define both SRI-4 and BICLA and for which there was relatively consistent evidence across all three studies. In all three studies, additional supportive evidence was noted in the analyses of the secondary endpoints, including a greater proportion of subjects on anifrolumab than placebo able to reduce oral corticosteroid use and a lower proportion of subjects on anifrolumab experiencing a flare of SLE disease activity, further supporting the effectiveness of anifrolumab 300 mg IV.

The current understanding of the role of Type I IFN in the pathogenesis of SLE^{4,5} supports the biological plausibility of targeting Type I IFN with anifrolumab in SLE and provides additional confirmatory evidence of the effectiveness of anifrolumab. In addition to the evidence provided from the clinical trials, mechanistic evidence is provided by the observed neutralization of the type I IFN gene signature in anifrolumab-treated subjects with a high baseline type I IFN gene signature in all three studies.

Therefore, based on the data generated from study 04 and additional confirmatory evidence from studies 1013 and 05, and mechanistic rationale, there is substantial evidence of effectiveness of the 300 mg dosing regimen of anifrolumab IV as treatment for adult patients with active SLE who are receiving standard SLE therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants at baseline.

The safety of anifrolumab was evaluated in a total of 837 adult SLE patients who received IV anifrolumab (150 mg, 300 mg, or 1000 mg) during clinical trials. Of these, 688 SLE patients were exposed to anifrolumab for at least 1 year and 263 patients were exposed for at least 3 years.

Integrated safety evaluation is based on two placebo-controlled datasets—one assessed through 52 weeks and one based on the 52-week controlled period and a placebo-controlled long-term extension up to three additional years. The three trials described above (1013, 05 and 04) provide data for 459 subjects treated with anifrolumab 300 compared with 466 on placebo for 52 weeks. Patients enrolled in the two phase 3 trials (05 and 04) who received placebo every 4 weeks for 52 weeks were randomized in a blinded fashion to continue on placebo or initiate treatment with anifrolumab 300 mg. Long-term comparisons including exposure beyond 52 weeks were measured for patients who were initially randomized to anifrolumab and continued on anifrolumab beyond 52 weeks, compared to patients who were initially randomized to placebo and later randomized to placebo beyond 52 weeks; in this dataset, there was greater overall exposure to anifrolumab than placebo as more patients from the anifrolumab arms than placebo arms continued beyond 52 weeks of treatment within the long-term extension study.

⁴ Lichtman EI, Helfgott SM, Kriegel MA. Emerging therapies for systemic lupus erythematosus— focus on targeting interferon-alpha. Clin Immuno 2012;143(3):210-21.

⁵ Pascual V, Farkas L, Banchereau J. Systemic lupus erythematosus: all roads lead to type I interferons. Curr Opin Immunol. 2006 Dec;18(6):676-82.

Overall, the safety profile of anifrolumab IV 300 mg IV every 4 weeks in the adult SLE population that participated in studies 1013, 04, and 05 (52-week controlled dataset) appeared to be similar to placebo, with the exception of certain infections (including herpes zoster) and infusion related reactions (including two cases of angioedema). One case of anaphylaxis was reported in a subject receiving the 150 mg dose. In addition, beyond 52 weeks (phase 3 long-term extension dataset), herpes zoster and other viral infections continued to occur at a higher rate in patients treated with anifrolumab 300 mg, and fatal respiratory infections occurred only in the anifrolumab 300 mg arm, including pneumonia and COVID-19 versus placebo.

In summary, the efficacy and safety data generated from studies 1013, 04, and 05, support a favorable benefit-risk assessment for approval of the 300 mg dosing regimen of anifrolumab IV as add-on treatment for adult patients with active SLE while receiving standard SLE therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants at baseline.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

To support the proposed indication, the Applicant provided the results from three clinical studies—phase 2 study CD-IA-MEDI-546-1013 (1013) and phase 3 studies D3461C00004 (04) and D3461C00005 (05), that evaluated anifrolumab IV 300 mg as well as two additional doses (150 mg and 1000 mg) in a total of 1,123 adults with active systemic lupus erythematosus (SLE) on stable immunosuppressive background medications. These were international, multicenter, randomized, double-blind, placebo-controlled, 52-week studies that evaluated the efficacy, safety, and immunogenicity of the proposed dose of 300 mg IV every 4 weeks in 925 adult subjects with active SLE receiving standard therapy.

Determination of substantial evidence of effectiveness in adult patients was based on efficacy results from one adequate and well-controlled study—phase 3 study (04). This was an appropriately designed, well-conducted study that adequately controlled for multiplicity, to characterize the efficacy and safety of anifrolumab in an adult population with active SLE. In study 04, anifrolumab 300 mg achieved a statistically significant and clinically meaningful higher response rate compared to placebo in the primary endpoint of BICLA at week 52, a composite of multiple measures of SLE improvement—anifrolumab 48% compared to placebo 31%, [risk difference (95% CI): 16.3 (6.3, 26.3)]. Additional supportive evidence for efficacy is provided in this study by the SRI-4 composite 52-week endpoint, where a higher proportion of anifrolumab 300mg IV subjects (56%) achieved response compared to the placebo group (37%)[risk difference (95% CI): 18.2 (8.1, 28.3)].

Confirmatory evidence of effectiveness is provided by study 1013, a phase 2 study designed to provide proof of concept and dose-ranging information, and a second phase 3 study (study 05). While an appropriate method for controlling multiplicity was not pre-specified in study 1013, a higher proportion of anifrolumab 300 mg IV subjects (53.5%) achieved the 52-week BICLA secondary endpoint as compared to the placebo group (25.7%)[risk difference (95% CI): 28.4 (15.3, 41.5)]. Additional supportive evidence for efficacy is provided by the SRI-4 composite 52-week endpoint in study 1013, for which a higher proportion of anifrolumab 300 mg IV subjects (62.6%) achieved response as compared to the placebo group (40.2%)[risk difference (95% CI):24.0 (10.9, 37.2)]. While a second phase 3 study (study 05) did not meet its primary objective and failed on the primary endpoint SRI-4, the results on BICLA and other secondary endpoints are largely consistent with effects observed in study 04 and study 1013 and are viewed as additional confirmatory evidence. In study 05, a higher proportion of anifrolumab 300 mg IV subjects achieved the 52-week BICLA endpoint over placebo. This effect was consistently observed in a post-hoc analysis (using revised restricted medication rules that are more consistent with clinical practice)—a higher proportion of anifrolumab 300 mg IV subjects (47%) achieved the 52-week BICLA endpoint as compared to the placebo group (30%)[risk difference (95% CI): 17.0 (7.2, 26.8)].

The proposed dose of 300 mg IV demonstrated consistent benefit both for the BICLA endpoint as well as for secondary endpoints of reduction

in daily steroid dose and reduction in SLE flare rate.

The safety of anifrolumab 300 mg IV every 4 weeks in the SLE clinical program was consistent with expected increased risk of infection due to immunosuppression, in particular for viral infections in which Type I IFN is a central part of the immune response. While the 52-week incidence of serious infections between placebo and anifrolumab 300 mg IV arms in all three studies submitted to support approval was balanced between anifrolumab and placebo arms—anifrolumab 4.8% (22/459) vs placebo 5.6% (26/466)—the proportion of subjects with any infections was higher in subjects treated with anifrolumab 300 mg IV (69.7%; 320/459) as compared to subjects in the placebo arms (55.4%; EAIR 99.9/100 PY). Herpes zoster infections, in particular, occurred at a higher rate in anifrolumab-treated subjects compared to placebo (6.1% vs 1.3%). In the 52-week controlled study period, fatal infections occurred in 0.4% of patients receiving anifrolumab and 0.2% of patients receiving placebo. In long-term, placebo controlled assessment of subjects on anifrolumab 300 mg beyond 52 weeks, a total of seven deaths were attributed to infections in anifrolumab-treated subjects (four pneumonia and three COVID-19) as compared to none on placebo. Overall, more cases of hypersensitivity reactions and infusion-related reactions (including two cases of angioedema) occurred in subjects receiving anifrolumab compared to placebo, and one case of anaphylaxis occurred in a patient receiving the 150 mg dose.

In summary, the efficacy and safety data generated from one adequate and well-controlled study—04—as well as confirmatory evidence from studies 1013 and 05, result in a favorable benefit-risk assessment for approval of the 300 mg IV every 4 weeks dosing regimen of anifrolumab as add-on treatment for adult patients with active SLE while receiving standard therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants.

A significant unmet medical need exists for safe and efficacious treatment for patients with SLE. In addition to the evidence provided from the clinical trials, the current understanding of the role of Type I IFN in the pathogenesis of SLE supports the biological plausibility of targeting Type I IFN with anifrolumab in SLE .

If approved, anifrolumab, a first-in-class biologic with a unique mechanism of action, will provide a new treatment option for patients with SLE.

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Systemic lupus erythematosus (SLE) is a chronic, multisystem, disabling autoimmune rheumatic disease of unknown etiology. Clinical manifestations of SLE can include constitutional symptoms, alopecia and rashes, serositis, inflammatory arthritis, renal disease, systemic vasculitis, lymphadenopathy, splenomegaly, hemolytic anemia, cognitive dysfunction, and other central nervous system involvement. SLE affects 200,000 to 1.5 million people in the United States and at least five million people worldwide,⁶⁷ with a particularly higher prevalence among racial/ethnic minority groups.⁸ SLE is a serious disease associated with increased morbidity and mortality with an estimate that between 10-15% of people with lupus will die prematurely due to complications of lupus.⁹ Uncontrolled, ongoing disease activity over time has been associated with poorer outcomes, such as organ damage and coronary artery disease in SLE.¹⁰ Higher doses of medications to control disease activity can also be harmful for many patients as they are associated with cumulative and irreversible organ damage (such as premature cataracts, retinopathy, osteoporotic fractures, cardiovascular damage, avascular necrosis, and infections).¹¹	SLE is a serious and potentially life-threatening disease that can impact any organ system. This disease can cause significant morbidity and mortality as well as impact on patients' function and quality of life.

⁶ Izmirly, P.M., Parton, H., Wang, L., McCune, W.J., Lim, S.S., Drenkard, C., Ferucci, E.D., Dall'Era, M., Gordon, C., Helmick, C.G. and Somers, E.C. (2021), Prevalence of Systemic Lupus Erythematosus in the United States: Estimates from a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. Arthritis & Rheumatology. Accepted Author Manuscript. <https://doi.org/10.1002/art.41632>.

⁷ Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. Expert Rev Clin Immunol. 2017 Aug;13(8):799-814.

⁸ Lim SS, Drenkard C. Epidemiology of lupus: an update. Curr Opin Rheumatol. 2015 Sep;27(5):427-32.

⁹ Wallace, D.J., & Hahn, B.H. (2013). Dubois' lupus erythematosus and related syndromes. (8th ed.) Philadelphia, PA: Elsevier Saunders.

¹⁰ Ibañez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. J Rheumatol. 2005 May;32(5):824-7.

¹¹ Durcan L, Petri M. Why targeted therapies are necessary for systemic lupus erythematosus. Lupus. 2016 Sep;25(10):1070-9.

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Aspirin • Corticosteroids • Hydroxychloroquine and other antimalarials • Belimumab • NSAIDs • Azathioprine • Mycophenolate Mofetil • Cyclophosphamide • Rituximab • Methotrexate Aspirin, corticosteroids, hydroxychloroquine and belimumab are FDA-approved for treatment of SLE Other therapies currently used in SLE management are used off-label	The toxicities associated with both the approved drugs for SLE as well as off-label treatments commonly used to treat SLE contribute to the long-term morbidity and mortality observed in patients with SLE. Only one targeted therapy –belimumab–has been approved for SLE in the last 60 years.¹² It targets one pathway and is therefore not effective in all patients or for all SLE disease manifestations.¹³ There is a significant unmet medical need for safe and efficacious treatment for adults with SLE.
Benefit	• Studies CD-IA-MEDI-546-1013 (1013), D3461C00004 (04), and D3461C00005 (05) were multicenter, international, randomized, double-blind, placebo-controlled studies that evaluated the efficacy and safety over 52 weeks of 300 mg IV anifrolumab every 4 weeks versus placebo every 4 weeks in 925 adult subjects with active SLE receiving standard therapy. • Primary endpoint was the week 52 BICLA response rate comparing the anifrolumab IV group versus placebo group in phase 3 study 04. Primary endpoint in phase 2 study 1013 was week 24 SRI-4 plus OCS tapering. Primary endpoint in phase 3 study 05 was week 52 SRI-4.	The Applicant has submitted substantial evidence meeting the evidentiary standard for the clinical effectiveness of anifrolumab 300 mg IV every 4 weeks in subjects with SLE who are receiving standard therapy based on one adequate and well-controlled phase 3 study and confirmatory evidence from two additional studies. These studies enrolled a population of subjects who were generally representative of the targeted US patient

¹² Wallace DJ. The evolution of drug discovery in SLE. Nat Rev Rheumatol 2015;11(10):616-20.

¹³ Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet 2019;393:2344-58.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	BICLA and SRI-4 at week 52 were pre-specified secondary endpoints in study 1013 and 05. • In study 04, a higher proportion of anifrolumab IV subjects (47.8%) achieved the 52-week BICLA primary endpoint as compared to the placebo group (31.3%)[risk difference (95% CI): 16.3 (6.3, 26.3); p=0.001]. • In study 1013, a higher proportion of anifrolumab IV subjects (53.5%) achieved the 52-week BICLA secondary endpoint as compared to the placebo group (25.7%)[risk difference (95% CI): 28.4 (15.3, 41.5)]. • In study 05 a higher proportion of anifrolumab IV subjects achieved the 52-week BICLA endpoint (37.2%) as compared to the placebo group (26.6%) [risk difference (95% CI): 10.1 (0.6, 19.7)]. • In a post-hoc analysis of the study 05 BICLA endpoint using the amended restricted medication rules intended to align with study 04, consistent effects were observed with a higher proportion of anifrolumab IV subjects (47.2%) achieving the 52-week BICLA endpoint as compared to the placebo group (29.9%)[risk difference (95% CI): 17.0 (7.2, 26.8)]. • For its primary 52-week SRI-4 endpoint, study 05 did not demonstrate statistically significant superiority over placebo. • Additional supportive evidence for efficacy is provided by the SRI-4 composite 52-week endpoint achieved in study 04 by a higher proportion of anifrolumab IV subjects (55.6%) as compared to the placebo group (37.4%)[risk difference (95% CI):18.2 (8.1, 28.3)] and in study 1013 by a higher proportion of anifrolumab IV subjects (62.6%) as compared to the placebo group (40.2%)[risk difference (95% CI):24.0 (10.9, 37.2)]. • Additional support for both the BICLA and SRI-4 findings came from	population and used mutually agreed upon primary and secondary endpoints that were designed to capture changes in patients' disease activity. Lower SLE disease activity as well as a decrease in the risk for severe SLE flares may result in less long-term end-organ damage from patients' underlying disease, less treatment with unapproved immunosuppressive agents commonly used to treat SLE with their own inherent toxicities, as well as fewer hospitalizations with fewer absent work days and ultimately less morbidity and mortality associated with this disease.

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	analysis of the individual BICLA and SRI components as well as from secondary endpoints.	
Risk and Risk Management	• Overall, the safety profile of anifrolumab IV assessed at a dose of 300 mg IV every 4 weeks in the adult SLE population that participated in studies 1013, 04 and 05 appeared to be similar to placebo. • Adverse events were reported in 87% of patients receiving anifrolumab 300 mg and 79% of patients receiving placebo. • The most commonly reported adverse events (≥5%) during anifrolumab treatment, irrespective of causality, were nasopharyngitis, upper respiratory infection, urinary tract infection, bronchitis, infusion-related reaction, headache, herpes zoster, back pain, sinusitis, and cough. • The proportion of patients with serious adverse events was 12% for anifrolumab 300 mg and 17% for placebo. • The proportion of patients who discontinued treatment due to adverse events was 4.1% for anifrolumab 300 mg and 5.2% for placebo. • There were only 2 deaths in the anifrolumab 300 mg IV group during the 52-week study period. • In the 52-week controlled trials, fatal infections occurred in 2/459 (0.4%) of patients receiving anifrolumab and 1/466 (0.2%) of patients receiving placebo. • In the entire anifrolumab IV clinical development program, including doses of 150 mg and 1000 mg IV during a 52-week period and ongoing, long-term, phase 3 extension study of 300 mg (up to a total of 4 years), there were 11 deaths in the anifrolumab IV group and 3	The Applicant has submitted adequate data on which to conclude the initial safety of anifrolumab 300 mg IV every 4 weeks in subjects with SLE who are receiving standard therapy. Review of the safety database demonstrated that anifrolumab-treated subjects, compared to subjects treated with placebo, experienced a greater frequency of adverse events, a greater number of fatal infections, herpes zoster infections, hypersensitivity reactions including anaphylaxis, and infusion-related reactions. Although no clear risk for malignancies has been identified with long-term treatment with anifrolumab in adults, there was a numerical imbalance with more total malignancies occurring in anifrolumab-treated subjects as compared to placebo. Nonclinical data and 52-week controlled trial data support the claim of potential risk of malignancy associated with anifrolumab, and it would be prudent to continue monitoring safety data from the ongoing placebo-controlled phase 3 long-term extension study (09) for the development of

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	deaths in the placebo group. In long-term, placebo controlled assessment of subjects on anifrolumab 300 mg beyond 52 weeks, a total of seven deaths were attributed to infections (4 pneumonia and 3 COVID-19) in anifrolumab-treated subjects as compared to none on placebo. • The number of subjects with serious infections was balanced between anifrolumab and placebo arms—anifrolumab 4.8% (22/459) and placebo 5.6% (26/466) • The number of subjects with any infection was higher in the anifrolumab IV group (69.7%) than the placebo group (55.4%) with increased rates of Nasopharyngitis (anifrolumab 300 16.3% vs placebo 9.4%); Upper Respiratory Infection (15.5% vs 9.7%); Bronchitis (9.8% vs 4.3%); Herpes Zoster (6.1% vs 1.3%); Influenza (2.6% vs 1.9%); and Latent TB (0.9% vs (0.2%). • Herpes zoster infections occurred in a higher proportion (6.1%) of anifrolumab IV patients than placebo (1.3%) during the 52-week study period. • There was one case of anaphylaxis with the anifrolumab 150 mg IV dose and no cases of anaphylaxis with the anifrolumab 300 mg IV dose. • There were more infusion related reactions (9.4% vs 7.1%) and hypersensitivity reactions (2.6% vs 0.6%) in the anifrolumab 300 mg IV group as compared to the placebo group. • There were 6 malignancies (including non-melanoma skin cancers) in the anifrolumab 300 mg IV group during the 52-week study period and 3 malignancies in the placebo group. Adding data from the ongoing phase 3 long-term extension study of 300 mg, there was one additional malignancy in the anifrolumab group for a total of 7, and	potential safety signals such as malignancies to occur with increasing exposure to the product. A post-marketing, required pediatric study to assess the safety, efficacy, and pharmacokinetics of anifrolumab plus background standard therapy in pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE) will be conducted. Based on the high proportion of women of child-bearing potential among SLE patients, a post-marketing required prospective pregnancy registry to evaluate the effects of anifrolumab on pregnancy and maternal and fetal/neonatal outcomes and a retrospective cohort study in a claims-based database to evaluate the effects of anifrolumab on pregnancy-related outcomes will be conducted. The pregnancy registry study may be conducted as part of a multiple-product or disease-based registry. A lactation study, milk only, in lactating women who receive anifrolumab to assess concentrations of anifrolumab in breast milk using a validated assay will be conducted. A mother-infant pair study may be required in the future depending on the results of the milk-only study.

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	there were 2 additional malignancies in the placebo group for a total of 5. • Many of the serious adverse events and discontinuation of study treatment in the anifrolumab IV safety database were related to underlying disease activity or infections. • There were no cases of active tuberculosis. • There were no cases of suicide/self-injury. • MACE events were rare and balanced between anifrolumab and placebo arms. • Limitations associated with the anifrolumab IV safety database include the lack of concomitant IV cyclophosphamide or other biologics including those that target B cells (e.g., rituximab or belimumab), and the lack of patients with severe renal lupus and central nervous system disease. The small numbers of patients available for subgroup analysis of gender (males), age (≥ 65 years of age as well as children ≤ 18 years of age), and race precludes determination of the product's safety profile in these subgroups.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that were submitted as part of the application include:		Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as	Section 8
	☒	Patient reported outcome (PRO)	
	☒	Observer reported outcome (ObsRO)	
	☒	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.		

2. Therapeutic Context

2.1. Analysis of Condition

Systemic lupus erythematosus (SLE) is a chronic, multisystem, disabling autoimmune rheumatic disease of unknown etiology. Clinical manifestations of SLE can include constitutional symptoms, alopecia and rashes, serositis, inflammatory arthritis, renal disease, systemic vasculitis, lymphadenopathy, splenomegaly, hemolytic anemia, cognitive dysfunction, and other central nervous system involvement. SLE affects approximately 200,000 to 1.5 million people in the United States and at least five million people worldwide,^{14,15} with a particularly higher prevalence among racial/ethnic minority groups.¹⁶ SLE is a serious disease associated with increased morbidity and mortality with an estimate that between 10-15% of people with lupus will die prematurely due to complications of lupus.¹⁷ Uncontrolled, ongoing disease activity over time has been associated with poorer outcomes, such as organ damage and coronary artery disease in SLE.¹⁸ Higher doses of medications to control disease activity can also be harmful for many patients as they are associated with cumulative and irreversible organ damage (such as premature cataracts, retinopathy, osteoporotic fractures, cardiovascular damage, avascular necrosis, and infections).¹⁹

Available Therapies

Available therapies to treat SLE are summarized in Table 1. Prior to the recent approval of belimumab, only three other drugs were specifically approved for SLE—aspirin and oral corticosteroids (OCSs) (both circa 1950) and hydroxychloroquine in 1955. For mild disease, first line treatments include anti-malarials (hydroxychloroquine) and OCSs (e.g., prednisone). Long-term use of hydroxychloroquine can cause retinopathy and poor adherence to treatment remains an issue with this drug.²⁰ Steroids remain a mainstay of treatment for mild to severe disease, however chronic steroid use is a contributing factor in long-term morbidity and early

¹⁴ Izmirly, P.M., Parton, H., Wang, L., McCune, W.J., Lim, S.S., Drenkard, C., Ferucci, E.D., Dall'Era, M., Gordon, C., Helmick, C.G. and Somers, E.C. (2021), Prevalence of Systemic Lupus Erythematosus in the United States: Estimates from a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis & Rheumatology*. Accepted Author Manuscript. <https://doi.org/10.1002/art.41632>.

¹⁵ Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. *Expert Rev Clin Immunol*. 2017 Aug;13(8):799-814.

¹⁶ Lim SS, Drenkard C. Epidemiology of lupus: an update. *Curr Opin Rheumatol*. 2015 Sep;27(5):427-32.

¹⁷ Wallace, D.J., & Hahn, B.H. (2013). *Dubois' lupus erythematosus and related syndromes*. (8th ed.) Philadelphia, PA: Elsevier Saunders.

¹⁸ Ibañez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. *J Rheumatol*. 2005 May;32(5):824-7.

¹⁹ Durcan L, Petri M. Why targeted therapies are necessary for systemic lupus erythematosus. *Lupus*. 2016 Sep;25(10):1070-9.

²⁰ Fanouriakis A, Bertsias G. Changing paradigms in the treatment of systemic lupus erythematosus. *Lupus Sci Med*. 2019 Feb 8;6(1):e000310.

cardiovascular mortality in patients with SLE.²¹ Additional treatment options for moderate to severe disease include immunosuppressants, such as methotrexate, azathioprine, and mycophenolate mofetil. The use of immunosuppressants is associated with an increased risk of infection, malignancy, cardiovascular disease, and bone marrow suppression, and are not effective in all patients for all manifestations of SLE.²² Only one targeted therapy has been approved for SLE in the last 60 years. Belimumab is a neutralizing anti-B-lymphocyte stimulator mAb.²³ It targets one pathway, while patients are likely to have different underlying immunopathological pathways driving their SLE disease manifestations.²⁴ As such, it is not effective in all patients. There is substantial unmet medical need in the treatment of SLE, particularly in patients with moderate or severe disease.

2.2. Analysis of Current Treatment Options

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for Adults with SLE						
Aspirin	Treatment of arthritis and pleurisy of SLE	1948	Initially 3g/d in divided doses: titrate up to plasma salicylate level 150-300mcg/ml for anti-inflammatory effect	Clinical Studies	GI bleeding and tinnitus at plasma salicylate levels $\geq$ 250 mcg/ml	Constitutional and musculo-skeletal manifestations and serositis. No longer used
Prednisone	During an exacerbation or as maintenance therapy in selected cases of SLE	1955	Up to 80 mg/day; use lowest dose to maintain adequate anti-inflammatory response	Clinical Studies	$\uparrow$ risk for infections, glucose intolerance, osteoporosis, glaucoma, cataracts, HT, osteonecrosis, and $\downarrow$ growth	Low dose: mucocutaneous and musculo-skeletal manifestations; serositis High dose: induction therapy for lupus nephritis, CNS disease, and immune cytopenias
Hydroxy-chloroquine	Treatment of discoid and SLE	1955	200 mg BID	Clinical Studies	Retinal and corneal deposits, GI complaints, rash, myalgia.	Constitutional, cutaneous, and musculoskeletal manifestations

²¹ Ruiz-Arruza et al. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2014 Aug;53(8):1470-6.

²² Campar A, Farinha F, Vasconcelos C. Refractory disease in systemic lupus erythematosus. *Autoimmun Rev* 2011;10:685–92.

²³ Wallace DJ. The evolution of drug discovery in SLE. *Nat Rev Rheumatol* 2015;11(10):616-20.

²⁴ Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. *Lancet* 2019;393:2344-58.

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

					Headache and hemolytic anemia in G6PD deficiency	
Belimumab	Treatment of active, autoantibody positive SLE despite standard of care; Treatment of lupus Nephritis	IV:2011 SC:2017 Lupus Nephritis: 2020	10mg/kg via IV infusion at 2-week intervals for the first 3 doses and then at 4-week intervals thereafter; 200 mg once weekly (for SLE) via SC injection	IV: Two phase 3 studies SC: One phase 3 study	↑risk for serious and fatal infections, hypersensitivity reactions, depression and suicidality	Musculoskeletal, mucocutaneous and immunological manifestations; Lupus Nephritis
Other Treatments (Off-Label)						
NSAIDs	-----	-----	Lowest effective approved dose	Published literature	GI bleeding, CV events, hepatic and renal toxicity, HTN, headache, aseptic meningitis, confusion	Constitutional and musculoskeletal manifestations, headaches and serositis
Azathioprine	-----	-----	2-2.5 mg/kg/d	Published literature	Myelosuppression, hepatotoxicity, malignancies, infections	Steroid sparing and maintenance therapy for lupus nephritis
Methotrexate	-----	-----	7.5-25 mg/week	Published literature	Mucositis, myelosuppression, hepatotoxicity, cirrhosis, pneumonitis, pulmonary fibrosis, infections	Cutaneous and musculoskeletal manifestations
Cyclophosphamide	-----	-----	IV bolus regimens of 0.5-1g/m body surface area once monthly for 6 months	Published literature	Myelosuppression, hemorrhagic cystitis, malignancy, lymphoproliferative disorders, infertility, and infections	Induction therapy for lupus nephritis, CNS disease, pulmonary hemorrhage, and systemic vasculitis
Mycophenolate Mofetil	-----	-----	500-1500 mg BID	Published literature	Myelosuppression, GI complaints, myalgia, infections	Induction and maintenance therapy for lupus nephritis

Source: Reviewer-generated based on referenced, published data

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Anifrolumab is a new molecular entity that is not currently marketed in the US or any other country. The current application is the initial BLA for anifrolumab and has been submitted to the Division of Rheumatology and Transplant Medicine for the proposed indication for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Agency had multiple interactions with the Applicant regarding the anifrolumab IV clinical program. At an end-of-phase 2 meeting on September 16, 2014, the Agency provided feedback on dose selection, endpoints, primary analyses, and controlling type 1 error in the phase 3 study designs for the clinical program. On May 24, 2018, the Agency provided written responses to a type C meeting request on the overall content, format, and proposed data presentation for the planned Biologics License Application (BLA). The FDA provided additional feedback on the Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS), and the Integrated Summary of Immunogenicity (ISE) for this BLA on October 29, 2018. For the BLA, the Applicant proposed to provide data from a phase 2 study (1013), and two phase 3 studies (04, 05).

Protocol Amendment 1—Change in Primary Endpoint

An amended protocol and statistical analysis plan for study 04 was submitted on May 31, 2019, after both phase 3 studies were completed; however, only the data for study 05 had been unblinded and analyzed. The database for study 05 was locked for the 52-week treatment period in August 2018. The Applicant reported that the study did not meet the primary endpoint of a statistically significant reduction in disease activity, as measured by SLE Responder Index of at least 4 (SRI-4) at 52 weeks. However, the Applicant indicated that secondary endpoints that were not SRI-4-based suggested there was a potentially clinically meaningful response to anifrolumab. Therefore, the Applicant proposed to change the primary and some key secondary endpoints for study 04 prior to its database lock and unblinding. The timeline for key activities leading to changes in the primary endpoint and key secondary endpoints in study 04 are summarized in Table 2.

Table 2. Key activities leading to the changes to the primary endpoint and key secondary endpoints for study 04

Date	Activity
August 23, 2018	Study 05 database lock and unblinding
September 27, 2018	All patients in study 04 had completed 52 weeks treatment
December 28, 2018 to February 7, 2019	End of trial notifications for study 04 submitted
May 10, 2019	In conjunction with the external Steering Committee for the anifrolumab phase 3 program, a decision was made to change the primary endpoint in study 04 plus 2 of 5 key secondary endpoints
May 23, 2019	Study 04 protocol amendment to reflect changes to primary and key secondary endpoints
May 24, 2019	Study 04 SAP amendment to reflect changes to primary and key secondary endpoints
August 19, 2019	Study 04 database lock and unblinding

The proposed changes to the primary and key secondary endpoints for study 04 were:

- Change from initial primary endpoint of SRI-4 response at week 52 to BICLA response at week 52
- Change in key secondary endpoint from SRI-4 response at week 52 in IFN test high subgroup to BICLA response at week 52 in IFN test high subgroup
- Added key secondary endpoint of proportion of subjects with $\geq 50\%$ reduction in number of swollen and tender joints at week 52 in subjects with ≥ 6 swollen and tender joints at baseline
- SRI-4 response at week 24 demoted from key to other secondary endpoint
- No change in key secondary endpoints of proportion of subjects who achieve an OCS dose ≤ 7.5 gm/day at week 40 maintained through week 52; proportion of subjects with $\geq 50\%$ reduction in CLASI activity score at week 12 in subgroup with baseline CLASI ≥ 10 ; annualized flare rate defined by 1 or more new BILAG-2004 A or 2 or more new B items compared to previous visit

The Applicant stated that the BICLA endpoint may have some advantages over the SRI-4 because (1) the 97 questions of the BILAG-2004 may assess more of the clinical diversity of the disease and (2) the BILAG-2004 requires the clinician to rate manifestations with multiple categories, rather than simply absent or present. The Applicant argues that this endpoint may be more comprehensive, give more balanced weight to affected body systems, and measure incremental improvements or worsening. The Applicant also notes that the BICLA endpoint retains the SLEDAI-2K, using it (alongside PGA) to exclude patients who worsen in ways not captured by BILAG-2004 from being classified as responders. Therefore, the Applicant proposed to replace the SRI-based endpoints in the hierarchy for study 04 with BICLA-based endpoints.

Protocol Amendment 2—Change in Restricted Medication Rules

In the phase 2 study and both phase 3 studies, patients randomized to treatment continued to receive standard of care therapy with OCSs, antimalarial agents, and/or immunosuppressants in addition to being randomized to receive either anifrolumab or placebo. The primary and several of the secondary endpoints, including all key secondary endpoints, were composite endpoints that include the condition “no use of restricted medications beyond the protocol-allowed threshold before assessment” in order for subjects to be considered responders. However, the Applicant indicated that, upon review of the unblinded data from study 05 after the week 52 database lock, some of the protocol-specified restrictions on medication were “not implemented as intended per protocol and were not appropriate based on clinical practice,” in particular regarding use of NSAIDs. A revised set of restricted medication rules, whereby every class of medication was reviewed to ensure clinical appropriateness, were applied to study data as post-hoc analyses in study 05 and were proposed to evaluate the unblinded phase 3 study (study 04). The change in restricted medication rules for NSAIDs, which had the largest impact on determination of responders versus non-responders (NR; due to taking a restricted medication), was as follows:

“Patients were classified as NR for all subsequent efficacy assessments if a new NSAID was initiated and/or there was an increase in NSAID dosage after day 1.”

was changed to:

“Initiation of a new NSAID within 14 days of week 52 and documented use on the day before the week-52 assessment led to classification as NR at the week-52 visit. NSAID use prior to week 50 did not lead to classification as NR.”

The May 2019 submission included the amended clinical study protocol and statistical analysis plan which reflect changes to the primary and key secondary endpoints as well as modifications to the restricted medication rules. The Division cautioned that the revision in the statistical plan to incorporate changes to the medication rules and primary endpoint may affect the overall interpretability of efficacy in the overall anifrolumab IV clinical program for SLE.

At a pre-BLA Type B meeting with the Applicant on February 20, 2020, the following comments/recommendations were communicated to the Applicant to facilitate review of the pending BLA submission:

- 1) Provide a justification for the discrepancies in the different study results observed. Specifically, the study design and patient populations appear to be similar between Studies 04 and 05; however, the differences in the results from these two studies are difficult to reconcile.
- 2) For each study (Study 04, 05, and 1013), present the results for BICLA and SRI-4 response rates using (a) the original medication rules, (b) the updated medication rules, and (c) ignoring adherence to medication rules or discontinuation treatment in determining response (i.e., using all observed data regardless of adherence).
- 3) Provide an examination of the components of the SRI-4 and BICLA endpoints for each

study (Study 04, 05, and 1013). It will be important to evaluate the treatment effect on the overall endpoint and each of the components of the composite outcome in supportive analyses based on all observed data collected, regardless of treatment discontinuation or protocol adherence. This will be particularly important given the uncertainty surrounding the medication rules for these studies.

- 4) Include a tipping point analysis that targets the treatment policy estimand, i.e., includes the observed data for subjects who would be considered non-responders due to treatment discontinuation or lack of adherence to restricted medication rules and consider.
- 5) Include adequate documentation and programs to facilitate replication for all analyses, including any post-hoc analyses, supplementary analysis, and sensitivity analyses presented.

Medical Policy and Program Review Council (MPPRC) Meeting January 22, 2021

The Division sought input from the MPPRC on the approvability of anifrolumab for treatment of moderate to severe SLE as well as any additional recommendations.

MPPRC Summary Recommendations: Given the markedly positive study 04, consistency with study 1013, and supportive evidence from the post hoc analysis of study 05, the Council deemed the evidence for effectiveness persuasive. In general, the Council considered two approaches, first considering 1013 an AWC (adequate and well-controlled) study, if sufficiently justified from statistical perspective, and study 04 as the second AWC study providing substantial evidence. Further discussions regarding the multiplicity control in 1013 were recommended. The second approach would be to consider 04 as the single AWC trial, and the other clinical data as providing confirmatory evidence.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical data from three studies (D3461C0004, D3461C00005, and CD-IA-MEDI-546-1013) were submitted to the Agency in support of a biologics licensing application (BLA) 761123 for anifrolumab to treat adult patients with moderate to severe, auto-antibody positive systemic lupus erythematosus (SLE) (b) (4). Clinical inspections of the Applicant AstraZeneca Pharmaceuticals L.P., and four clinical investigators (Dr. Anurekha Chadha, site 7904, Dr. Sabeen Najam, site 7834, Dr. Phillip Waller, site 7815, and Dr. Eric Lee, site 7825) were conducted in support of this application.

Maintenance of blinding was adequate throughout for all three studies (DC346C00004, DC346100005, CD-IA-MEDI-546-1013.) The data and safety monitoring board (DSMB) consisted of multi-disciplinary group of two rheumatologists, one infectious disease, one nephrologist, and one biostatistician. On 1/25/2019, DSMB minutes document how study D3461C00005 did not meet the primary efficacy endpoint. Study D3461C00005 was closed out and high level, aggregate efficacy and safety data were presented to the full DSMB, (b) (4) and (b) (4) attendees. The Applicant and (b) (4) medical team remained blinded to study D3461C00004. The DSMB reviewed the Closed Report (partially unblinded by masked treatment arms) for study D3461C00004 during the closed session.

In general, the Applicant appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this Applicant appear acceptable in support of this biologic license application.

Based on the results of the clinical investigators and Applicant inspections, Protocols D3461C0004, D3461C00005, and CD-IA-MEDI-546-1013 appear to have been conducted adequately, and the data generated appear acceptable in support of the proposed indication. Of note, the OSI review team identified issues with the data generated from two sites, Dr. Sabeen Najam and Dr. Phillip Waller, because of failure to prepare and maintain adequate and accurate source records for study D3461C00004. However, this was limited to the two sites and was considered related to the use of site-specific software, which was used only by these two sites. No data integrity issues were identified at Anurekha Chadha and Dr. Eric Lee sites. A sensitivity analysis conducted by our statistical reviewers confirms that the exclusion of the data generated from Dr. Sabeen Najam and Dr. Phillip Waller sites does not impact the overall efficacy conclusions.

Overall, based on completed OSI inspections as well as robustness of the efficacy data, the conclusions on efficacy to support approval are reliable.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761123 for anifrolumab manufactured by AstraZeneca. The data submitted in this application are adequate to support the conclusion that the manufacture of anifrolumab is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

Glycosylation analysis of anifrolumab showed that it contains (b) (4) % galactose-alpha-1,3-galactose (alpha-gal) on the product Fc domain. Alpha-gal on proteins is a known allergen that may produce anti-alpha-gal IgE mediated anaphylactic and hypersensitivity reaction. Detail analysis of the clinical data, especially the anaphylaxis and hypersensitivity cases, demonstrated that risk of alpha-gal associated hypersensitivity and anaphylaxis for SAPHNELO was low (see clinical section for detail).

The product quality postmarketing commitment between OPQ and the Applicant listed below should be included in the action letter:

Implement (b) (4) of anifrolumab drug product and update module 3.2.P.3.4 of the BLA with (b) (4) as a Critical Process Parameter.
Final report submission: 9/2023

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant has conducted a comprehensive program of pharmacology, pharmacokinetic (PK), and toxicology studies with anifrolumab to support clinical development and the BLA submission. All studies submitted to support approval have been reviewed previously under IND 101849. The key findings from the nonclinical studies are cited and summarized in this review to support the approval of BLA 761123. The Applicant has also submitted extractables and leachables studies and safety assessments, which have been reviewed under this BLA (see Section 16.3). The safety assessment of impurities from the drug substance and drug product is reviewed in Section 16.3.

Pharmacology studies demonstrated that anifrolumab bound to IFNAR1 and inhibited the expression of Type-I IFN responsive genes in peripheral blood mononuclear cells (PBMCs) and the expression of differentiation markers and cytokines/chemokines from monocytes. An anifrolumab mouse surrogate was effective in a murine model of scleroderma and an accelerated NZB/W F1 murine model of lupus.

Anifrolumab had no or reduced binding to Fc Gamma Receptors I (FcγRI), FcγRIIA, FcγRIIB, or FcγRIIIA in vitro. No complement dependent cytotoxicity (CDC) or antibody dependent cellular cytotoxicity (ADCC) were noted in vitro. In vitro anifrolumab-positive human and cynomolgus monkey tissue binding was consistent with published reports of broad expression of IFNAR in the corresponding tissues.

The effect of anifrolumab on the cardiovascular (CV) system was evaluated in a GLP-compliant 39-week general IV toxicity study in monkeys (Study# 7140-129). In this study, cynomolgus monkeys were given 40 IV infusion (30 minutes) doses of anifrolumab at 5 and 50 mg/kg/week once a week (QW) or 40 subcutaneous (SC) injection doses of anifrolumab at 15 and 60 mg/kg/week QW. Electrocardiography (ECG) parameters and blood pressure (BP) parameters were measured once during the predose phase, on Days 3 and 276 of the dosing phase, and on Day 83 of the recovery phase for these animals after they were anesthetized with ketamine. No drug-related adverse CV findings were noted. In another 4-week IV toxicity study in cynomolgus monkeys with lower systemic exposures (see Section 5.4), ECG parameters and BP were measured within 1 hr. post dosing on Day 22 (weekly dose, Study# (b) (4) 263.01). No drug-related adverse CV findings were noted.

GLP-compliant toxicology studies up to 39 weeks indicated that anifrolumab was well-tolerated in cynomolgus monkeys. No drug-related adverse clinical sign changes were noted. No drug-related CV toxicity was noted. Besides anti-drug antibody (ADA)-induced minimal arteritis in multiple organs in a few male animals given 40 doses of anifrolumab at 50 mg/kg/week (IV) or 60 mg/kg/week (SC), no additional drug-related adverse effect was noted. Further, anifrolumab

was not found to induce reproductive and developmental toxicity. In the GLP-compliant 39-week toxicity study in sexually mature cynomolgus monkeys, no drug-related effects on reproductive organs/tissues, semen analysis, spermatogenesis analysis, or menstrual cycle were present. In the GLP-compliant enhanced prenatal and postnatal development (ePPND) study in pregnant cynomolgus monkeys, no drug-related adverse effects in maternal animals or infants (body growth, behavior, functional, morphological, and skeletal development, and T-cell-dependent antibody response) were noted. The plasma exposures of anifrolumab at the no-observed-adverse-effect levels (NOAELs) for general toxicity and reproductive and developmental toxicity are >59- and 28-fold higher than the human exposure (AUC) at the MRHD.

Genetic toxicity studies have not been conducted with anifrolumab as they are generally not applicable for biotechnology-derived pharmaceuticals. Carcinogenicity studies have not been conducted with anifrolumab, however the existing literature from studies with IFNAR1- and IFNAR2-deficient mice and mice administered IFN α/β and anti-IFN- α/β antibodies suggested that IFNAR blockade increased carcinogenic potential in rodents. The Applicant and review team have agreed on proposed language to describe this finding based on the pharmacology of anifrolumab in the product labeling.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Multiple in vitro pharmacology studies have been conducted identifying the mechanism of action and activity of anifrolumab. None of the primary or secondary pharmacology studies were conducted in compliance with GLP. In the opinion of the nonclinical reviewer, this is a typical approach in drug research and does not affect the integrity of the application.

Primary pharmacology:

Anifrolumab is a first-in-class product targeting IFNAR1. An Established Pharmacologic Class (EPC) assessment was conducted. Based on following studies, anifrolumab is considered a Type I Interferon Receptor Antagonist.

- Anifrolumab has high affinity for IFNAR1 expressed on human PBMCs with KD of 0.29 nM (Study# RIA546-0002);
- Anifrolumab bound to the sub-domain 3 of human IFNAR1 (265-307) with residues 276-279 being identified as the critical epitope (Study# RIA546-0004);
- Anifrolumab competitively inhibited the binding of IFN- α 2a to IFNAR in Daudi cells (Study# RIA546-0003);
- Anifrolumab inhibited
 - IFN-stimulated response elements (ISRE) activation induced by all the recombinant human IFN- α subtypes (Study# RIA546-0006) and SLE sera (Study# RIA546-0008);

- the expression of Type-I IFN responsive genes (*USP18*, *HERC5/6*, *IFIT1/3/5*, *G1P2/3*, *MX1/2*, *OAS1/2*, *IFI44*, *IFI44L*, *Ly6E*) from PBMCs by sera of SLE patients (Study# RIA546-0005);
- the expression of differentiation markers (CD123 and CD38) and cytokines/chemokines (IL-6, IL-10, MCP-1, MCP-2) from monocytes by leukocyte-IFNs (Study# RIA546-0005);
- Anti-murine IFNAR1 MAb 5A3 (anifrolumab surrogate) was effective in a murine model of scleroderma (Study# RIA546-0007) and an accelerated NZB/W F1 murine model of lupus (Study# RIA546-0011).

In cross-species studies, anifrolumab was found to

- have high affinity for IFNAR1 expressed on cynomolgus monkey PBMCs with KD of 0.65 nM (Study# RIA546-0002);
- inhibit ISRE activation induced by most cynomolgus recombinant type I IFNs with IC₅₀ values comparable to the corresponding human subtypes with the exception of the IFN-α1, IFN-α4, and IFN-α6 subtypes (Study# RIA546-0006);
- have no effect on murine IFN-α-mediated ISRE activation in cells expressing murine IFNAR1 (Study# RIA546-0006).

Secondary pharmacology:

- Anifrolumab had no or significantly reduced binding to FcγRI and FcγRIIIA in vitro (Study# RIA546-0001);
- Anifrolumab had no binding to FcγRIIA or FcγRIIB in vitro (Study# RIA546-0010);
- Anifrolumab bound to Fc Gamma Neonatal Receptor (FcRn) with KD similar to wild type in vitro, suggesting the normal IgG recycling property (Study# RIA546-0010);
- Anifrolumab did not induce CDC in human CD20+ IFNAR1+ target Daudi B cells (Study# RIA546-0009);
- Anifrolumab did not induce ADCC in IFNAR expressing 293F cells (Study# RIA546-0001 and RIA546-0012).

Safety Pharmacology

No stand-alone safety pharmacology studies were conducted with anifrolumab. The effect of anifrolumab on the CV system was evaluated in a GLP-compliant 39-week general IV toxicity study in monkeys (Study# 7140-129). In this study, cynomolgus monkeys were given 40 IV infusion (30 minutes) doses of anifrolumab at 5 and 50 mg/kg/week QW or 40 SC injection doses of anifrolumab at 15 and 60 mg/kg/week QW. ECG parameters and BP parameters were measured once during the predose phase, on Days 3 and 276 of the dosing phase, and on Day 83 of the recovery phase for these animals after they were anesthetized with ketamine. No drug-related adverse CV findings were noted. In another 4-week IV toxicity study in cynomolgus monkeys with lower systemic exposures (see Section 5.4), ECG parameters and BP were measured within 1 hr. post dosing on Day 22 (weekly dose, Study# (b) (4) 263.01). No drug-related adverse CV findings were noted.

The effect of anifrolumab on the central nervous system or respiratory system was not evaluated. However, no related clinical sign changes were noted in general toxicity studies described in Section 5.5.1.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	100% absorption for IV route
Distribution	N/A for biologics
Metabolism	N/A for biologics
Excretion	N/A for biologics
TK data from general toxicology studies	<u>Monkey</u> (single IV toxicity, Study# 7140-131) <i>Tmax: 0.0208 d</i> <i>T1/2: 0.29, 1.29, and 2.48 d for 0.03, 0.3, and 1 mg/kg doses, respectively</i> <i>Clearance (Cl): 140, 25.2, and 14.4 mL/kg/d for 0.03, 0.3, and 1 mg/kg doses, respectively</i> <i>Dose proportionality: proportional</i> <u>Monkey</u> (4-week IV toxicity, Study# (b) (4) 263.01) <i>Tmax: 0.104 d</i> <i>T1/2: 5.57 and 10.1 d for 5 and 30 mg/kg doses in week 4, respectively</i> <i>Dose proportionality: more than dose proportional due to anti-drug antibody (ADA) at lower doses;</i> <i>Gender difference: no</i> <i>Accumulation: 1-fold increase at 30 mg/kg</i> <u>Monkey</u> (39-week IV and SC toxicity, Study# 7140-129) <i>Tmax: 0.0208 d for IV, 2 to 3 d for SC route</i> <i>T1/2: 16.3 and 20.7 d for IV, 15.7 and 19.4 d for SC in week 39, respectively</i> <i>Dose proportionality: proportional</i> <i>Gender difference: no</i> <i>Accumulation: 3.77- to 4.49-fold increase for IV, 5.29- to 6.12-fold increase for SC</i>
TK data from reproductive toxicology studies	<u>Monkey</u> (Prenatal and Postnatal Development, IV route, Study# (b) (4) 263.11) <i>Tmax: 0.0208 d</i> <i>T1/2: 11.3 to 17.5 d</i> <i>Dose proportionality: proportional</i> <i>Accumulation: 1.6- to 2.0-fold increase</i> <i>AUC_{0-14d}: 20900 µg.d/mL for the NOAEL of 60 mg/kg IV</i> <i>Milk: detected</i> <i>Placenta transfer: highly possible due to 11- to 22-fold higher level of anifrolumab in infant serum on Day 30 after birth than maternal milk on lactation Day 25 to 30.</i>

Anifrolumab and Safety Margins

Adequate safety margins of anifrolumab were obtained supporting the corresponding clinical studies during the development.

Nonclinical			Clinical Safety Margins for MRHD (300 mg /60 kg) ^a	
Study	NOAEL (mg/kg, IV)	AUC (µg.d/mL)	AUC _{0-28d} = 1177 µg.d/mL ^b	AUC _{0-28d} = 1472 µg.d/mL ^b
39-week monkey	General: 50	AUC _{0-7d} : 21600	73x	59x
ePPND monkey	Maternal and Developmental: 60	AUC _{0-14d} : 20900	36x	28x

a: MRHD based on draft label submitted under BLA 761123 on 7/31/2020

b: The AUC_{0-28d} between weeks 48 to 52 in patients with SLE receiving repeat IV dosing of 5 mg/kg anifrolumab (Q4W for 52 weeks) was 1177 and 1472 µg.d/mL for high and low Type 1 IFN gene signature subjects, respectively (refer to the Applicant's response to information request dated 01/22/2021 under BLA 761123).

5.5. Toxicology

5.5.1. General Toxicology

General toxicity studies with anifrolumab were conducted in cynomolgus monkeys following single and repeated IV and SC administration with dosing durations up to 39 weeks. Cynomolgus monkey was selected as the pharmacologically relevant species based on comparable binding affinity and neutralization ability in cynomolgus monkey cells (COS-7) but not murine cells (MLE-12). All of the pivotal GLP-compliant studies were reviewed previously under IND 101849 (*DARRTS Reference ID: 2892411 and 4763101*). Key findings for the 39-week repeat-dose study are summarized below. Since no additional findings were noted in shorter-term toxicity studies, results from single dose and 4-week repeat-dose studies are not included in the table below.

39-week Intravenous Infusion Repeat-Dose Toxicity Study in Monkeys

Study title/ number: 39-week Repeat Subcutaneous Injection and Intravenous Infusion Toxicity, Toxicokinetic, and Immunogenicity Study with MEDI-546 in Cynomolgus Monkeys with a 12-week Recovery Period (Study# 7140-129)

Key Study Findings

- Minimal arteritis was noted in 4 males given 50 mg/kg via IV infusion or 60 mg/kg via SC injection with less severity in recovery animals. Heart, kidney, and pancreas were the major organs affected. The incidence of arteritis was likely due to ADA-mediated formation of immunocomplexes.

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (Vehicle control, IV-SC), 5 (LD-IV), 50 (HD-IV), 15 (LD-SC), and 60 (HD-SC) mg/kg, QW

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Route of administration: IV infusion (30 minutes) or SC injection
 Formulation/Vehicle: IV formulation (b) (4) mM histidine (b) (4)
 (b) (4) % lysine and (b) (4) % polysorbate 80, pH (b) (4)
 SC formulation (b) (4) : (b) (4) mM histidine (b) (4) % trehalose, (b) (4) % polysorbate 80, pH (b) (4)
 Species/Strain: Cynomolgus monkeys
 Number/Sex/Group: 6/sex/group (3/sex/group underwent a 12-week recovery period)
 Age: 5-7 years old for males and 3-4 years old for females
 Satellite groups/ unique design: None
 Deviation from study protocol affecting interpretation of results: None
 LD-IV: low dose intravenous, HD-IV: high dose intravenous
 LD-SC: low dose subcutaneous, HD-SC: high dose subcutaneous

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	None
Feed Consumption	None
Dermal Irritation	None
Ophthalmoscopy	None
ECG and blood pressure	None
Hematology and Coagulation	None
Clinical Chemistry	None
Urinalysis	None
Gross Pathology	None
Organ Weights	No drug-related adverse changes were noted.
Histopathology Adequate battery: Yes	Drug-related adverse findings were noted as minimal arteritis in multiple organs in 3 HD-IV males and 1 HD-SC male. Heart, kidney, and pancreas were major organs affected. Partial recovery was noted. The arteritis could be due to the deposit of ADA-mediated immunocomplexes based on positive staining of anifrolumab, monkey IgM, and complement component 3b (C3b) but not monkey IgG from kidney samples of 2 HD-IV monkeys with arteritis. Drug-related non-adverse findings were noted in the spleen and mandibular/axillary lymph nodes (LNs) with minimal increase in lymphoid follicle size and/or number noted in all drug-treated groups and persistence during the recovery period.
Semen Analysis	No drug-related effects on sperm motility, sperm morphology, or sperm concentration/count were noted.
Spermatogenesis Analysis	No drug-related changes in stage progression of the spermatogenic cycle, cell associations or cell proportions expected to be present during spermatogenesis were noted.

Menstrual cycle	No drug-related changes on menstruation were noted.
Immunophenotyping	No drug-related changes in absolute or relative peripheral blood immunophenotyping were noted.
Complement C3 and Bb Analysis	Minimal increase in mean C3 concentration in HD-IV males (1.20- to 1.28-fold) and HD-SC males (1.11- to 1.26-fold) from Days 85 through 274 was noted.
NOAEL	Males: 5 mg/kg/dose IV and 15 mg/kg/day SC due to arteritis (since arteritis attributed to immunogenicity in monkeys was not considered predictive of effects in human, the 50 mg/kg/dose IV and 60 mg/kg/dose SC can be used to support the safety of clinical studies.) Females: 50 mg/kg/dose IV and 60 mg/kg/dose SC

General toxicology; additional studies

In a GLP-compliant single-dose toxicity study, cynomolgus monkeys were given a single IV infusion (30 minutes) dose of anifrolumab at 0.003, 0.03, 0.3, and 1 mg/kg (Study# 7140-131). No drug-related toxicity was noted. ADA was detected in all dose groups with the highest antibody titers occurring on Day 29 at 1 mg/kg. The NOAEL was 1 mg/kg ($AUC_{0-t} = 75.8 \mu\text{g.d/mL}$).

In a GLP-compliant 4-week repeat-dose toxicity study with a 7-week recovery period, cynomolgus monkeys were given 4 IV infusion (30 minutes) doses of anifrolumab at 0.5, 5, and 30 mg/kg/week QW (Study# (b) (4) 263.01). The only toxicity noted was a transient (up to 4 days during the first 9 days) finding of dry feces in a dose-related manner. No hypersensitivity reaction was observed. ADA was detected in all dose groups, but the percentage of monkeys with positive titers decreased with increasing anifrolumab doses. The NOAEL was 30 mg/kg ($AUC_{0-7d} = 11,100 \mu\text{g.d/mL}$).

5.5.2. Genetic Toxicology

Genetic toxicity studies have not been conducted with anifrolumab. Genetic toxicity studies are generally not applicable for biotechnology-derived pharmaceuticals such as anifrolumab, as discussed in the ICH S6(R1) guidance document.

5.5.3. Carcinogenicity

Carcinogenicity studies have not been conducted with anifrolumab. However, the existing literature from studies with IFNAR1- and IFNAR2-deficient mice and mice administered IFN α/β and anti-IFN- α/β antibodies suggested that IFNAR blockade increased carcinogenic potential in rodents.

5.5.4. Reproductive and Developmental Toxicology

Enhanced Prenatal and Postnatal Development

Study title/ number: Assessment of Effects of MEDI-546 on Pre- and Postnatal Development When Administered by Intravenous Infusion Once Every Two weeks to Pregnant Cynomolgus Monkeys Starting on Gestation Day 20 to Early Lactation Period (Study# (b) (4) 263.11)

Key Study Findings

- No drug-related adverse effects in maternal animals or infants (F1) were noted for anifrolumab given once every two weeks (Q2W) via IV infusions up to 60 mg/kg IV;
- Anifrolumab was detected from maternal milk on Lactation Day (LD) 25-30;
- Anifrolumab was detected from infant serum on the day after birth (DB) 30 at much higher levels than the maternal milk, suggesting that anifrolumab is transferred via the placenta.

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (Vehicle control), 30 (LD-IV), and 60 (HD-IV) mg/kg, Q2W

Route of administration: IV

Formulation/Vehicle: (b) (4) mM histidine (b) (4) % lysine and (b) (4) % polysorbate 80, pH (b) (4)

Species/Strain: Cynomolgus monkeys

Number/Sex/Group: 16-17/female/group

Satellite groups: None

Study design: Animals (F0) were given control or drug-treatment Q2W via IV infusion (10 mL/kg/hour for 30 minutes) beginning on Gestation Day (GD) 20 and continued to at least LD 28. F1 infants were evaluated for developmental toxicities up to DB 213. No study of F2 generation was conducted.

Deviation from study protocol affecting interpretation of results: No

LD-IV: low dose intravenous, HD-IV: high dose intravenous

Observations and Results

Generation	Major Findings
F0 Dams	• No drug-related maternal toxicity; • No drug-related change of gestation length; • No drug-related effect on embryo/fetal viability, <i>in utero</i> embryo-fetal growth, or heart rate.
F1 Generation	• No drug-related mortality; • No drug-related effect on body weight, eyes, or heartbeat; • No drug-related hematology, coagulation, or clinical chemistry changes; • No drug-related effect on response to Keyhole Limpet Hemocyanin (KLH) challenge; • No drug-related effect on behavior, functional, morphological, or skeletal development; • No drug-related macroscopic or microscopic findings.
F2 Generation	Not conducted.

5.5.5. Other Toxicology Studies

Tissue cross reactivity

Staining of Alexa Fluor-488 -labeled anifrolumab was noted in many human and cynomolgus monkey tissues, which is consistent with published reports of broad expression of IFNAR in tissues (Study# IM1595 and IM1596).

Excipients, impurities, extractables and leachables

Refer to Appendix 16.3 for nonclinical assessment. No nonclinical safety concerns were identified.

6. Clinical Pharmacology

6.1. Executive Summary

Anifrolumab is a monoclonal antibody (mAb) that inhibits subunit 1 of the type I interferon receptor (IFNAR1). AstraZeneca submitted BLA 761123 on July 31, 2020 seeking the marketing approval for anifrolumab for the treatment of adults with moderate to severe systemic lupus erythematosus (SLE) (b) (4). The proposed dosing regimen is 300 mg every 4 weeks administered as an intravenous (IV) infusion.

BLA 761123 consists of eight clinical and clinical pharmacology studies, including two phase 1 studies, three phase 2 studies, and three phase 3 studies. In addition, three reports for population PK analysis, exposure-response modeling, and integrated summary of immunogenicity were submitted.

The following are the major clinical pharmacology findings of the current review:

1. Anifrolumab exhibits non-linear PK in the dose range of 100 mg to 1000 mg with AUC increased more than dose-proportionally due to IFNAR1-mediated clearance. Following the every 4 weeks IV administrations of anifrolumab, steady-state was reached by Day 85. The steady state exposure (AUC) for 1000 mg q4w is approximately 4 fold higher compared to the steady state exposure of 300 mg q4w. The steady state exposure (AUC) for 300 mg q4w is approximately 3 fold higher compared to the steady state exposure of 150 mg q4w.
2. The dosing regimen of anifrolumab has been adequately explored. Results from phase 2 dose-ranging study (1013) showed that while both 300 mg and 1000 mg q4w dosing regimens were efficacious in SLE patients, 1000 mg dosing did not provide additional treatment benefit. Therefore, IV 300 mg q4w dosing regimen was selected for phase 3 studies (04 and 05). A 150 mg dose group was included in the Phase 3 program to further elucidate dose response. The responder rate was numerically lower at 150 mg q4w. Exposure-response analysis for efficacy and safety indicated that the proposed IV 300 mg q4w dosing regimen provides the optimal benefit-risk balance in patients with SLE.
3. No dose adjustment of anifrolumab is recommended for any intrinsic or extrinsic factors.
4. In Phase 3 studies 04 and 05, 6 out of 352 subjects (1.7%) with anifrolumab IV 300 mg q4w treatment were detected ADA positive post baseline. Due to the limited number of subjects, no conclusion could be drawn regarding the impact of positive ADA on anifrolumab PK, PD, efficacy, and safety.
5. In patients with SLE, following the administration of anifrolumab at 300 mg IV q4w for 52 weeks, neutralization ($\geq 80\%$) of type I IFN gene signature was observed from week 4 to week 52 in blood samples of patients with elevated levels of type I IFN inducible

genes. This PD marker returned to baseline levels within 8 to 12 weeks following withdrawal of anifrolumab at the end of the 52-week treatment period. However, the clinical relevance of the type I IFN gene signature neutralization is unclear.

6. In SLE patients with positive anti-dsDNA antibodies at baseline (Studies 04 and 05), treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies over time through week 52.
7. In patients with low complement levels (C3 and C4), increases in complement levels were observed in patients receiving anifrolumab through week 52.

6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the clinical pharmacology data submitted under BLA 761123. This submission is recommended for approval from a clinical pharmacology perspective for the treatment of patients with SLE.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Anifrolumab is a mAb that inhibits IFNAR1. It exhibits non-linear PK in the dose range of 100 mg to 1000 mg due to IFNAR1-mediated clearance. Population PK analysis showed baseline type I IFN gene signature status and body weight have a significant impact on anifrolumab CL, but were not considered clinically relevant.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is 300 mg every 4 weeks administered as an IV infusion.

Therapeutic Individualization

None

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

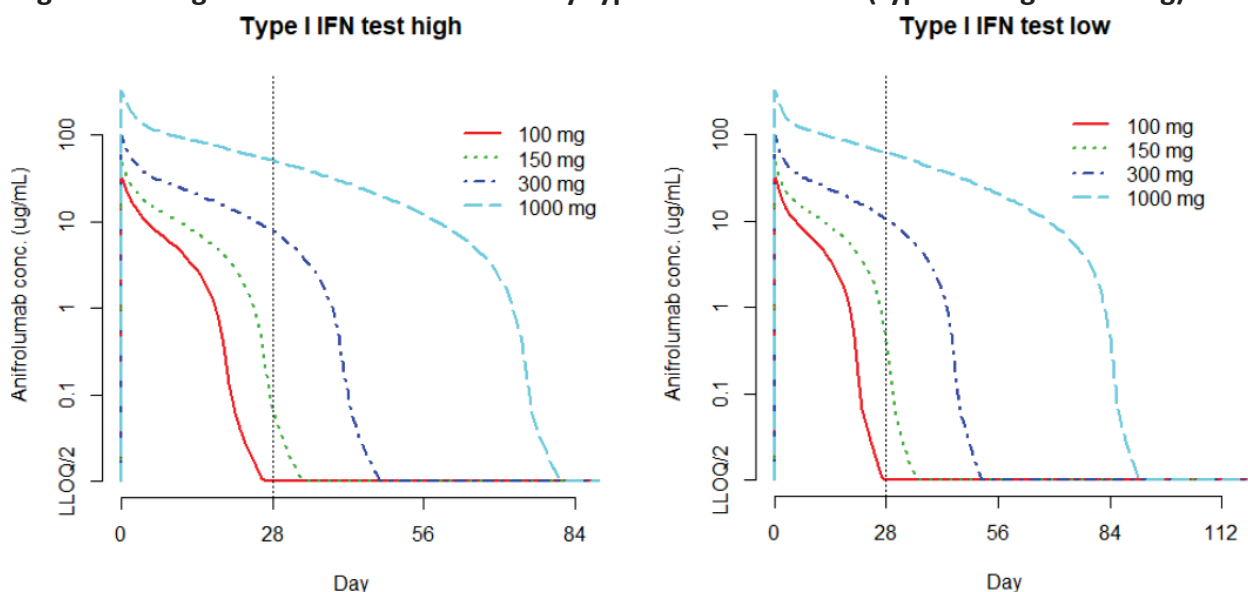
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Anifrolumab is a mAb that inhibits IFNAR1. Based on population PK analysis, anifrolumab exhibits non-linear PK in the dose range of 100 mg to 1000 mg with AUC increased more than

dose-proportionally due to IFNAR1-mediated clearance and the estimated clearance for anifrolumab is 0.193 L/day (Figure 1).

Following the every 4 weeks IV administrations of anifrolumab, steady-state was reached by Day 85 (Figure 2). There was minimal accumulation in C_{max} after multiple dosing with an accumulation ratio of 1.36 at the 300 mg dose level and 1.43 at the 1000 mg dose level (Table 3). Mean C_{trough} doubled after multiple doses with an accumulation ratio of 2.49 at the 300 mg dose level and 2.29 at the 1000 mg dose level (Figure 2, Table 3). Based on population pharmacokinetics, the steady state exposure (AUC) for 1000 mg q4w is approximately 4 fold higher compared to the steady state exposure of 300 mg q4w. The steady state exposure (AUC) for 300 mg q4w is approximately 3 fold higher compared to the steady state exposure of 150 mg q4w.

Figure 1. Model-predicted concentration-time profiles of anifrolumab 100, 150, 300, and 1000 mg after a single dose IV administration by type I IFN test status (typical weight of 70 kg)



(Source: Figure 12 of Summary of Clinical Pharmacology Studies)

Table 3. Summary of anifrolumab serum concentrations in SLE patients (Study 1013)

Parameter	Statistic	Anifrolumab					
		300 mg			1000 mg		
		IFNGS ^a low	IFNGS ^a high	Combined	IFNGS ^a low	IFNGS ^a high	Combined
C _{max} (µg/mL) ^b							
Day 1	n	24	74	98	26	78	104
	Mean (SD)	86.1 (61.0)	81.7 (65.9)	82.8 (64.5)	235 (64.5)	252 (84.4)	248 (79.9)
Day 169	n	21	65	86	21	66	87
	Mean (SD)	116 (78.0)	108 (59.0)	110 (63.7)	421 (117)	361 (141)	375 (137)
Day 337	n	21	62	83	17	50	67
	Mean (SD)	115 (51.5)	131 (68.4)	127 (64.6)	475 (129)	427 (143)	439 (140)
C _{trough} (µg/mL), mean (SD)							
Day 29	n	23	72	95	24	75	99
	Mean (SD)	11.5 (7.38)	6.82 (5.31)	7.95 (6.17)	57.5 (21.7)	43.3 (24.7)	46.8 (24.6)
Day 169	n	20	67	87	21	66	87
	Mean (SD)	23.3 (16.0)	17.0 (11.5)	18.4 (12.9)	154 (68.3)	95.7 (50.6)	110 (60.5)
Day 365	n	21	62	83	19	52	71
	Mean (SD)	28.3 (16.6)	22 (14.9)	23.6 (15.5)	197 (101)	139 (80.2)	154 (89.2)

Data derived from: Clinical PK report Table 5.3-1 in study 1013 CSR Section 16.1.13 (Module 5.3.5.1)

^a Type I IFN gene signature (4-gene) test status at baseline.

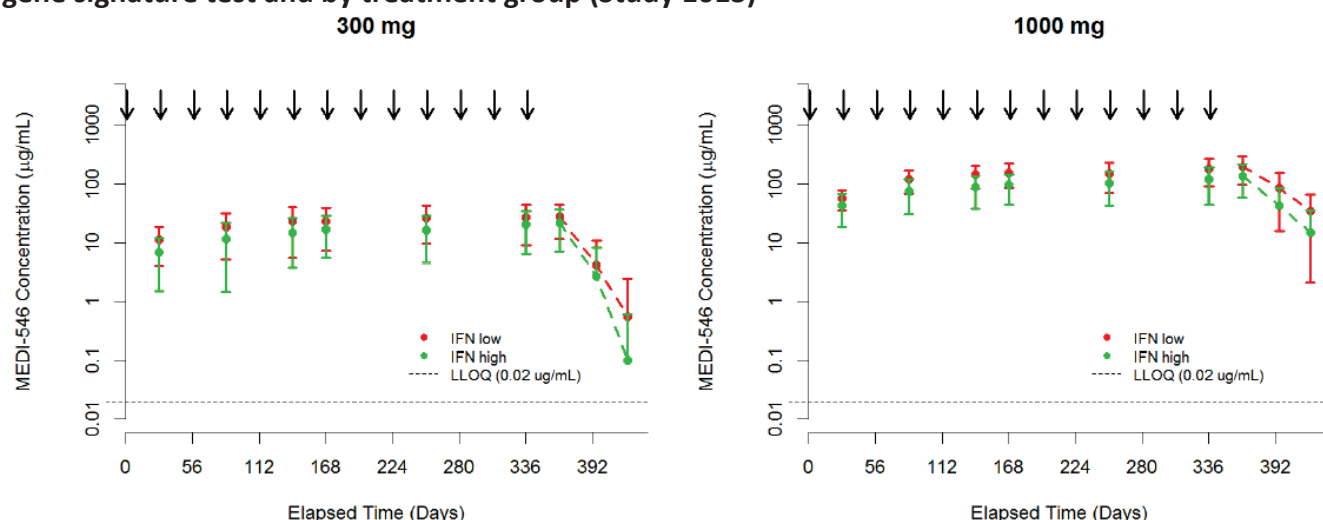
^b Postdose samples collected 15 minutes after the end of the infusion.

2.55% (76/2979) of samples were excluded from the summary due to missed doses or deviation in PK sampling times from protocol-specified collection times.

C_{max}, maximum concentration; C_{trough}, trough concentration; IFN, interferon; IFNGS, interferon gene signature; n, number of patients in analysis; PK, pharmacokinetic; SD, standard deviation; SLE, systemic lupus erythematosus.

(Source: Table 5 of Summary of Clinical Pharmacology Studies)

Figure 2. Mean predose anifrolumab serum concentration-time profiles by baseline type I IFN gene signature test and by treatment group (Study 1013)



Error bars represent standard deviation of the mean. Arrows represent dosing. Dashed lines represent elimination phase.

IFN, interferon; LLOQ, lower limit of quantitation; MEDI-546, anifrolumab.

(Source: Figure 3 of Summary of Clinical Pharmacology Studies)

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

This submission consists of 8 clinical and clinical pharmacology studies, including 2 phase 1 studies, 3 phase 2 studies, and 3 phase 3 clinical studies (Table 4). The proposed indication of anifrolumab was based on the three studies submitted to support approval (phase 2 study 1013 and phase 3 studies 04 and 05 (see section 7 and 8). The PD assessment of anifrolumab, i.e. the 21-gene type I IFN signature, provided supportive evidence of effectiveness.

What is the PD effect of Anifrolumab?

Type 1 IFN gene signature

Anifrolumab is a human IgG1k mAb that binds to IFNAR1 and inhibits type I IFN signaling by blocking the biologic activity of type I IFNs. Type I IFN signaling leads to the transcription activation and expression of over 100 genes, of which a subset of 21 genes was shown to be robustly upregulated by type I IFNs and used to monitor the impact of IFNAR blockade in blood. The 21-gene type I IFN signature was assessed in clinical studies as a PD biomarker of anifrolumab activity.

The SLE patient population has been stratified based on a 4-gene type I IFN gene signature test, where the genes in the subset were the most highly expressed in the target SLE patient population and the test results (high or low) were based on the over-expression of type I IFN-inducible genes. Approximately 75% patients in study 1013 and 82-83% patients in Studies 04 and 05 were type I IFN gene signature test high at baseline.

In the pooled PD analysis, 300 mg and 1000 mg resulted in $\geq 80\%$ median neutralization of the type I IFN gene signature by week 4 and attained over 52-week treatment period in patients with high type I IFN gene signature, whereas a much less extent of PD neutralization was observed in the 150 mg group (Figure 3). While neutralization of the type I IFN gene signature reflects the direct pharmacological effect of anifrolumab and there is a clear dose-dependent PD response, its clinical relevance is still unclear as the PD response is higher in the non-responders on the 300 mg arm compared to the responders on the 150 mg arm (Figure 4).

Table 4. Overview of anifrolumab clinical studies

Study number	Study type and design	Study population	Dose(s) of anifrolumab	Mode of admin.	Frequency of admin.	Dosing date(s)	PK, ADA, and PD sampling dates ^a
MI-CP180	Phase I; SAD/MAD; OL	M and F; 19-77 years of age; scleroderma	0.1, 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg	IV infusion over ≥ 60 min for doses ≤ 10 mg/kg or ≥ 120 min for doses > 10 mg/kg	Single-dose	Day 0	PK: predose on Days 0, 1, 7, 14, 21, 28, 56, 84, and postdose at 30 minutes from end of infusion on Day 0. ADA: Days 0 (predose), 28, 56, 84 PD: Days 0, 1, 7, 14, 28, 56, 84
			0.3, 1.0, or 5.0 mg/kg	IV infusion over ≥ 60 min	Weekly $\times 4$	Days 0, 7, 14, and 21	PK: predose on Days 0, 1, 7, 14, 21, 22, 28, 56, 84, 105 and postdose at 30 minutes from end of infusion on Days 0, 7, 14, and 21. ADA: Days 0 (predose), 28, 56, 84, 105 PD: Days 0, 1, 7, 14, 28, 56, 84, 105
D3461C00006	Phase I, RD/DB/PC	M and F; 19-55 years of age, healthy volunteers	300 or 600 mg	SC or IV infusion over 30 min	Single-dose	Day 1	PK: predose on Day 1 and postdose at 5 minutes after end of IV infusion (cohort 2 only), at 24 and 48 hours postdose, and at follow-up visits on Days 5, 8, 11, 15, 22, 29, 42, 57, and 85 (± 1 day) ADA: Days 1, 5, 29, and 85 PD: NA
CD-IA-MEDI-546-1013	Phase II; RD/DB/PC	M and F; 18-65 years of age; patients with SLE receiving standard of care	300 or 1000 mg	IV infusion over 60 min	Q4W for 52 weeks	Week 0 (Day 1) and Q4W thereafter through Day 337 (48 weeks)	PK: predose and postdose at 15 minutes after end of infusion on Days 1, 29, 85, 141, 169, 253, and 337 (and Days 365, 396, and 422 ± 7 days during follow-up period) ADA: Days 1, 85, 141, 169, 253, and 337 (and Days 365, 396, and 422 ± 7 days during follow-up period) PD: Days 1, 29, 85, 141, 169, 253, and 337 (and Days 365, 396, and 422 ± 7 days during follow-up period)
CD-IA-MEDI-546-1145	Phase II; RD/DB/PC	Patients who completed study 1013	300 mg ^b	IV infusion over ≥ 30 min	Q4W for up to 3 years (156 weeks)	Week 0 (Day 1) and Q4W thereafter through Week 156.	PK: Day 1 and Weeks 12, 24, 36, 48, 72, 96, 120, 144, and 156 (and 28 and 85 ± 7 days after last dose during follow-up period) ADA: Day 1 and Weeks 12, 24, 36, 48, 72, 96, 120, 144, and 156 (and 28 and 85 ± 7 days after last dose during follow-up period) PD: Day 1 and Weeks 12, 24, 36, 48, 72, 96, 120, 144, and 156 (and 28 and 85 ± 7 days after last dose during follow-up period)

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

D3461C00002 (Japan only)	Phase II; OL/DE	M and F; 20-61 years of age; patients with SLE receiving standard of care	100, 300, or 1000 mg (Stage I) 300 mg (Stage II)	IV infusion over $\geq$ 60 min (Stage I) IV infusion over $\geq$ 30 min (Stage II)	Q4W for 52 weeks (Stage I) Q4W for 156 weeks (Stage II)	Day 1 and Q4W thereafter through Day 337 (48 weeks) for Stage I and through Day 1093 (156 weeks) for Stage II	PK: Stage I: predose and postdose within 30 minutes after end of infusion on Day 1; on Days 2, 8, 15, 22; and predose on Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309; predose and postdose within 30 minutes after end of infusion on Day 337, (and on follow-up Days 338, 344, 351, 365, 393, and 422). Stage II: predose on Days 85, 169, 253, 337, 505, 673, 841, 1009, and 1093 (and follow-up Days 1121, 1149, and 1178). ADA/PD: Days 1, 29, 85, 141, 169, 253, 337, (and follow-up Day 365) (Stage I); Days 85, 169, 253 337, 505, 673, 841 1009, and 1093 (and follow-up Days 1121 and 1178) (Stage II)
D3461C00004	Phase III; RD/DB/PC	M and F; 18-69 years of age; patients with SLE receiving standard of care	300 mg	IV infusion over $\geq$ 30 min	Q4W for 52 weeks	Week 0 (Day 1) and Q4W thereafter through Week 48	PK: predose Week 0 (Day 1) and Weeks 12, 24, 36, 48, and 52, and postdose 15 $\pm$ 5 minutes after end of infusion on Weeks 0 and 48. ADA: Week 0 (Day 1) and Weeks 12, 24, 36, 48, and 52 PD: Week 0 (Day 1) and Weeks 12, 24, 36, and 52
D3461C00005	Phase III; RD/DB/PC	M and F; 18-69 years of age; patients with SLE receiving standard of care	150 or 300 mg	IV infusion over $\geq$ 30 min	Q4W for 52 weeks	Week 0 (Day 1) and Q4W thereafter through Week 48	PK: predose Week 0 (Day 1) and Weeks 12, 24, 36, 48, and 52, and postdose 15 $\pm$ 5 minutes after end of infusion on Weeks 0 and 48 ADA: Week 0 (Day 1) and Weeks 12, 24, 36, 48, and 52 PD: Week 0 (Day 1) and Weeks 12, 24, 36, and 52
D3461C00009	Phase III; RD/DB/PC	M and F; 18-69 years of age; patients with SLE receiving standard of care	300 mg	IV infusion over $\geq$ 30 min	Q4W for up to 39 doses	Week 0 (Day 1) and Q4W thereafter up to Week 152	PK: predose Week 0 (Day 1) and Weeks 12, 24, 36, 52, 76, 104, 128 and 156, and postdose 15 $\pm$ 5 minutes after end of infusion on Weeks 0, 12, 24, 36, 52, 76, 104, and 128 ADA: Week 0 (Day 1) and Weeks 24, 52, 104, and 156 PD: Week 0 (Day 1) and Weeks 4, 12, 52, 104, and 156

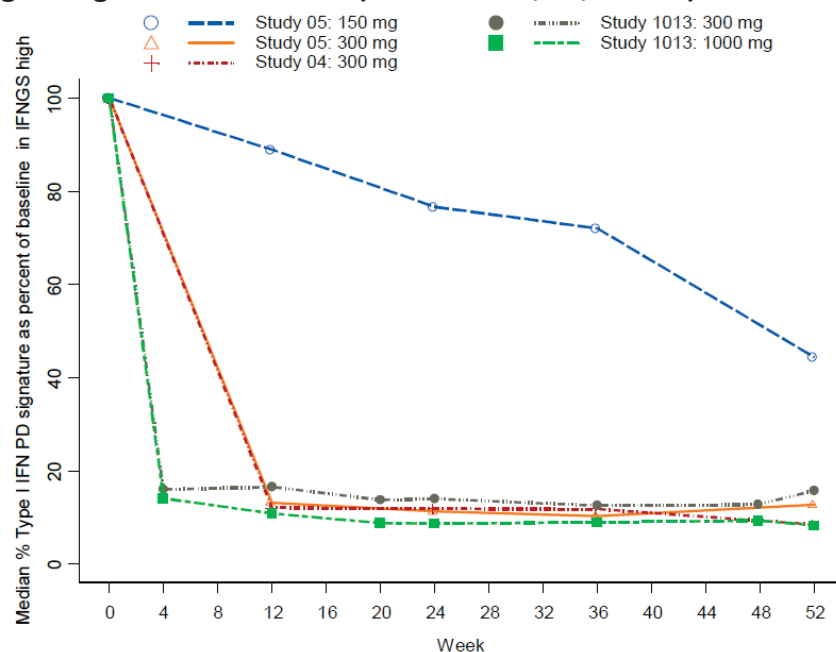
^a All samples are predose except where otherwise noted.

^b The original protocol-specified dose was 1000 mg IV Q4W but was amended to 300 mg based on population modeling of study 1013 interim data.

ADA, anti-drug antibody; DB, double-blind; DE, dose escalation; IV, intravenous; MAD, multiple ascending dose; NA, not applicable; OL, open label; PC, placebo-controlled; PD, pharmacodynamic; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; RD, randomized; SAD, single ascending dose; SC, subcutaneous; SLE, systemic lupus erythematosus.

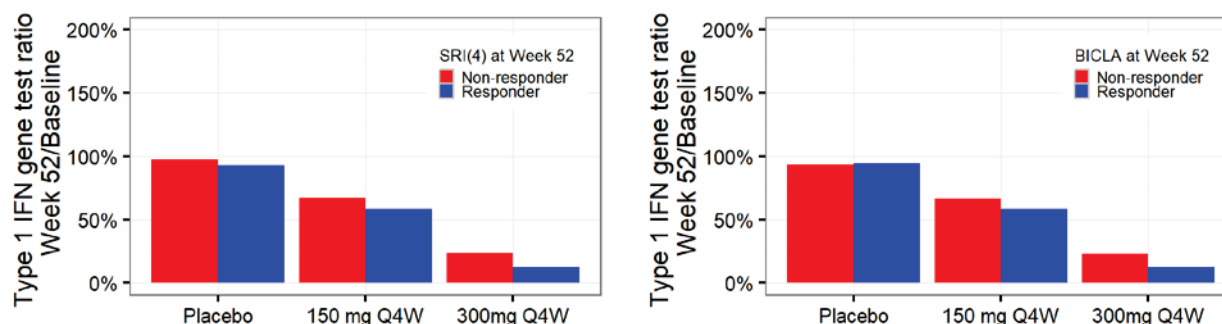
(Source: Table 2 of Summary of Clinical Pharmacology Studies)

Figure 3. Type I IFN gene signature as percent of baseline in SLE patients with high type I IFN gene signature at baseline (studies 1013, 04, and 05)



(Source: Figure 13 of Summary of Clinical Pharmacology Studies)

Figure 4. BICLA and SRI(4) response rates at week 52 vs. median neutralization of the type I IFN gene signature in type I IFN test high patients from anifrolumab 150 and 300 mg in studies 04 and 05



(Source: FDA analysis)

Immunology/serology (anti-dsDNA antibodies, C3, C4)

In the pooled phase 3 studies (Studies 04 and 05), for SLE patients with positive anti-dsDNA antibodies at baseline (median levels of anti-dsDNA were 50.1 U/mL and 53.0 U/mL, in the anifrolumab 300 mg and placebo groups, respectively), treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibody levels over time through week 52 compared with the placebo group (median change from baseline of -14.82 U/mL vs -5.37 U/mL at week 52).

In the pooled phase 3 studies (Studies 04 and 05), the mean levels of C3 at baseline were 0.691 g/L in the anifrolumab 300 mg group and 0.701 g/L in the placebo group. For patients with an abnormal C3 level at baseline, the anifrolumab 300 mg group had greater numerical increases in C3 levels over the 52 weeks compared with the placebo group (mean change from baseline of 0.13 g/L vs 0.04 g/L at week 52). The mean levels of C4 at baseline were 0.073 g/L in the anifrolumab 300 mg group and 0.072 g/L in the placebo group. In patients with low/abnormal complement levels at baseline, normalization of C4 was observed at week 52 in 22.6% (n=19) of patients receiving anifrolumab and in 7.1% (n=6) of patients receiving placebo.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

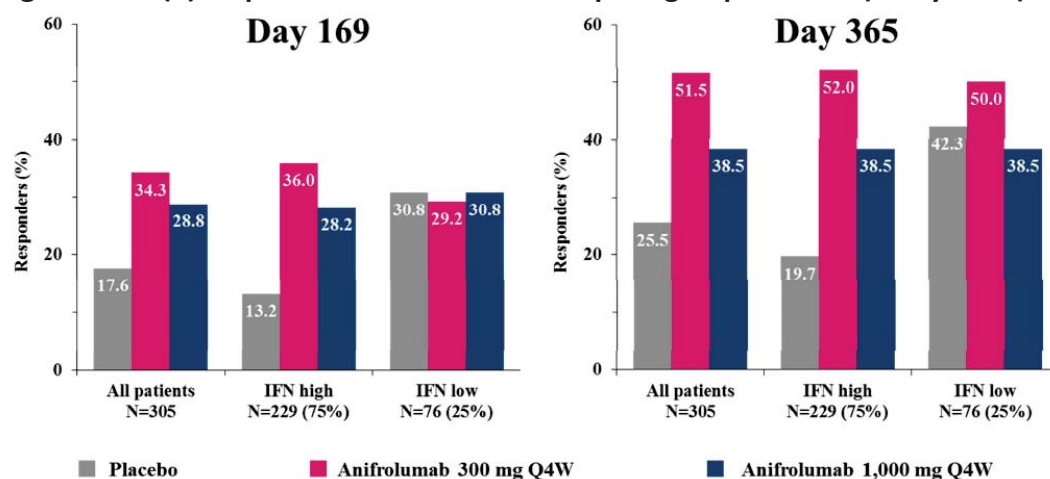
The proposed dosing regimen, IV 300 mg q4w, is appropriate for the general patient population for the treatment of patients with SLE.

Phase 2 dose-ranging study

Study 1013 is a phase 2, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 IV dosing regimens in subjects with chronic, moderately-to-severely active SLE with an inadequate response to SOC SLE. A total of approximately 300 subjects were randomized (1:1:1) to receive IV dose of anifrolumab 300 or 1000 mg or placebo q4w for 48 weeks. Results indicated that both 300 mg and 1000 mg treatment groups showed statistical improvement in the primary endpoint, SRI(4) with OCS tapering at week 24, over placebo and the response rates were similar between 300 mg and 1000 mg (34.3% and 28.8%, respectively, versus 17.6% in placebo). Thus, 300 mg q4w was considered appropriate for the Phase 3 program.

As 300 mg and 1000 mg appear to be on the plateau part of the dose-response curve for efficacy, a 150 mg dose group was included in the Phase 3 program to elucidate dose response and provide additional data to characterize benefit risk.

Figure 5. SRI(4) response rate without OCS tapering requirement (study 1013)

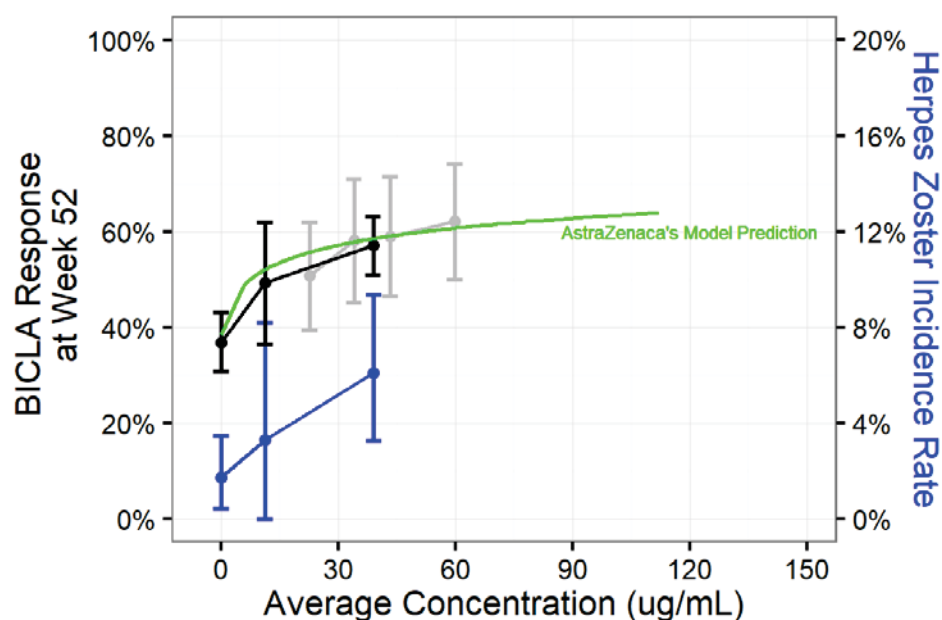


(Source: Figure 11.4.1.1-1 of Study 1013 CSR)

Exposure-response for efficacy and safety

The Applicant conducted exposure response (ER) analysis based on the two phase 3 studies with two dosing regimens (300 mg q4w, 150 mg q4w). The exposure response relationships for efficacy endpoints (BICLA and SRI(4)) and the safety event of interest (herpes zoster) are depicted in Figure 6 and Figure 7 below. For details in ER analysis, see section 16.4.3 Exposure Response Relationship.

Figure 6. Exposure response (BICLA) relationship in patients with type I IFN gene signature test high who completed treatment

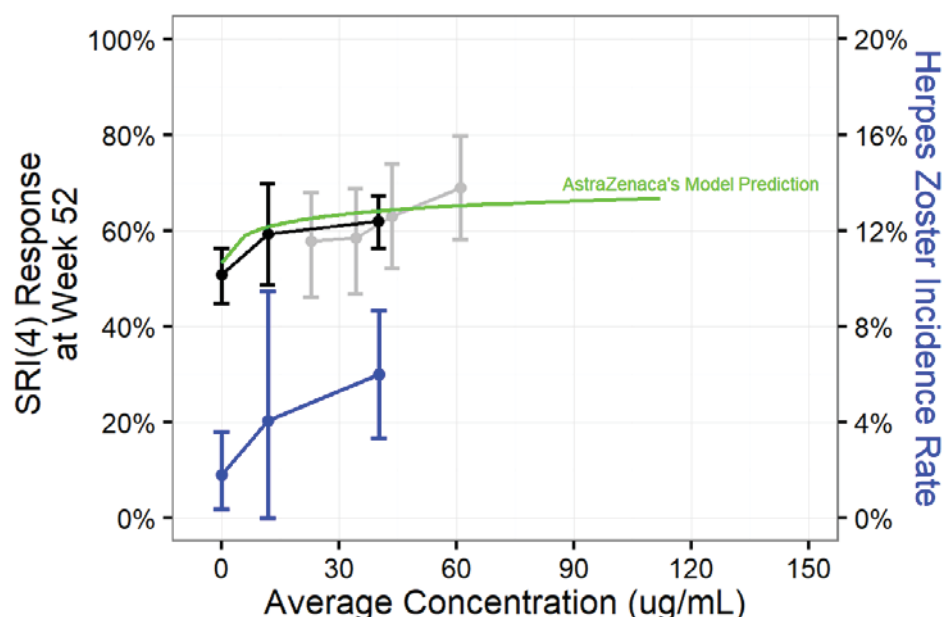


Exposure response for SRI(4) by treatment (placebo, 150 mg, 300 mg)

Exposure response for SRI(4) by exposure based quartiles of 300 mg
Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

(Source: reviewer's analysis Figure 33)

Figure 7. Exposure response (SRI(4)) relationship in patients who completed treatment



Exposure response for SRI(4) by treatment (placebo, 150 mg, 300 mg)
Exposure response for SRI(4) by exposure based quartiles of 300 mg
Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

(Source: reviewer's analysis Figure 37)

For the exposure-response for efficacy, for both BICLA and SRI(4), both responder rates were at its maximal levels at 300 mg q4w without further improvement at 1000 mg q4w, and numerically lower at 150 mg q4w. For the exposure-response for safety, the observed herpes zoster incidence rates in the Phase 2 study were 2.0%, 5.1%, and 9.5% for placebo, 300 mg q4w, and 1000 mg q4w, respectively. This result was consistent with the incidence rate observed in the Phase 3 studies, and together supported a dose dependent herpes zoster incidence rate from 150 mg to 1000 mg. These efficacy and safety ER analyses supported the 300 mg q4w dosing regimen as the optimized dosing regimen.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No dose adjustment is needed for subpopulations based on intrinsic factors.

In population PK analysis, body weight and baseline type I IFN status were identified as significant covariates. Patients with higher body weight and type I IFN test high patients were found to have higher CL, however, the difference was not considered clinically relevant.

Patients with high UPCR appeared to have higher CL, but the impact on PK was not significant. The exclusion criteria for UPCR was 2 mg/mg (or 226.30 mg/mmol) in the SLE clinical trials. Other intrinsic factors such as race/ethnicity/region, age, sex, and renal/hepatic function tests have no impact on the PK. See section 16.4 for details.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Anifrolumab is a mAb and proposed to be administered through IV infusion. There are no clinically relevant food-drug or drug-drug interactions.

Based on population PK analysis, concomitant use of oral corticosteroids, anti-malarials, immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine), NSAIDs, ACE inhibitors, and HMG-CoA reductase inhibitors did not significantly affect the PK of anifrolumab.

What is the incidence of ADA? What is the impact of ADA on the PK, PD, safety, and clinical outcomes of the biological product (e.g., therapeutic protein)?

In phase 3 studies 04 and 05, 6 out of 352 subjects (1.7%) with anifrolumab IV 300 mg q4w treatment and 17 out of 357 subjects (4.8%) with placebo were detected ADA positive post baseline. Due to the limited number of subjects, no conclusion could be drawn regarding the impact of positive ADA on anifrolumab PK, PD, efficacy, and safety.

Refer to the OBP review regarding the bioanalytical assay for immunogenicity assessment.

Table 5. Summary of ADA responses in phase 3 studies 04 and 05

Category		Anifrolumab 300 mg		Placebo	
		High IFNGS (N = 298)	All (N = 360)	High IFNGS (N = 301)	All (N = 365)
Any ADA results available	n ^a	297	359	301	365
ADA prevalence (positive at any visit, baseline, and/or post baseline)	m (%) ^b	24 (8.1)	25 (7.0)	31 (10.3)	35 (9.6)
nAb prevalence	m (%) ^b	2 (0.7)	2 (0.6)	6 (2.0)	7 (1.9)
Baseline ADA result available	n ^a	295	355	297	361
ADA positive only at baseline	m (%) ^b	12 (4.1)	13 (3.7)	4 (1.3)	4 (1.1)
Baseline and ≥ 1 post-baseline ADA result available	n ^a	292	352	293	357
ADA positive at both baseline and post baseline	m (%) ^b	6 (2.1)	6 (1.7)	14 (4.8)	15 (4.2)
ADA incidence (ADA positive post baseline or boosted ^c pre-existing baseline titers)	m (%) ^b	6 (2.1)	6 (1.7)	14 (4.8)	17 (4.8)
Negative/missing ADA at baseline and ≥ 1 post-baseline ADA result available	n ^a	277	338	279	342
ADA positive only post baseline (treatment induced) ^d	m (%) ^b	6 (2.2)	6 (1.8)	13 (4.7)	16 (4.7)
ADA persistently positive ^e	m (%) ^b	4 (1.4)	4 (1.2)	5 (1.8)	7 (2.0)
ADA transiently positive ^f	m (%) ^b	2 (0.7)	2 (0.6)	8 (2.9)	9 (2.6)
ADA positive with titer ≤ median of maximum titer ^g	m (%) ^b	3 (1.1)	3 (0.9)	8 (2.9)	11 (3.2)
ADA positive with titer > median of maximum titer ^g	m (%) ^b	3 (1.1)	3 (0.9)	5 (1.8)	5 (1.5)
nAb negative at baseline ^h and ≥ 1 post-baseline ADA result available	n ^a	291	351	292	356
nAb incidence ⁱ	m (%) ^b	1 (0.3)	1 (0.3)	5 (1.7)	6 (1.7)
nAb persistently positive ^j	m (%) ^b	1 (0.3)	1 (0.3)	4 (1.4)	4 (1.1)

Baseline is defined as the last measurement prior to randomization and dose administration on Day 1.

a Number of patients with ADA results available in each category.

b Number and percentage of patients with a positive result in each category; denominator uses n (defined above).

c An increase in baseline ADA titer by ≥ 4-fold during the study period.

d Treatment induced: ADA developed post baseline (after first dose of IP) in a patient who is ADA negative at baseline or has missing ADA assessment at baseline.

e Persistently positive ADA: Treatment-induced ADA detected at 2 or more assessments (with ≥ 16 weeks between first and last positive) or detected at last assessment.

f Transiently positive ADA: Treatment-induced ADA detected but not fulfilling the conditions of persistently positive.

g Median titer is defined as the median of the maximum titers post baseline (in patients with treatment-induced ADA) for each patient in the treatment group.

h nAb negative at baseline includes patients who are ADA negative at baseline.

i nAb incidence: nAb positive at post-baseline time points only (i.e., nAb negative at baseline).

j Persistently positive nAb is defined as nAb positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment (patients are nAb negative at baseline).

(Source: Table 6 of Integrated Summary of Immunogenicity)

Question on clinically relevant specifications (TBD)?

None

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Table 6. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
CD-IA-MEDI-546-1013	01438489	Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of MEDI-546 in Subjects with SLE	52-week study of Anifrolumab 300 mg and 1000 mg vs Placebo every 4 weeks IV infusion	SRI-4 + OCS Tapering at week 24	52 weeks	307	Adults with Active SLE	79 study sites in 15 countries
D3461C 00005	02446912	Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Two Doses of Anifrolumab in Adult Subjects with Active SLE	52-week study of Anifrolumab 150 mg and 300 mg vs Placebo every 4 weeks IV infusion	SRI-4 at week 52	52 weeks	460	Adults with Active SLE	146 study sites in 18 countries
D3461C 00004	02446899	Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active SLE	52-week study of Anifrolumab 300 mg vs Placebo every 4 weeks IV infusion	BICLA at Week 52	52 weeks	373	Adults with Active SLE	113 study sites in 16 countries
D3461C	0279	Multicenter,	(Ongoing) Up to 3-year	Number of	Up to 3 years	556	Subjects	175 study

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

00009	4285	Randomized, Double-blind, Placebo-controlled Phase 3 Extension Study to Characterize the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active SLE	extension Anifrolumab 300 mg vs Placebo every 4 weeks IV infusion	patients with TEAEs and TESAEs	beyond initial 52 weeks in studies 05 and 04		who completed studies 05 & 04	sites in 18 countries
Studies to Support Safety								
CD-IA-MEDI-546-1145	0175 3193	Phase 2, Open-label Extension Study to Evaluate Long term Safety of MEDI-546 in Adults with SLE	Up to 3-year extension Anifrolumab 300 mg vs Placebo every 4 weeks IV infusion [prior to Feb 12, 2015 protocol amendment, dose of Anifrolumab was 1000 mg]	Number of patients with TEAEs and TESAEs	Up to 3 years beyond initial 52 weeks in study 1013	218	Subjects who completed study 1013	57 study sites in 15 countries

7.2. Review Strategy

The clinical review program supporting registration of anifrolumab for the treatment of SLE consisted of 1 Phase 2 trial (CD-IA-MEDI-546-1013) and 2 Phase 3 trials (D3461C00004 and D3461C00005). See section 8.3 for a detailed description of these studies.

No pooling of data was performed for the efficacy analysis. For the evaluation of safety, the 52-week safety data for the 300 mg IV dose was summarized in the clinical study reports for studies 1013, 04 and 05.

The application contained double-blind safety data from adult SLE patients collected over 52 weeks of 300 mg IV anifrolumab dosing in studies 1013, 04 and 05. Safety data for all 3 doses of anifrolumab (150 mg, 300 mg, and 1000 mg) from studies 1013, 04 and 05 plus study 1145 (open-label extension from study 1013) and for the 300 mg dose in study 09 (placebo-controlled long-term extension from studies 04 and 05) were also included for completeness.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. CD-IA-MEDI-546-1013 (Phase 2), D3461C00004 (Phase 3), and D3461C00005 (Phase 3)

Trial Designs

Study 1013

Study CD-IA-MEDI-546-1013 (1013) was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study. Patients were randomized in a 1:1:1 fashion to MEDI-546 (anifrolumab) 1000mg, MEDI-546 300mg, or placebo (Figure 8). Anifrolumab or placebo was administered as an IV infusion via an infusion pump for approximately 60 minutes every 4 weeks for a total of 13 doses (first dose at Day 1 (week 0) and last dose at Day 337 (week 48)). All patients were to be followed for 85 days after Day 337 through Day 422 (week 60). Randomization was stratified by (SLEDAI-2K) score at screening (< 10 points vs ≥ 10 points), Day 1 OCS dose (< 10 mg/day vs ≥ 10 mg/day of prednisone or equivalent), and the results of a diagnostic test for type I IFN signature in whole blood at screening using a 4-gene type I IFN test (positive vs negative).

The study design included oral corticosteroid (OCS) tapering targets. Patients who experienced an increase in SLE activity were permitted one burst of OCS or intramuscular corticosteroids between Day 1 and 71, however, were required to taper to Day 1 levels or less within 14 days and to complete by Day 71, otherwise they would be declared non-responders for the primary and disease activity related secondary endpoints. Further, patients who required an increase of OCS above Day 1 dose levels after Day 71 were to be declared non-responders for the primary endpoint and disease activity related secondary endpoints at Day 169 (week 24). In addition, patients who were unable to reduce OCS to < 10 mg/day and $\leq$ Day 1 dose of prednisone or equivalent by Day 85 and unable to maintain OCS doses < 10 mg/day and $\leq$ Day 1 dose of prednisone or equivalent until Day 169 were to be declared non-responders for the primary endpoint at Day 169 (week 24).

Patients were also permitted to receive one additional burst of OCS or intramuscular corticosteroids between Days 169 and 281 and were not to be declared a non-responder for disease activity secondary endpoints at Day 365 (week 52) if they tapered to Day 169 levels or less within 14 days and completed by Day 281. Patients who required an increase of OCS above the minimum of Day 1 dose or Day 169 dose level after Day 281 were to be declared non-responders for disease activity secondary endpoints at Day 365 (week 52). Patients who were unable to reduce OCS to < 10 mg/day and $\leq$ Day 1 dose of prednisone or equivalent by Day 281 and unable to maintain OCS doses < 10 mg/day and $\leq$ Day 1 dose until Day 365 were to be declared non-responders for certain disease activity secondary endpoints at Day 365 (week 52).

Investigators should have tapered OCS based on disease activity in all subjects throughout the study, as permitted between Days 1 and 113 and between Days 169 and 309. Patients who permanently discontinued from receiving investigational product were to be followed for safety. Further, two follow-up visits were scheduled for Day 396 (week 56) and Day 422 (week 60).

Key inclusion criteria include:

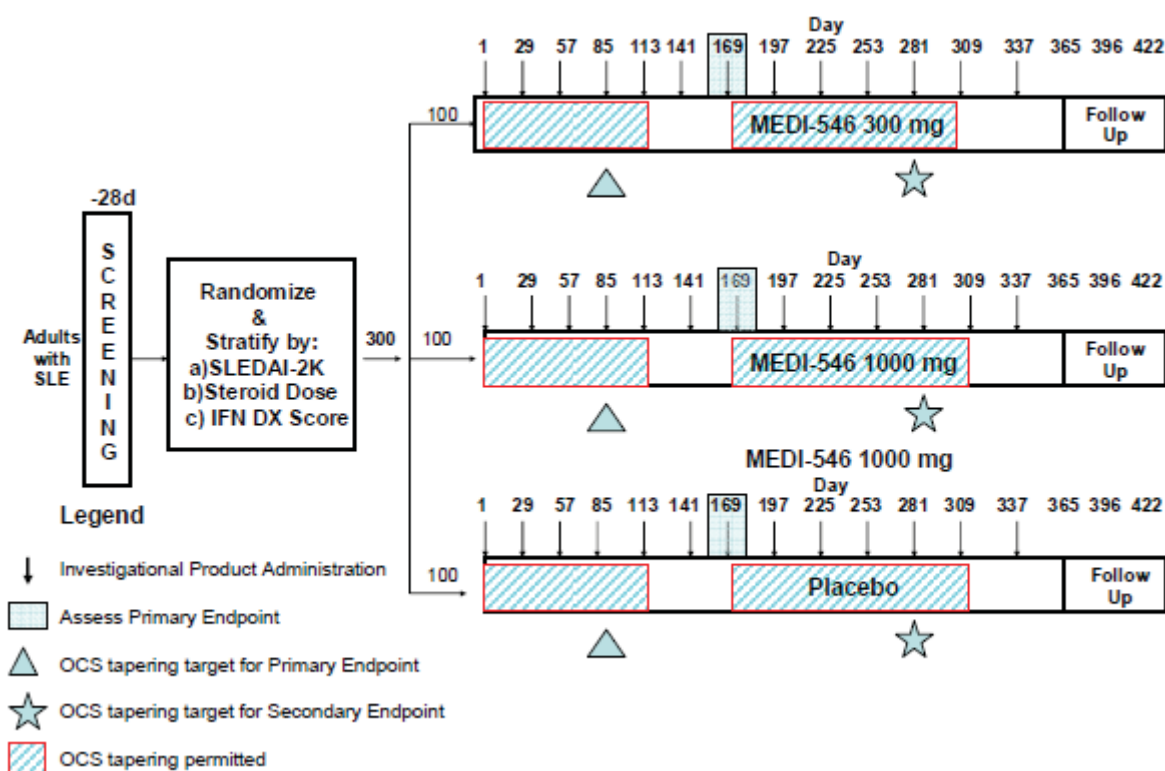
- 18 to 65 years of age
- Fulfilled at least 4 of the 11 American College of Rheumatology (ACR) classification criteria for SLE
- Diagnosis of pediatric or adult SLE with chronic disease activity requiring ongoing treatment or observation for ≥ 24 weeks prior to screening
- Prior to Day 1, external adjudication group confirmation of both:
 - At screening, SLEDAI-2K score ≥ 6 points and “Clinical” SLEDAI-2K score ≥ 4 points:
 - At least one of the following:
 - BILAG-2004 Index A disease in ≥ 1 body/organ system
 - BILAG-2004 Index B disease in ≥ 2 body/organ systems
- Day 1 “Clinical” SLEDAI-2K score ≥ 4 points
- Physician Global Assessment (MDGA) ≥ 1.0 on a 0 to 3 Visual Analog Scale (VAS) scale at screening

Key exclusion criteria included:

- Receipt of any of the following:
 - Any new oral prednisone therapy (or equivalent) anytime from 2 weeks prior to signing of the informed consent through Day 1 or any change in current oral prednisone dose (or equivalent) anytime from 2 weeks prior to Day 1
 - Any new dose of any of the following anytime in the 12 weeks prior to signing of the informed consent or change in current dose anytime in the 8 weeks prior to signing of the informed consent through Day 1: azathioprine; any antimalarial; mycophenolate mofetil/mycophenolic acid; and oral, SC, or intramuscular methotrexate
- Receipt of any of the following:
 - Azathioprine > 200 mg/day
 - Mycophenolate mofetil/mycophenolic acid > 2.0 g/day
 - Oral, SC, or intramuscular methotrexate > 25 mg/week
 - Any change in the route of administration of oral, SC, or intramuscular methotrexate anytime within the 8 weeks prior to signing of the informed consent
- Receipt of any of the following slow-acting immunosuppressants:
 - Etanercept ≤ 4 weeks prior to signing the informed consent form
 - Adalimumab, infliximab, or golimumab ≤ 12 weeks prior to signing the informed consent form
 - Rituximab or belimumab ≤ 48 weeks prior to signing the informed consent form

- Active severe or unstable neuropsychiatric SLE that would have made the subject unsuitable for the study or unable to fully understand the informed consent
- Within 8 weeks prior to screening, active severe SLE-driven renal disease or unstable renal disease (e.g., clinically significant increase in creatinine or active urinary sediment) that in the opinion of the investigator would have made the subject unsuitable for the study
- History of, or current, inflammatory joint or skin disease other than SLE that in the opinion of the investigator could have interfered with the inflammatory arthritis or skin assessments and confounded the disease activity assessments
- History of any non-SLE disease that had required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to randomization

Figure 8. Design for study 1013



Source: CSR Page 20
MEDI-546=Anifrolumab

Study 05

Study D3461C00005 (05) was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study. Patients were randomized in a 1:1:1 fashion to anifrolumab 300mg, anifrolumab 150mg, or placebo (Figure 9). Anifrolumab or placebo was administered as

an IV infusion via an infusion pump over a minimum of 30 minutes, every 4 weeks for a total of 13 doses. Randomization was stratified using the following factors: SLEDAI-2K score at screening (<10 points vs ≥ 10 points); week 0 (Day 1) OCS dose (<10 mg/day vs ≥ 10 mg/day prednisone or equivalent); and results of a type I IFN gene signature test (high vs low).

From week 0 (Day 1) to week 12, patients were permitted only 1 burst of corticosteroids for an increase in SLE disease activity or to control non-SLE related. Patients receiving more than 1 burst during the first 12 weeks of treatment were considered non-responders for subsequent assessments of disease activity, regardless of the reason for the burst (SLE or non-SLE activity).

Permitted medications for SLE standard of care are described in the protocol. Patients who discontinued investigational product (IP) were encouraged to continue to undergo all study-related visits/procedures for the full treatment period (52 weeks) in order to support the final efficacy and safety analysis.

Key Inclusion Criteria:

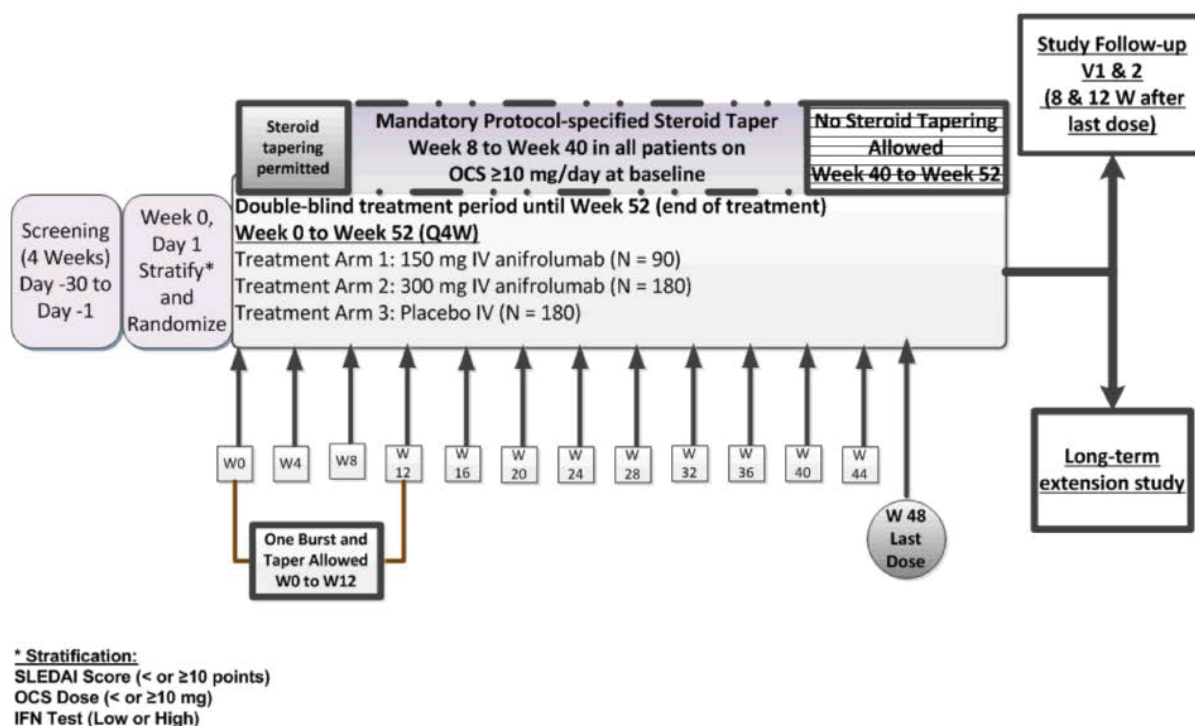
- Between 18 and 70 years of age, inclusive, at the time of screening
- Fulfilled at least 4 of the 11 ACR modified 1982 classification criteria for SLE
- Had a diagnosis of pediatric or adult SLE according to the ACR 1982 revised criteria ≥ 2 4 weeks prior to signing the ICF
- At Screening, disease activity adjudication group confirmation of:
 - SLEDAI-2K Criteria: SLEDAI-2K score ≥ 6 points and “Clinical” SLEDAI-2K score ≥ 4 points. The “Clinical” SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures:
 - Includes points from the following clinical components: arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, or vasculitis
 - Excludes points attributed to a fever, an SLE headache, and organic brain syndrome
 - BILAG-2004 Level Criteria: At least 1 of the following:
 - BILAG-2004 level A disease in ≥ 1 organ system
 - BILAG-2004 level B disease in ≥ 2 organ systems
 - Physician Global Assessment (PGA) score ≥ 1.0 on a 0 to 3 VAS at screening
- OCS dose stable for at least 2 weeks prior to randomization
- Stable SLE standard of care treatment at the time of randomization

Key Exclusion Criteria:

- Receipt of any of the following:
 - Azathioprine >200 mg/day
 - Mycophenolate mofetil >2 g/day or mycophenolic acid >1.44 g/day
 - Oral, SC, or IM methotrexate >25 mg/week
 - Mizoribine >150 mg/day

- Any change in route of administration of oral, SC, or IM methotrexate anytime within the 8 weeks prior to signing of the ICF through Day 1
- History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome
- Active severe SLE-driven renal disease where, in the opinion of the PI, protocol specified standard of care was insufficient and utilization of a more aggressive therapeutic approach, such as adding IV cyclophosphamide and/or high dose IV pulse corticosteroid therapy or other treatments not permitted in the protocol, was indicated

Figure 9. Design for study 05

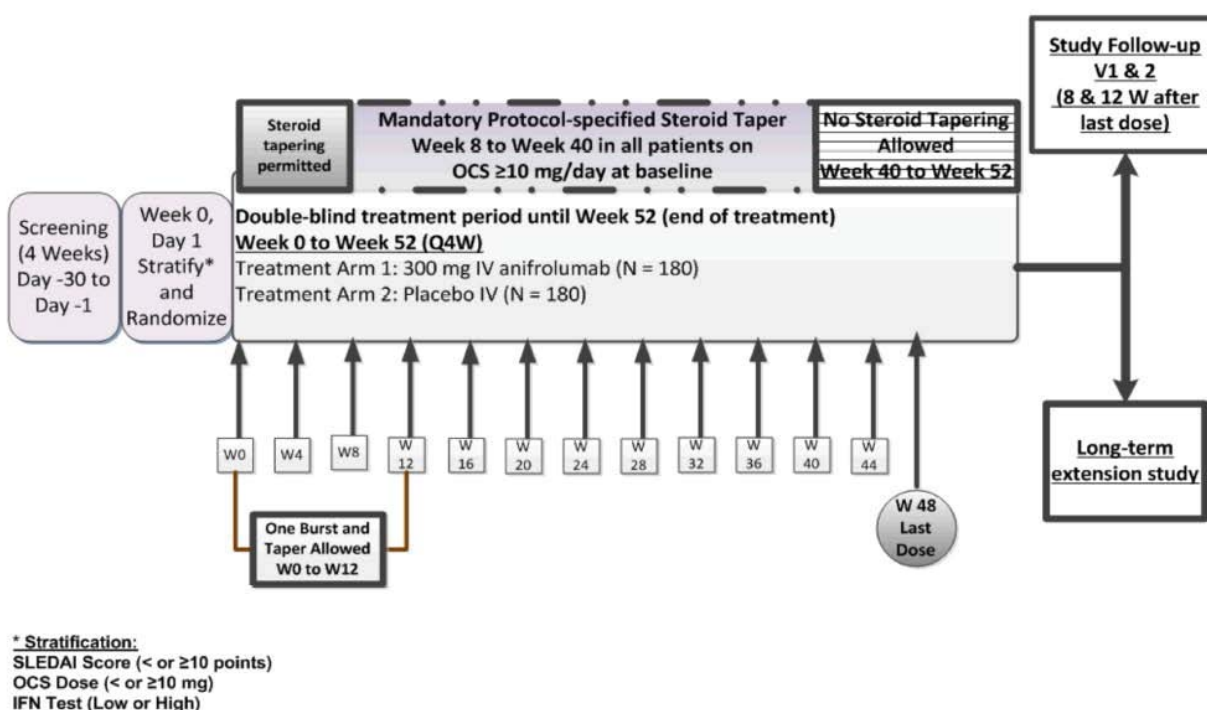


Source: CSR Page 22

Study 04

Study D3461C00004 (04) was a 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study. Patients were randomized in a 1:1 fashion to anifrolumab 300mg or placebo (Figure 10). Since the design and conduct were highly similar to study 05, refer to above for key elements and inclusion/exclusion criteria.

Figure 10. Design for Study 04



Source: CSR Page 21

Study Endpoints

Primary Endpoints

Study 1013: SRI-4 + OCS tapering at week 24 (evaluated in the whole population and Type I IFN High subgroup), which is a composite of the following:

- Reduction in baseline SLEDAI-2K disease activity score of ≥ 4 points
- No worsening in MDGA defined as an increase of ≥ 0.3 from baseline on a 0 to 3 visual analog scale
- No worsening in BILAG-2004 defined as ≥ 1 new A or ≥ 2 new B items compared to baseline
No discontinuation of IP
- Patients who need a burst of OCS or intramuscular corticosteroids need to satisfy the following:
 - No increase in dose of antimalarials or disease modifying anti-rheumatic above Day 1 levels or added new antimalarials/disease modifying anti-rheumatic between Day 1 and Day 169
 - No IV corticosteroid between Day 1 and Day 169
 - No increase in oral corticosteroids (OCS) above Day 1 dose or intramuscular/intra-articular (IM/IA) injection of corticosteroid after Day 71 and up to Day 169

- No more than one course of burst of corticosteroid between Day 1 and Day 71. One course of burst is defined as burst of OCS above Day 1 dose (up to a maximum dose of 40mg/day prednisone or equivalent and no increase in OCS dose for > 14 days above Day 1 dose) or 1 IM injection of corticosteroids (≤160 mg methylprednisone or equivalent) or 2 IA injections of corticosteroids
- Reduce OCS to < 10mg/day and ≤ Day 1 dose of prednisone or equivalent by Day 85 and maintain OCS dose < 10mg/day and ≤ Day 1 dose until Day 169 (Note: this criterion applies to subjects with OCS ≥ 10 mg/day at baseline)

Study 05: SRI-4 at week 52, which is a composite of the following:

- A reduction in baseline SLEDAI-2K disease activity score of ≥ 4 points
- No worsening in PGA defined as an increase of ≥ 0.3 from baseline on a 0 to 3 PGA visual analog scale
- No worsening in BILAG-2004 defined as ≥ 1 new A or ≥ 2 new B items compared to baseline
- No discontinuation of IP
- No initiation of restricted medication beyond the protocol-allowed threshold before week 52

Study 04: BICLA at week 52, which is a composite of the following: No worsening from baseline in SLEDAI-2K defined as an increase of > 0 points

- No worsening in PGA defined as an increase of ≥ 0.3 from baseline on a 0 to 3 PGA visual analog scale
- Reduction of all baseline BILAG-2004 A to B/C/D and baseline B to C/D and no worsening in other organ systems defined as ≥ 1 new A or ≥ 2 new B items compared to baseline
- No discontinuation of IP
- No initiation of restricted medication beyond the protocol-allowed threshold before week 52

The original pre-specified endpoint for study 04 was SRI-4 at week 52. See section below on statistical analysis plan for further discussion.

From the construction of these endpoints, the Applicant used a composite strategy in the handling of discontinuation of treatment and/or use of excess immunosuppressants/restricted medication. As supplemental analyses, since we are interested in the efficacy outcomes regardless of treatment discontinuation and/or use of excess immunosuppressants/restricted medication, evaluation of the endpoints using a treatment policy strategy was considered for SRI-4 and BICLA in each of the 3 studies. In other words, to be considered a responder, the patient only needs to satisfy the SLEDAI-2K, BILAG-2004, and MDGA/PGA criteria, irrespective of discontinuation of IP, excess of OCS medication/initiation of restricted medication, or OCS tapering. Demonstrating favorable efficacy of anifrolumab when applying the treatment policy strategy would lessen concerns with differences relating to use of restricted medication rules across the three studies and strengthen the overall confidence in the study results and

conclusions.

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Secondary Endpoints

Study 1013

No secondary endpoints were specified under a multiplicity control method, however, the following were examined as exploratory:

- BICLA at week 52
- SRI-4 at week 52
- OCS at week 52
- CLASI at week 12
- Joint reduction at week 52
- Annual flare rate through week 52

Study 05

- Maintaining OCS reduction at week 52
- CLASI response at week 12
- SRI-4 in type I IFN test high patients
- SRI-4 at week 24
- Annual flare rate through week 52

The following endpoints were also examined in post-hoc analyses using study 04 restricted medication rules. As such, the results were considered exploratory.

- Maintaining OCS reduction at week 52
- CLASI response at week 12
- Joint reduction at week 52
- BICLA in type I IFN test high patients

Study 04

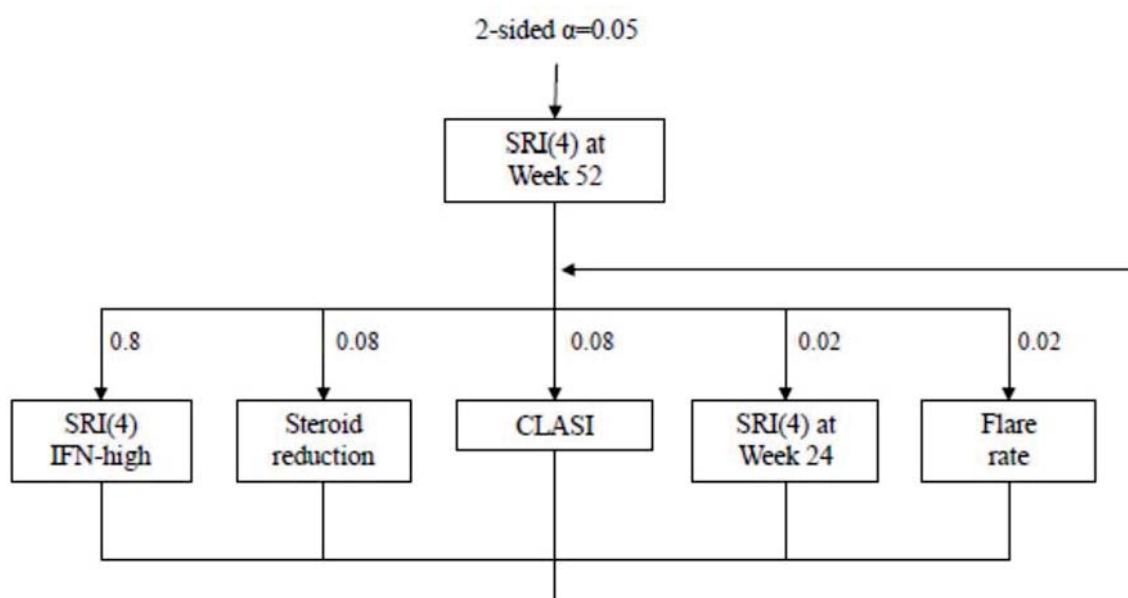
- Maintaining OCS reduction at week 52
- CLASI response at week 12
- Joint reduction at week 52
- BICLA in type I IFN test high patients
- Annual flare rate through week 52

Multiplicity control

Study 1013: The testing procedures specified that a global trend test (Cochran-Armitage trend test) for the 1000 mg and 300 mg doses would be performed in the overall population and the diagnostic positive subpopulation (i.e., type I IFN test high patients). No multiplicity adjustment for the two populations was applied and alpha was pre-specified to be 0.10. If the test in the overall population was significant at 0.10, then each dose would be compared to placebo at a significance level of 0.10, without specification of order. No other adjustments were planned for the secondary endpoints.

Study 05: The primary and key secondary endpoints were tested using a weighted Holm procedure. The procedure applies alpha recycling according to the weights shown in Figure 11 below:

Figure 11. Study 05 Alpha Recycling for Weighted Holm Procedure



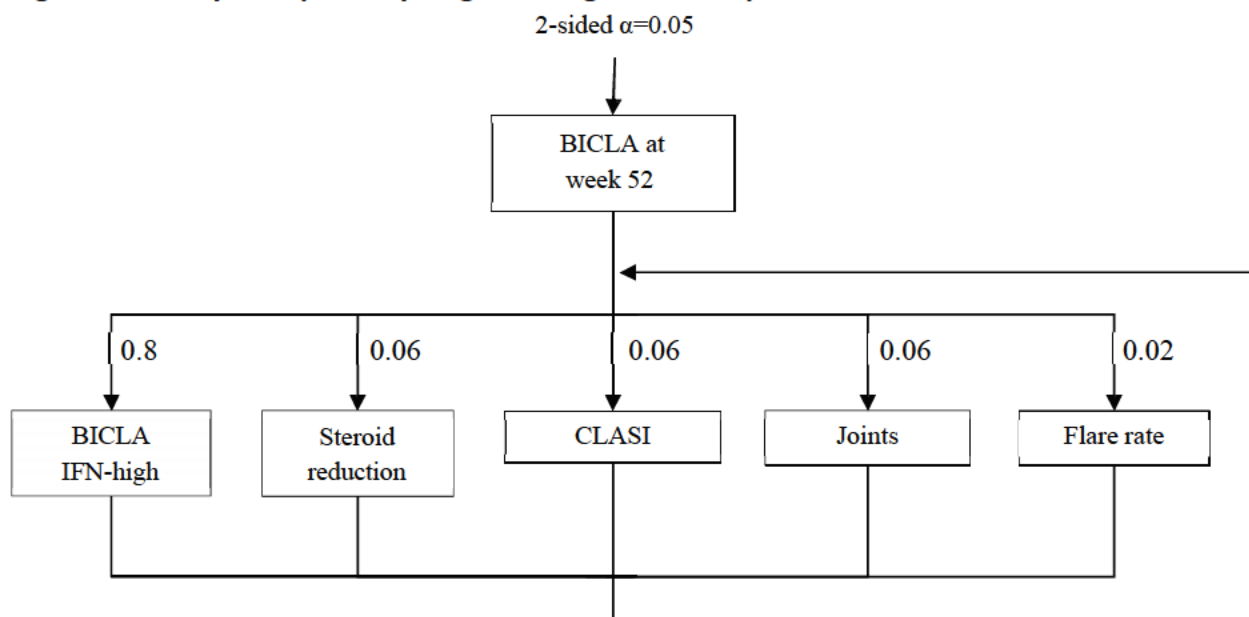
Source: CSR Page 75

SRI(4): Systemic Lupus Erythematosus Responder Index

CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index

Study 04: The primary and key secondary endpoints were tested using a weighted Holm procedure. The procedure applies alpha recycling according to the weights shown in Figure 12 below:

Figure 12. Study 04 Alpha recycling for Weighted Holm procedure



Source: CSR Page 71

SRI(4): Systemic Lupus Erythematosus Responder Index

CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index

Statistical Analysis Plans

Study 1013

There were two versions of the statistical analysis plan (SAP), with the final version finalized in April 2014. It does not appear that this SAP was reviewed by the Agency.

Primary Endpoint:

The primary endpoint of SRI-4 + OCS tapering at week 24 was tested in the 1000mg and 300mg arms against placebo in the whole population using the Cochran-Armitage trend test, and likewise both doses were tested in the Type I IFN High subgroup. Subsequently, each dose was nominally tested separately against placebo in each population. Below are described the pre-specified methods used in the analyses.

- Analysis populations:
 1. Whole population - Modified Intent-to-Treat (mITT): All randomized subjects who received any investigation product and had a baseline primary efficacy measurement.
 2. Type I IFN High subgroup: Subset of mITT population who are in the type I IFN High subgroup

- Handling of week 24 missing data: Missing intermittent week 24 data (complete or partial) were imputed by LOCF. Dropouts with no observed week 20 data were considered as non-responders.
- Analysis methods:
 - Using the mITT: Logistic regression with treatment, screening SLEDAI-2K Score (< 10 points, ≥ 10 points), OCS usage at baseline (< 10 mg/day, ≥ 10 mg/day), and results of 4-gene diagnostic test at screening (positive, negative) as factors.
 - Using the Type I IFN High subgroup: Logistic regression with treatment, screening SLEDAI-2K Score (< 10 points, ≥ 10 points), and OCS usage at baseline (< 10 mg/day, ≥ 10 mg/day) as factors

For easier comparison and interpretability, the difference of proportions using Cochran-Mantel-Haenszel (CMH) weights adjusted for stratification factors are also reported in the results section.

Exploratory Secondary Endpoints:

Below are described the pre-specified methods for the analysis of exploratory secondary endpoints.

- All responder endpoints were to be analyzed using a logistic regression with the pre-specified stratification factors. Missing intermittent data were imputed by LOCF, otherwise the patient was considered a non-responder. For easier interpretability of the treatment effects in this review, the difference of proportions using CMH weights are reported instead of the results of the logistic regression. Annual flare rate was analyzed with a negative binomial regression with pre-specified stratification factors and log (follow up time) as an offset variable. Patients lost to follow-up had their times censored at time of dropout.

Study 05 and Study 04

For study 05, there was 1 version of the SAP, which was finalized in May 2015. This SAP was reviewed by the agency.

For study 04, there were 4 versions of the SAP, with the final version being finalized in July 2019. Two of the versions were reviewed by the agency; the original version and the final version. The final version was updated to reflect the change in the primary and secondary endpoints and restricted medication rules based on the recommendation of the external Steering Committee.

Primary Endpoint:

Below are described the pre-specified methods for the primary endpoint for study 05 and 04.

- Analysis population: Full analysis set (FAS) defined as patients who were randomized and received at least 1 dose of investigational product.

- Handling of week 52 missing data (complete or partial): For patients who had an available week 48 observation, this was used to impute week 52, i.e., last observation carried forward (LOCF). If week 48 data is not available, then the patient was considered a non-responder.
- Analysis methods: The difference in proportions was evaluated using Cochran-Mantel-Haenszel weights stratified by screening SLEDAI-2K score (< 10 points, ≥ 10 points), week 0 OCS dose (< 10 mg/day, ≥ 10 mg/day), and results of type I IFN test at screening (high, low).

Secondary Endpoints:

Below are described the pre-specified methods for the analysis of secondary endpoints for study 04 and study 05.

- Analysis population: Full analysis set (FAS).
- All responder endpoints were evaluated using a difference in proportions calculated with Cochran-Mantel-Haenszel weights for the pre-specified stratification factors. Missing data were imputed if data from the previous visit was available, otherwise patients were considered to be non-responders.
- Annual flare rate was analyzed with a negative binomial regression with pre-specified stratification factors and log (follow up time) as an offset variable. Patients lost to follow-up had their times censored at time of dropout.

Protocol Amendments

Study 1013: There were 2 amendments to the protocol, with the last version of the protocol being finalized in September 2014. Changes to the protocol included modifying the unblinding language for the interim and staged analyses and changing the safety monitoring committee to the MedImmune/AstraZeneca safety review committee.

Study 05: There were 5 versions of the protocol, with the last version of the protocol being finalized in May 2016. Some changes to the protocol included changes to the inclusion/exclusion criteria, clarification on restricted medications, unblinding procedures, and study personnel.

Study 04: There was 6 versions of the protocol, with the last version of the protocol being finalized in May 2019. The last version reflected the change in the primary endpoint from SRI-4 to BICLA in with the external Steering Committee after failure of the SRI-4 in study 05. Some major changes to the protocol included changes to the inclusion/exclusion criteria, clarification on restricted medications, unblinding procedures, and study personnel. Further changes included key secondary endpoints and restricted medication rules.

Considerations on the Clinical Endpoints

Primary Endpoints Considerations:

The question of how best to measure treatment response in SLE remains an open one.²⁵ Current SLE trial endpoints are based on measures of disease activity including the SLEDAI-2K and BILAG. These disease indices are used to calculate a disease activity score, and trial endpoints may be determined based on specifying thresholds for improvement.²⁶ The SLEDAI-2K is a composite global disease activity index developed using consensus techniques in which 24 manifestations are scored across nine organ systems and marked as present or absent over the preceding 30 days according to binary cutoffs.²⁷ Advantages of the SLEDAI-2K include construct validity and the ability to predict major outcomes such as organ damage and mortality.²⁸ However, drawbacks of the SLEDAI-2K include the possibility of different disease patterns to result in the same total score, while improvement or worsening in other organ systems may not be reflected in the score; furthermore, the dichotomous scoring may not allow for variations in the severity of manifestations, which reduces sensitivity to change when used to assess treatment response.²⁹ The BILAG disease activity index is a set of organ-based scales rather than a composite score; the current version (BILAG-2004) comprises of nine organ systems with 97 descriptors, and each is scored as new or recurring, worse, same, improving, or not present during the past 30 days as defined by a glossary. These scores are combined to assign each organ an A–E grade: A (major activity), B (intermediate activity), C (mild or stable disease), D (previous involvement but currently inactive), and E (no previous activity).³⁰ The BILAG index has undergone extensive testing of reliability and validity for the purpose of measuring disease activity; however, it was not developed as a measure of treatment response, and there are limitations to its adaptation for the purpose of a clinical trial endpoint. Although gradations in severity mean that the BILAG-2004 is more sensitive to change than the SLEDAI-2K,³¹ predefined discrete thresholds may still limit responsiveness to differences between treatment arms in a clinical trial. Another potential drawback of the BILAG-2004 is that it is a

²⁵ Connelly K, Golder V, Kandane-Rathnayake, and Eric Morand: Clinician-reported outcome measures in lupus trials: a problem worth solving. *Lancet Rheumatology*. Volume 3, Issue 8, E595-E603, August 01, 2021. Published Online June 7, 2021; [https://doi.org/10.1016/S2665-9913\(21\)00119-3](https://doi.org/10.1016/S2665-9913(21)00119-3).

²⁶ American College of Rheumatology Ad Hoc Committee Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for systemic lupus erythematosus clinical trials: measures of overall disease activity. *Arthritis Rheum* 2004; 50: 3418–26.

²⁷ Touma Z, Urowitz MB, Gladman DD. SLEDAI-2K for a 30-day window. *Lupus* 2010; 19: 49–51.

²⁸ Arora S, Isenberg DA, Castrejon I. Measures of adult systemic lupus erythematosus: disease activity and damage. *Arthritis Care Res (Hoboken)* 2020; 72 (suppl 10): 27–46.

²⁹ Fortin PR, Abrahamowicz M, Clarke AE, et al. Do lupus disease activity measures detect clinically important change? *J Rheumatol* 2000; 27: 1421–28.

³⁰ Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2005; 44: 902–06.

³¹ Ward MM, Marx AS, Barry NN. Comparison of the validity and sensitivity to change of 5 activity indices in systemic lupus erythematosus. *J Rheumatol* 2000; 27: 664–70.

transitional index requiring comparison of the current state with the previous month to assign improvement or worsening, so two patients with identical current activity can score differently.

The potential limitations of the individual instruments SLEDAI-2K and BILAG-2004 to serve as clinical trial endpoints has led to the development of composite indices such as the SRI and the BICLA, which are currently the most common primary efficacy endpoints used in SLE clinical trials. An SRI response was originally defined as a reduction in SLEDAI of 4 points or more, with the requirement of no BILAG worsening (1A or 2Bs) or deterioration from baseline Physician Global Assessment of 0.3 or more. The SRI was developed on the basis of post-hoc analysis of data from a phase 2 trial of belimumab and was then used as a successful endpoint in two phase 3 belimumab trials.³² Because the SRI responder classification is mostly driven by SLEDAI-2K improvement, i.e. a 4 point improvement in SLEDAI-2K score to achieve the SRI-4 endpoint, it has the potential disadvantage of not being able to detect partial improvements; furthermore, highly weighted disease manifestations can drive the SLEDAI-2K reduction needed for an SRI response while lower weighted domains might not result in the threshold needed for achieving a response. A BICLA response is defined as (1) at least one gradation of improvement in all BILAG A and B scores present at baseline; (2) no new BILAG A, or 2 or more new BILAG B scores; (3) no worsening of total SLEDAI-2K score from baseline; and (4) no deterioration in Physician Global Assessment (≥ 10 mm on a 100 mm scale).³³ In contrast to the SRI responder index which requires complete improvement in at least one organ system but not necessarily improvement in all affected organ systems, the BICLA threshold can be achieved not only by complete resolution but also by substantial partial improvement in multiple affected organs. Both SRI-4 and BICLA are considered valid indices,³⁴ however they may demonstrate discordant responses with some subjects achieving one but not the other threshold for improvement. This type of discordance was observed for first phase 3 study of anifrolumab (study 05), in which a number of subjects in the placebo arm achieved improvement on SRI-4 but not BICLA (discussed in more detail below). There is also some evidence that the placebo response rates may be higher with SRI-4 than BICLA.³⁵

The Applicant provided adequate justification for changing the primary endpoint to BICLA in its second phase 3 trial from SRI-4, as described above. The Applicant proposed that this endpoint is more comprehensive, gives more balanced weight to affected body systems, and measure

³² Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63: 3918–30.

³³ Wallace DJ, Strand V, Furie R, et al. Evaluation of treatment success in systemic lupus erythematosus clinical trials: development of the British Isles Lupus Assessment Group-based composite lupus assessment endpoint. 2011 ACR/ARHP Annual Scientific Meeting. Chicago, IL, USA; Nov 8, 2011 (abstr 2265).

³⁴ Guidance for Industry: Systemic Lupus Erythematosus—Developing Medical Products for Treatment (June 2010); <https://www.fda.gov/media/71150/download>.

³⁵ Tselios K, Wakani L, Gladman DD, Su J, Urowitz MB. Response to placebo in non-renal, non-neuropsychiatric systemic lupus erythematosus: a systematic review and pooled analysis. *Rheumatology (Oxford)*. 2021 Jan 5;60(1):73-80.

incremental improvements or worsening. The Applicant also noted that this endpoint retains the SLEDAI-2K, using it (alongside PGA) to exclude patients who worsen in ways not captured by BILAG-2004 from being classified as responders. Furthermore, the FDA guidance³⁴ endorses the use of the BILAG questionnaire stating, “the BILAG is the preferred index to study reduction in disease activity in clinical trials.” Given the endorsement of BILAG in the SLE guidance, the choice of the BICLA primary endpoint for the second anifrolumab phase 3 study was deemed reasonable by the Agency.

Secondary Endpoints: CLASI

The Applicant proposed to use the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) as a secondary endpoint measuring response of SLE cutaneous disease activity to anifrolumab as compared to placebo.³⁶ In consultation with the Division of Dermatology and Dentistry, it has been determined that the CLASI is not a fit-for purpose instrument for measurement of reduction of skin disease in SLE subjects (b) (4)

and considers its use exploratory based on the following considerations:

1. The CLASI Total Activity Score is driven by the erythema component of the scale, with 39 of a possible 70 total points being potentially attainable just from the erythema score (if each anatomic site received the highest rating of 3; the likelihood of this occurring is unclear). While the extent of cutaneous involvement may be reflective of disease activity, it is not clear that the depth of erythema correlates with the level of activity. Further, the appearance of erythema may be influenced by the inherent depth of an individual’s pigmentation, differing in presentation in a fair-skinned person compared to a darkly-pigmented person. It is unclear how the difference in clinical presentation of erythema in different skin types might impact scoring of the depth of erythema. Indeed, erythema in dark skin may even be missed by an untrained observer.
2. The eruption of acute cutaneous lupus erythematosus (ACLE), e.g. the butterfly rash of SLE, occurs most frequently during an acute SLE flare. Some authors describe that the lesions of ACLE “can be quite ephemeral, lasting only hours, days, or weeks...” Therefore, for some individuals (i.e. those with transitory lesions), resolution of ACLE may not reflect a positive treatment response, but may, instead, simply be coincident to treatment.
3. The CLASI Activity scale does not address lesion morphology (other than mucosal ulcers). For cutaneous lesions other than alopecia, the scale measures three

³⁶ Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol 125:889 –894, 2005.

secondary characteristics: erythema on a three-point scale, scaling on a two-point scale, and verrucosity/hypertrophy as a single point at the extreme for scaling.

4. The presentations of cutaneous LE are highly variable, and each CLASI score represents a bundling of different cutaneous signs into a single score. Each subject's activity score may represent a different combination of clinical signs. For example, there are several possible ways for arriving at a Total Activity Score of, say, "12": This total could reflect the presence of erythema at several sites; it could reflect erythema with mucous membrane involvement, erythema with scale and alopecia, etc. Therefore, a decrease in CLASI might reflect improvement in different elements of the scale (e.g. improvement in alopecia or erythema) depending on what elements on the scale contributed to an individual's baseline score. Simply reporting a decrease in the CLASI does not permit or present a clinical picture of the nature of improvement, as one would not be able to determine what elements on the CLASI were impacted by study treatment and made for the reduction in score.

Therefore, the review team determined that the CLASI results are not easily interpretable

(b) (4)

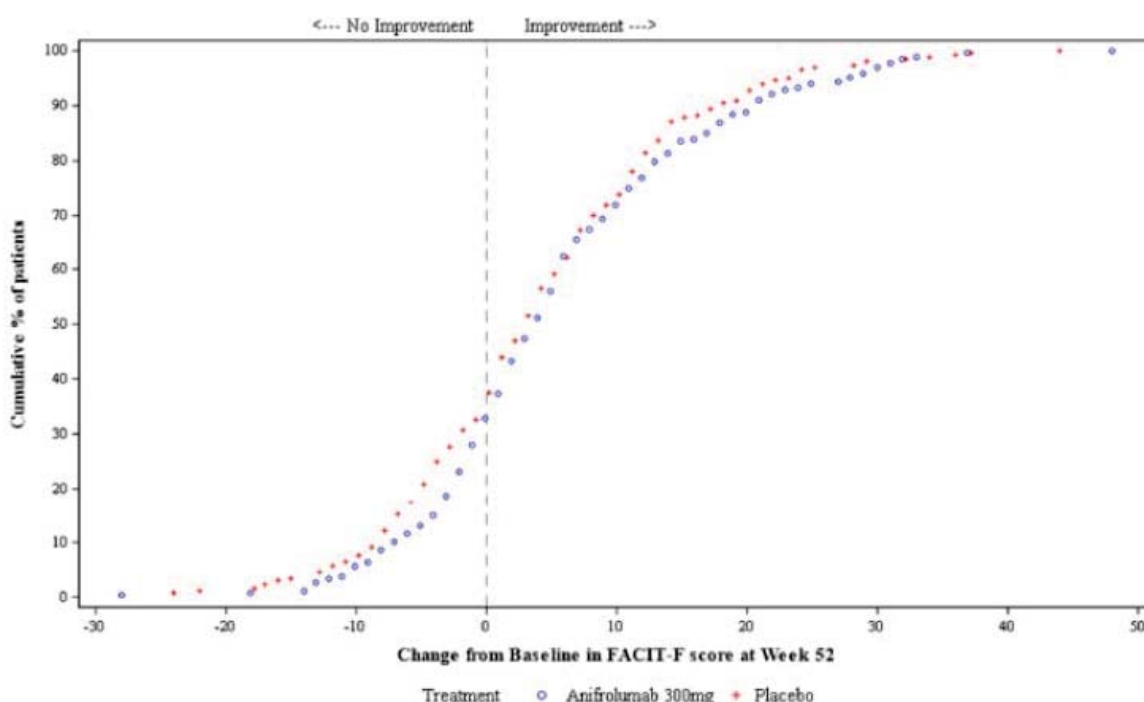
(b) (4)

Secondary Endpoints: FACIT-Fatigue

The Applicant proposed to use the FACIT-Fatigue (FACIT-F) as a secondary endpoint measuring response of SLE patient fatigue to anifrolumab as compared to placebo.³⁷ In consultation with Division of Clinical Outcome Assessment, it has been determined that, while fatigue appears to be an important and common symptom in patients with SLE, the Applicant did not submit sufficient evidence to support interpretation of FACIT-F scores. It is unclear whether changes in the FACIT-F total score in the anifrolumab clinical program are clinically meaningful. The threshold for clinically meaningful within-patient change to assess fatigue severity in the clinical trials could not be estimated using anchor-based methods as the clinical trials did not include appropriate anchor scales. Based on the empirical distribution function (eCDF) curves and item-level analyses, there does not appear to be a difference in the change from baseline at Week 52 in FACIT-F total scores between treatment arms in the phase 3 studies (see Figure 13). FACIT-F items have limitations related to content validity that present additional challenges to interpreting FACIT-F data in the Applicant's clinical trials.

³⁷ Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. J Rheumatol. 2011;38(4):672-679.

Figure 13. Pooled Studies 04 and 05: Cumulative distribution function of FACIT-F score change from baseline at Week 52, by treatment arm



FACIT-F, Functional Assessment of Chronic Illness Therapy-fatigue

Baseline is defined as the measurement prior to randomization and dose administration on Day 1.

Pooled data excludes 150 mg dose group from study 05.

Positive change from baseline values indication improvement.

Missing data are not imputed.

Source: Clinical Outcome Assessment Review Memorandum dated June 3, 2021, p. 8

8.1.2. Study Results

Compliance with Good Clinical Practices

According to statements included in the report for the three studies submitted to support approval (studies 1013, 05, and 04), the Applicant certified that this study was conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki 2008 or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable country-specific requirements including the constitution of independent ethics committees as per 21 CFR 312.3(b).

During the studies (prior to unblinding) it was discovered that one site in each of studies 04 and 05 had sustained non-compliance with protocol procedures, so the sites were closed. A decision was made and documented in the study SAP to exclude all 11 randomized patients from these 2

sites in the full analysis set (see Section 6.1, study 04 CSR and study 05 CSR in Module 5.3.5.1). Key data from these excluded patients are listed in the respective CSR.

Financial Disclosure

The Applicant completed FDA Form 3454 to document financial conflicts of interest and arrangements with clinical investigators. As per this form, the Applicant certified that no financial arrangement had been entered into with the listed clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a, b, and f).

Patient Disposition

A total of 626 patients in study 1013 and 1496 patients in the two phase 3 studies (studies 04 and 05) combined were enrolled. A total of 307 patients were randomized at 73 sites in 14 countries in study 1013 (Table 7). A total of 365 patients in study 04 and 457 patients in study 05 met eligibility criteria and were randomized into the studies at 219 sites in 28 countries (Table 8).

Table 7. Patient disposition (all randomized patients) in study 1013

Patient Disposition	Number (%) of patients			
	Anifrolumab 300 mg	Anifrolumab 1000 mg	Placebo	Total
Patients randomized	100	104	103	307
Patients in the full analysis set ^a	99	104	102	305
Patients who completed the study ^b	84 (84.0)	85 (81.7)	77 (74.8)	246 (80.1)
Patients who did not complete the study ^b	16 (16.0)	19 (18.3)	26 (25.2)	61 (19.9)
Reasons for not completing study				
Death	0	1 (1.0)	0	1 (0.3)
Lost to follow-up	2 (2.0)	2 (1.9)	4 (3.9)	8 (2.6)
Withdrawal of consent	3 (3.0)	8 (7.7)	11 (10.7)	22 (7.2)
Other	11 (11.0)	8 (7.7)	11 (10.7)	30 (9.8)
Sponsor decision	1	4	4	9
Patient choice/patient moved	1	1	2	4
Investigator decision	1	0	0	1
AE/SAE	1	1	2	4
Received prohibited medication	0	0	1	1
Missed first follow-up visit/did not complete all 3 follow-up visits	5	2	2	9
Inadequate venous access	2	0	0	2

Source: Table 10.1.1-1 and Table 11.1-1 in study 1013 CSR in Module 5.3.5.1

Percentages based on all randomized patients

^a Referred to as “mITT population” in the study 1013 CSR: All randomized subjects who received any investigational product and had a baseline primary efficacy measurement.

^b Patients who discontinued investigational product also discontinued the study per protocol

Table 8. Patient disposition in studies 04 and 05

Patient Disposition	Number (%) of patients						
	Study 04			Study 05			
	Anifrolu mab 300 mg	Placebo	Total	Anifrolu mab 150 mg	Anifrolu mab 300 mg	Placebo	Total
Patients in the full analysis set ^a	180	182	362	93	180	184	457
Patients who completed the study ^b	156 (86.7)	136 (74.7)	292 (80.7)	76 (81.7)	146 (81.1)	148 (80.4)	370 (81.0)
Patients withdrawn from the study	24 (13.3)	46 (25.3)	70 (19.3)	17 (18.3)	34 (18.9)	36 (19.6)	87 (19.0)
Patients who completed week 52 ^c	162 (90.0)	145 (79.7)	307 (84.8)	80 (86.0)	153 (85.0)	157 (85.3)	390 (85.3)
Patients withdrawn from the study before week 52	18 (10.0)	37 (20.3)	55 (15.2)	13 (14.0)	27 (15.0)	27 (14.7)	67 (14.7)
Patients who completed investigational product ^d	153 (85.0)	130 (71.4)	283 (78.2)	75 (80.6)	145 (80.6)	146 (79.3)	366 (80.1)
Patients discontinued investigational product	27 (15.0)	52 (28.6)	79 (21.8)	18 (19.4)	35 (19.4)	38 (20.7)	91 (19.9)
Adverse event	5 (2.8)	14 (7.7)	19 (5.2)	6 (6.5)	13 (7.2)	8 (4.3)	27 (5.9)
Condition under investigation worsened	2 (1.1)	4 (2.2)	6 (1.7)	1 (1.1)	1 (0.6)	4 (2.2)	6 (1.3)
Lack of efficacy	2 (1.1)	12 (6.6)	14 (3.9)	3 (3.2)	3 (1.7)	9 (4.9)	15 (3.3)
Lost to follow-up	2 (1.1)	3 (1.6)	5 (1.4)	0	0	2 (1.1)	2 (0.4)
Severe non-compliance to protocol	0	1 (0.5)	1 (0.3)	2 (2.2)	0	2 (1.1)	4 (0.9)
Withdrawal by patient	7 (3.9)	16 (8.8)	23 (6.4)	5 (5.4)	15 (8.3)	13 (7.1)	33 (7.2)
Other	9 (5.0)	2 (1.1)	11 (3.0)	1 (1.1)	3 (1.7)	0	4 (0.9)
Patients continued to study 09 ^e	133 (73.9)	104 (57.1)	237 (65.5)	69 (74.2)	126 (70.0)	129 (70.1)	324 (70.9)

Source: Table 1.1.1.1, Appendix 2.7.3.6.1 in Module 5.3.5.3

^a The full analysis set comprises all randomized patients who received at least one dose of investigational product. In study 04, 1 patient in the anifrolumab 300 mg group and 2 patients in placebo group who were randomized, did not receive treatment with investigational product.

^b Completion of the studies is based upon the number of patients who completed week 52 (Visit 14) and either continued to study 09, the long-term extension study, or completed Follow-up Visit 2 regardless of number of doses of investigational product that were received.

^c Completion of week 52 is based upon the number of patients completing up to and including week 52 (Visit 14) regardless of number of doses of investigational product that were received.

^d Completion of investigational product is based upon the number of patients completing treatment with investigational product up to and including week 48 (Visit 13.)

^e Continuation to study 09, the long-term extension study, is based on the week 52 status of the eCRF.

Similar percentages of patients completed investigational product across the 3 studies: study 1013 (80.1%), study 04 (78.2%), and study 05 (80.1%) (Table 7 and Table 8). In study 04 and study 1013, fewer patients in the anifrolumab 300 mg group prematurely discontinued investigational product compared with the placebo group (15.0% vs 28.6% in study 04 and 16.0% vs 25.2% in study 1013). In study 05, similar percentage of patients across the treatment

groups discontinued investigational product prematurely (19.4% in anifrolumab 150 mg, 19.4% in anifrolumab 300 mg, and 20.7% in placebo). Discontinuations due to lack of efficacy were fewer in the anifrolumab 300 mg group compared with placebo in studies 04 and 05 (not recorded in study 1013). In studies 04 and 1013, there were fewer withdrawals by subject/withdrawal of consent in the anifrolumab 300 mg group than in the placebo group.

Protocol Violations/Deviations

A small number of patients had an important protocol deviation (as defined in ICH E3 1995): 14/362 (3.9%) and 18/457 (3.9%) patients in the full analysis sets of studies 04 and 05, respectively, and 10/307 randomized patients (3.3%) in study 1013. Overall, the most frequent important protocol deviations were related to the timing of the laboratory procedures for the PK, investigational product, inclusion criteria, principal investigator oversight/delegation/training, and 'other' reasons. The treatment groups were balanced with respect to both incidence and type of important protocol deviations. With the exception of the 11 patients from the 2 sites that were closed because of sustained non-compliance with protocol procedures, no other patients were excluded from the full analysis sets because of deviations from the protocol. There were no concerns regarding protocol deviations in terms of study conduct or the safety of patients. Also, the numbers and types of protocol deviations were judged not to influence the study outcome.

Specific details for protocol deviations are shown in Table 9, Table 10, and Table 11.

Table 9. Summary of study 1013 protocol deviations (10 total)

Country	Deviation
USA	Non-compliance (Subject was discontinued due to pregnancy)
USA	Enrollment Criteria (Inclusion Criteria)
USA	Dosing (Administered a single dose of anifrolumab 1000 mg rather than assigned dose)
Taiwan	Non-compliance (Samples collected for blood biomarker study were without consent)
USA	Non-compliance (Samples collected for blood biomarker study were without consent)
Columbia	Enrollment Criteria (Inclusion Criteria)
Columbia	Dosing (Missed > 2 consecutive doses of investigational product)
Hungary	Non-compliance (Samples collected for blood biomarker study were without consent)
Mexico	Concomitant Medication (Subject received OCS out of tapering period)
Poland	Enrollment Criteria (Exclusion Criteria)

Source: Section 10.2, study 1013 CSR

Table 10. Summary of study 04 protocol deviations

Important protocol deviation	Number of subjects (%)		
	Anifrolumab 300 mg	Placebo	Total
Number of subjects with at least 1 important deviation	5 (2.8)	9 (4.9)	14 (3.9)
Investigational product	2 (1.1)	1 (0.5)	3 (0.8)
Lab data	0	5 (2.7)	5 (1.4)
Informed consent	1 (0.6)	1 (0.5)	2 (0.6)
PI oversight/delegation/training	2 (1.1)	2 (1.1)	4 (1.1)

Source: Section 6.2, study 04 CSR

Percentages are based upon all subjects in the full analysis set.

Note that the same subject may have had more than 1 important protocol deviation.

Table 11. Summary of study 05 protocol deviations

Important protocol deviation	Number of subjects (%)		
	Anifrolumab 300 mg	Placebo	Total
Number of subjects with at least 1 important deviation	7 (3.9)	8 (4.3)	18 (3.9)
Inclusion criteria	1 (0.6)	2 (1.1)	3 (0.7)
Exclusion criteria	0	1 (0.5)	1 (0.2)
Investigational product	1 (0.6)	2 (1.1)	5 (1.1)
Visit window	0	0	1 (0.2)
Informed consent	1 (0.6)	0	1 (0.2)
Concomitant medication	0	1 (0.5)	1 (0.2)
PI oversight	2 (1.1)	0	2 (0.4)
Other	2 (1.1)	2 (1.1)	5 (1.1)

Source: Section 6.2, study 05 CSR

Percentages are based upon all subjects in the full analysis set.

Note that the same subject may have had more than 1 important protocol deviation.

Table of Demographic Characteristics

The demographic characteristics of the patients in the 300 mg and placebo arms were broadly similar across the 3 studies submitted to support approval and are representative of the target population of patients with moderate to severe SLE despite standard therapy (Table 12). The mean age was between 39.1 and 43.1 years and the majority of patients were female (91.2% to 93.9%). Approximately 40% of the patients had a BMI of ≥ 28 kg/m². Overall, races were well represented.

All 3 studies included patients from all geographic regions (Table 12). One of the few differences between the studies was the geographic placement of the studies:

- Study 04 had a higher proportion of patients from the Asia-Pacific region (14.6%) compared with studies 05 (5.3%) and 1013 (5.9%) and was the only study to include patients from Japan.
- Study 05 had a higher proportion of patients from Europe (37.9%) compared with

studies 04 (26.8%) and 1013 (25.6%).

- o Study 1013 had a higher proportion of patients from Latin America (36.7%) than studies 04 (18.5%) and 05 (13.6%).
- o All 3 studies had similar proportions (approximately one-third) of patients from USA/Canada.

Table 12. Demographic characteristics for efficacy and safety analysis in the 3 studies submitted to support approval (studies 04, 05, and 1013)

Demographic Characteristic		Study 04		Study 05		Study 1013	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
Age (years)	N	180	182	180	184	99	102
	Mean	43.1	41.1	42.0	41.0	39.1	39.3
	SD	11.95	11.47	11.99	12.30	11.9	12.9
	Median	44.0	42.0	40.5	41.0	38.0	39.0
	Minimum	18	19	18	18	19	18
	Maximum	69	66	68	69	65	65
Age subgroups ^a , n (%)	< 18	0	0	0	0	NA	NA
	≥ 18 to < 65	175 (97.2)	181 (99.5)	169 (93.9)	178 (96.7)	NA	NA
	≥ 65	5 (2.8)	1 (0.5)	11 (6.1)	6 (3.3)	NA	NA
Sex, n (%)	Female	168 (93.3)	170 (93.4)	165 (91.7)	171 (92.9)	93 (93.9)	93 (91.2)
	Male	12 (6.7)	12 (6.6)	15 (8.3)	13 (7.1)	6 (6.1%)	9 (8.8%)
BMI ^b , n (%)	≤ 28 kg/m ²	107 (59.4)	114 (62.6)	98 (54.4)	109 (59.2)	NA	NA
	> 28 kg/m ²	73 (40.6)	68 (37.4)	82 (45.6)	75 (40.8)	NA	NA
Race ^c , n (%)	White	110 (61.1)	107 (58.8)	125 (69.4)	137 (74.5)	35 (35.4)	41 (40.2)
	Black or African American	17 (9.4)	25 (13.7)	29 (16.1)	23 (12.5)	19 (19.2)	12 (11.8)
	Asian	30 (16.7)	30 (16.5)	11 (6.1)	5 (2.7)	3 (3.0)	13 (12.7)
	Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
	Native American or Alaska Native	4 (2.2)	1 (0.5)	0	1 (0.5)	4 (4.0)	0
	Other	11 (6.1)	11 (6.0)	15 (8.3)	18 (9.8)	37 (37.4)	35 (34.3)
	Missing or Multiple Categories Checked	8 (4.4)	8 (4.4)	0	0	1 (1.0)	1 (1.0)
Geographic ^d , n (%)	Asia-Pacific	27 (15.0)	26 (14.3)	11 (6.1)	6 (3.3)	2 (2.0)	10 (9.8)
	Europe	51 (28.3)	46 (25.3)	64 (35.6)	76 (41.3)	20 (20.2)	25 (24.5)
	Latin America	35 (19.4)	32 (17.6)	24 (13.3)	25 (13.6)	39 (39.4)	37 (36.3)
	USA/Canada	64 (35.6)	68 (37.4)	75 (41.7)	72 (39.1)	37 (37.4)	28 (27.5)
	Rest of the world	3 (1.7)	10 (5.5)	6 (3.3)	5 (2.7)	1 (1.0)	2 (2.0)

Derived from Table 1.1.3.1 and Table 1.1.3.5, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 11.2.1-1 in study 1013

BLA 761123 Multi-disciplinary Review and Evaluation Saphnelo (anifrolumab-fnia) for adults with SLE

CSR in Module 5.3.5.1; Table 0001.143.3, Appendix 2.7.3.6.5 in Module 5.3.5.3.

Percentages are based upon all patients in the full analysis set for the indicated study and treatment group.

^a Study 1013: ≤ 45 years, 67.7% anifrolumab 300 mg and 70.6% placebo group; > 45 years 32.3% anifrolumab 300 mg and 29.4% placebo

^b Study 1013 Mean (SD) BMI: 26.58 (5.87) anifrolumab 300 mg group; 26.12 (6.64) placebo group

^c Study 1013 Race “other”: patients from Latin America [mestizo or mestiza] who did not identify with the race definitions provided

^d **Asia-Pacific:** Australia, Japan, New Zealand, South Korea, Singapore, Taiwan

Europe: Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Poland, Romania, Russia, Spain, Ukraine, United Kingdom

Latin America: Argentina, Brazil, Chile, Colombia, Mexico, Peru

Rest of world: India, Israel, South Africa

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline SLE disease characteristics

The inclusion or exclusion criteria were consistent across the studies, and the baseline SLE disease characteristics of the patients were broadly similar and consistent with a moderate to severe active SLE population (Table 13). At baseline, patients in study 05 had slightly higher mean PGA scores than patients in study 04, indicative of more active disease, and had more moderate to severe skin involvement (CLASI activity score ≥ 10 and BILAG ‘A’ mucocutaneous items). In the two phase 3 studies, baseline SLEDAI-2K organ system involvement were also generally balanced, with the exception of baseline active hematology and immunology higher in the anifrolumab 300 mg group than placebo in study 04 (Table 14). Other than that, the baseline disease characteristics were generally balanced between the studies and between study arms.

In all 3 studies, patients in the anifrolumab 300 mg and placebo arms had moderate to severe disease activity at baseline, as indicated by mean SLEDAI-2K scores of 10.7 to 11.5, and 59.6% to 73.4% of patients with a SLEDAI-2K score of ≥ 10; mean BILAG-2004 scores of 18.6 to 19.8; and median PGA scores of 1.68 to 1.87 (Table 13). Overall, 45.0% to 52.5% of patients had severe disease in at least 1 organ system (BILAG-2004 level A), and 41.4% to 50.6% of patients had moderate disease in at least 2 organ systems (BILAG-2004 level B). Patients had a median duration of disease/time since diagnosis of 65.75 to 94.5 months (Table 13).

Table 13. Baseline SLE disease characteristics in the 3 studies submitted to support approval (studies 04, 05, and 1013)

SLE disease characteristic at baseline ^a		Study 04		Study 05		Study 1013	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
SLEDAI-2K score	< 10 points, n (%)	51 (28.3)	51 (28.0)	55 (30.6)	49 (26.6)	40 (40.4)	41 (40.2)
	≥ 10 points, n (%)	129 (71.7)	131 (72.0)	125 (69.4)	135 (73.4)	59 (59.6)	61 (59.8)
	Mean (SD)	11.4 (3.64)	11.5 (3.88)	11.3 (4.04)	11.5 (3.50)	10.7 (3.7)	11.1 (4.4)
	Median	11.0	10.0	10.0	10.5	10.0	10.0
	Min, max	6, 25	4, 26	4, 32	6, 24	6, 24	6, 29

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

BILAG organ system scoring (Overall)	At least one A, n (%)	81 (45.0)	95 (52.2)	93 (51.7)	84 (45.7)	52 (52.5)	49 (48.0)
	No A and at least 2 Bs, n (%)	91 (50.6)	78 (42.9)	79 (43.9)	84 (45.7)	41 (41.4)	48 (47.1)
	No A and < 2 Bs, n (%)	8 (4.4)	9 (4.9)	8 (4.4)	16 (8.7)	6 (6.1)	5 (4.9)
PGA score	Mean (SD)	1.68 (0.41)	1.76 (0.40)	1.87 (0.40)	1.84 (0.40)	1.86 (0.39)	1.77 (0.44)
	Median	1.60	1.70	1.90	1.90	1.90	1.80
	Min, max	0.8, 2.8	0.9, 2.6	1.0, 2.7	0.6, 2.8	0.9, 2.6	0.8, 2.8
CLASI activity score	< 10, n (%)	131 (72.8)	142 (78.0)	122 (67.8)	130 (70.7)	72 (72.7)	76 (74.5)
	≥ 10, n (%)	49 (27.2)	40 (22.0)	58 (32.2)	54 (29.3)	27 (27.3)	26 (25.5)
	Mean (SD)	8.3 (7.94)	7.6 (7.75)	8.5 (7.26)	8.1 (6.66)	7.5 (6.3)	6.7 (5.1)
	Median	6.0	5.5	6.0	6.0	5.0	5.0
	Min, max	0, 51	0, 52	0, 41	0, 35	1, 36	0, 26
Active joint count	Mean (SD)	5.7 (5.58)	7.1 (6.49)	7.1 (5.74)	6.3 (4.49)	11.4 (7.2)	10.0 (7.0)
	Median	4.0	5.0	6.0	6.0	11.0	7.5
	Min, max	0, 28	0, 28	0, 25	0, 23	0, 28	0, 28
Swollen joint count	Mean (SD)	6.2 (5.65)	7.4 (6.55)	7.4 (5.79)	7.0 (4.80)	8.6 (6.0)	8.3 (6.4)
	Median	5.0	6.0	6.0	6.0	7.0	6.0
	Min, max	0, 28	0, 28	0, 25	0, 23	0, 25	0, 26
Tender joint count	Mean (SD)	9.0 (7.07)	11.0 (7.89)	11.7 (7.50)	10.6 (7.17)	12.2 (7.1)	10.5 (7.4)
	Median	7.0	10.0	10.5	10.0	11.0	8.0
	Min, max	0, 28	0, 28	0, 28	0, 28	2, 28	0, 28
Time from initial SLE diagnosis to randomization (months)	Mean (SD)	130.2 (109.3)	107.7 (99.2)	116.2 (97.0)	103.4 (90.3)	95.91 (76.8)	90.59 (86.29)
	Median	94.5	78.0	88.0	79.5	71.40	65.75
	Min, max	6, 555	6, 494	0, 450	4, 503	7.1, 360.9	6.9, 403.5
IFN gene signature	High, n (%)	150 (83.3)	151 (83.0)	148 (82.2)	151 (82.1)	75 (75.8)	76 (74.5)
	Low, n (%)	30 (16.7)	31 (17.0)	32 (17.8)	33 (17.9)	24 (24.2)	26 (25.5%)
Anti-dsDNA levels ^b	Positive, n (%)	86 (47.8)	73 (40.1)	81 (45.0)	82 (44.6)	56 (72.7)	66 (80.5)
	Negative, n (%)	94 (52.2)	109 (59.9)	99 (55.0)	102 (55.4)	21 (27.3%)	16 (19.5%)
	Missing, n (%)	0	0	0	0	22	20
ANA	Normal (titer<1:80), n (%)	12 (6.7)	12 (6.6)	11 (6.1)	14 (7.6)	1 (1.0%)	3 (2.9%)
	Abnormal (titer ≥ 1:80), n (%)	160 (88.9)	165 (90.7)	164 (91.1)	165 (89.7)	98 (99.0%)	99 (97.1%)
	Missing, n (%)	8 (4.4)	5 (2.7)	5 (2.8)	5 (2.7)	0	0
Complement C3 level	Normal, n (%)	108 (60.0)	110 (60.4)	122 (67.8)	119 (64.7)	71 (71.7)	59 (57.8)
	Low, n (%)	72 (40.0)	72 (39.6)	58 (32.2)	65 (35.3)	28 (28.3)	43 (42.2)
Complement C4 level	Normal, n (%)	131 (72.8)	136 (74.7)	145 (80.6)	145 (78.8)	78 (78.8)	77 (75.5)
	Low, n (%)	49 (27.2)	46 (25.3)	35 (19.4)	39 (21.2)	21 (21.2)	25 (24.5)

Derived from Table 1.1.4.1, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 11.2.2-1, Table 14.2.2.7.1, Table 14.2.2.7.3, Table 14.2.2.7.5, Table 14.2.2.8.5, Table 14.2.2.8.7, and Table 14.2.2.22.2 in study 1013 CSR in Module 5.3.5.1; Table 0001.143.1, Appendix 2.7.3.6.5 in Module 5.3.5.3.

^a All characteristics are measured at baseline unless otherwise indicated.

^b The Farr assay, the most specific method for detecting dsDNA auto-antibodies, was used in study 1013—an abnormal anti-dsDNA (Farr assay) was defined as value ≥ 5 IU/mL

Table 14. Baseline SLEDAI-2K organ system involvement in Studies 04, 05 and 1013

SLEDAI-2K Organ System Involvement at Baseline	Study 04				Study 05				Study 1013			
	Anifrolumab 300 mg (N = 180)		Placebo (N = 182)		Anifrolumab 300 mg (N = 180)		Placebo (N = 184)		Anifrolumab 300 mg (N = 99)		Placebo (N = 102)	
	n	%	n	%	n	%	n	%	n	%	n	%
Hematologic and Fever	35	19	23	13	20	11	22	12	9	9	11	11
Immunology	127	71	112	62	110	61	118	64	43	43	53	52
Muco-cutaneous	174	97	173	95	174	97	178	97	99	100	100	98
Musculoskeletal	168	93	171	94	167	93	178	97	97	98	99	97
Vascular	21	12	22	12	18	10	18	10	6	6	7	7

Derived from Table 2.3.1.9, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 14.2.2.3.14 Study 1013

Referring to organ system components of the SLEDAI-2K, the patients in the 300 mg and placebo arms in studies 04, 05 and 1013 had multi-organ involvement at baseline with the most common organ manifestations of SLE disease being musculoskeletal, mucocutaneous and immunological (Table 14). Based on BILAG-2004 organ items, the most common organ systems with baseline BILAG A or B severity in all three studies (1013, 04 & 05) in the 300 mg and placebo arms were mucocutaneous and musculoskeletal (as shown in Table 13 of the Summary of Clinical Efficacy). Almost all patients had active skin disease (CLASI activity score > 0) with a mean CLASI score of 6.7 to 8.5, and 22.0% to 32.2% of patients in the 300 mg and placebo arms had moderate to severe skin disease (CLASI activity score ≥ 10 points) (Table 13). Across the studies, the majority of patients had active joint manifestations, with 88.9% to 92.4% of patients having swollen joints (median joint counts of 5.0 to 7.0), and 93.3% to 100% of patients having tender joints (median joint counts of 7.0 to 11.0).

The baseline immunology/serology characteristics were similar across the studies. The majority of patients were classified as type I IFN gene signature test high at screening (74.5% to 83.3%) (Table 13). While all patients had to be auto-antibody positive, the baseline results were:

- ANA positivity in most patients (88.9% to 99.0%)
- Anti-dsDNA positivity in 40.1% to 47.8% of patients in studies 04 and 05, and 72.2% to 80.5% of patients in study 1013 (which used the Farr assay, the most specific method for detecting dsDNA antibodies). Note, that study 1013 also used a multiplex assay, but a different type (with different cut-off values) to the multiplex assay used in studies 04 and 05.
- Abnormal (low) C3 levels (28.3% to 42.2%)
- Abnormal (low) C4 levels (19.4% to 27.2%)

Baseline SLE-related SOC treatments

All patients were required to be on stable doses of standard of care (SOC) treatments for SLE for an appropriate period of time prior to entering the study. The baseline disease-related SOC treatments across the 3 studies were generally similar and balanced between treatment groups (Table 15 and Table 16).

Study patients had moderate or severe SLE (SLEDAI-2K ≥ 6 , at least one A or two B BILAG-2004 scores, and PGA ≥ 1) at baseline despite SOC, indicated by 45.6% to 62.7% of patients taking ≥ 10 mg/day OCS and 45.1% to 51.5% of patients taking immunosuppressants at baseline across the 3 studies (Table 15 and Table 16).

Table 15. SLE-related SOC treatments at baseline in study 1013

SLE-related treatments at baseline ^a		Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
OCS dose (mg/day) (prednisone or equivalent) excluding patients not taking OCS	n (%)	79 (79.8)	88 (86.3)
	Mean (SD)	11.4 (6.4)	12.8 (8.2)
	Median	10.0	10.0
	Min, max	1.25, 30.00	2.50, 40.00
OCS dose ≥ 10 mg/day	n (%)	55 (55.6)	64 (62.7)
Antimalarials	n (%)	76 (76.8)	75 (73.5)
Immunosuppressants	n (%)	51 (51.5)	46 (45.1)
Azathioprine	n (%)	23 (23.2)	19 (18.6)
Methotrexate	n (%)	19 (19.2)	16 (15.7)
Mycophenolate	n (%)	11 (11.1)	11 (10.8)
NSAIDs	n (%)	NA	NA

Derived from Table 11.2.2-1 in 1013 CSR, Table 0001.143.2, Appendix 2.7.3.6.5 in Module 5.3.5.3.

^a Corticosteroids and other immunomodulatory medications used on or after screening visit and before study Day 1 are counted once for each patient

Table 16. SLE-related SOC treatments at baseline in studies 04 and 05

SLE-related treatments at baseline ^a		Study 04		Study 05	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
OCS dose (mg/day) (prednisone or equivalent) excluding patients not taking OCS	n (%)	141 (78.3)	151 (83.0)	150 (83.3)	153 (83.2)
	Mean (SD)	10.6 (6.4)	10.7 (7.6)	12.8 (12.0)	11.9 (7.7)
	Median	10.00	10.00	10.00	10.00
	Min, max	1.0, 40.0	1.0, 40.0	2.0, 99.0	2.5, 40.0
OCS dose ≥ 10 mg/day	n (%)	87 (48.3)	83 (45.6)	103 (57.2)	102 (55.4)
Anti-malarials	n (%)	119 (66.1)	133 (73.1)	124 (68.9)	134 (72.8)
Immunosuppressants	n (%)	88 (48.9)	86 (47.3)	85 (47.2)	91 (49.5)
Azathioprine	n (%)	30 (16.7)	27 (14.8)	32 (17.8)	34 (18.5)
Azathioprine dose (mg/day)	Median	100.00	100.00	100.00	100.00
Methotrexate	n (%)	34 (18.9)	35 (19.2)	22 (12.2)	38 (20.7)
Methotrexate dose (mg/week)	Median	15.50	15.00	15.00	15.00
Mycophenolate	n (%)	23 (12.8)	23 (12.6)	31 (17.2)	22 (12.0)
Mycophenolate dose (g/day)	Median	1.50	1.44	1.47	1.00
Mizorbine (Japan only)	n (%)	4 (2.2)	3 (1.6)	NA	NA
Mizorbine dose (mg/day)	Median	125.00	150.00	NA	NA
NSAIDs	n (%)	41 (22.8)	45 (24.7)	31 (17.2)	35 (19.0)

Derived from Table 1.1.7.1, Appendix 2.7.3.6.1 in Module 5.3.5.3.

^a Baseline defined as the last measurement prior to randomization and investigational product dose administration on Day 1

Fewer patients in study 04 (48.3% anifrolumab and 45.6% placebo) were taking ≥ 10 mg/day OCS, than in study 05 (57.2% anifrolumab and 55.4% placebo) and study 1013 (55.6% anifrolumab and 62.7% placebo). However, the majority of patients in the 3 studies were on a stable OCS dose at baseline. For these patients, the mean dose of OCS was 10.6 mg/day to 12.8 mg/day (Table 16). About two-thirds of patients in studies 04 and 05 were taking an OCS in combination with immunosuppressants and/or anti-malarials.

Across the studies, 66.1% to 76.8% of patients in the anifrolumab 300 mg and placebo treatment arms were taking anti-malarials.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Table 15 and Table 16 describe the baseline use of standard of care treatment. Table 8 describes the disposition of patients who completed/discontinued investigational product for studies 05 and 04. In study 05, the proportion of patients who completed investigational product was 80.6% on both anifrolumab 300mg and 150mg, and 79.3% on placebo. In study 04, the proportion of patients who completed investigational product was 85.0% on anifrolumab 300mg and 71.4% on placebo. For study 1013, the proportion of patients who completed investigational product was 73.1% on anifrolumab 1000mg, 87.9% on anifrolumab 300mg, and 69.6% on placebo.

In study 1013, the number of patients who exceeded OCS after randomization was 14 (13.5%) on anifrolumab 1000mg, 18 (18.2%) on anifrolumab 300mg, and 15 (14.7%) on placebo. In study 05, under the pre-specified set of restricted medication rules, the number of patients who initiated restricted medication after randomization was 66 (36.7%) on anifrolumab 300mg, 36 (38.7%) on anifrolumab 150mg, and 70 (38.0%) on placebo. Under the study 04 set of restricted medication rules, the number of patients who initiated restricted medication after randomization was 40 (22.2%) on anifrolumab 300mg, 21 (22.6%) on anifrolumab 150mg, and 56 (30.4%) on placebo. In study 04, the number of patients who initiated restricted medication after randomization was 36 (20.0%) on anifrolumab 300mg, and 59 (32.4%) on placebo. We note these patients were classified as non-responders in endpoints that pre-specified the prohibition of such initiation of restricted medication.

Efficacy Results – Primary Endpoint

Data Capture for the Primary Endpoint

Table 17 below summarizes the data collected for study 1013 at week 24 and 52. At week 24, 9.5% of patients had missing data and 21.6% had missing data at week 52. Missing intermittent data were imputed by LOCF as noted in the table. Each arm had higher missing data rates at week 52 and the placebo arm had a substantially higher proportion of subjects with missing data compared to anifrolumab 300mg at both week 24 and 52. The increase in missing data at week 52 compared to week 24 may be attributed to the later timepoint after the primary endpoint assessment at week 24.

Table 17. Data capture at week 24 and week 52 for study 1013

		Ani 1000mg (N=104)	Ani 300mg (N=99)	Placebo (N=102)	Total (N=305)
Week 24	Available [n(%)]	95 (91.3)	94 (94.9)	87 (85.3)	276 (90.5)
	No imputation	91	90	82	263
	Based on imputation	4	4	5	13
	Missing [n(%)]	9 (8.7)	5 (5.1)	15 (14.7)	29 (9.5)
Week 52	Available [n(%)]	79 (76.0)	88 (88.9)	72 (70.6)	239 (78.4)
	No imputation	78	87	69	234
	Based on imputation	1	1	3	5
	Missing [n(%)]	25 (24.0)	11 (11.1)	30 (29.4)	66 (21.6)

Source: Statistical Reviewer's Analysis

Table 18 and Table 19 below summarize data capture for study 05 and 04, respectively, at week 52. Both studies had approximately 14-15% missing data at week 52. The Applicant pre-specified that missing week 52 data, either complete or partial (i.e., missing one or more items within a component) would be imputed with week 48 data, if available. This is indicated by "based on imputation" in the following tables. If week 48 data was not available, the patient was to be classified as a non-responder. Compared to Table 8 (the Applicants tabulations), there are minor discrepancies in the number of patients who completed week 52. This is due to patients being labeled as having completed week 52 by the Applicant, however, they have 1 or more missing components (hence labeled as missing by the statistical reviewer), or patients not being considered as having completed week 52 by the Applicant, but had week 52 data imputed via week 48 data.

Table 18. Data capture at week 52 for study 05

	Ani 300mg (N=180)	Ani 150mg (N=93)	Placebo (N=184)	Total (N=457)
Available [n(%)]	155 (86.1)	80 (86.0)	156 (84.8)	391 (85.6)
No imputation	139	73	139	351
Based on imputation	16	7	17	40
Missing [n(%)]	25 (13.9)	13 (14.0)	28 (15.2)	66 (14.4)

Source: Statistical Reviewer's Analysis

Table 19. Data capture at week 52 for study 04

	Ani 300mg (N=180)	Placebo (N=182)	Total (N=362)
Available [n(%)]	161 (89.4)	147 (80.8)	308 (85.1)
No imputation	146	132	278
Based on imputation	15	15	30
Missing [n(%)]	19 (10.6)	35 (19.2)	54 (14.9)

Source: Statistical Reviewer's Analysis

Study 1013

The pre-specified analysis of the primary endpoint of SRI-4 + OCS tapering at week 24 was conducted in the whole population and in the subset of type I IFN test high patients. As alpha was prespecified at 0.10, the odds ratio and corresponding 90% confidence intervals are reported comparing anifrolumab 1000 mg and 300 mg to placebo. To aid in interpretability with study 05 and 04, the 95% confidence intervals are shown. The results were significant in the overall population and in the subset of type I IFN test high patients based on the pre-specified alpha of 0.10, as the p-values from the Cochran-Armitage global trend test were 0.07 and 0.03 respectively. However, no adjustments were made for the evaluation of the endpoint in two populations. The pairwise comparisons of each dose to placebo for the overall population and the subset of type I IFN test high patients are reported in Table 20.

Table 20. Study 1013: SRI-4 + OCS tapering response at week 24 in whole population and type I IFN test high patients

Population	Treatment	n/N (%)	Anifrolumab vs. Placebo		
			OR	90% CI	95% CI
Whole	Ani 1000mg	30/104 (28.8%)	1.94	(1.08, 3.49)	(0.96, 3.90)
	Ani 300mg	34/99 (34.3%)	2.38	(1.33, 4.26)	(1.19, 4.77)
	Placebo	18/102 (17.6%)			
Type I IFN High	Treatment	n/N (%)	Anifrolumab vs. Placebo		
			OR	90% CI	95% CI
Type I IFN High	Ani 1000mg	22/78 (28.2%)	2.65	(1.27, 5.53)	(1.11, 6.36)
	Ani 300mg	27/75 (36.0%)	3.55	(1.72, 7.32)	(1.50, 8.40)
	Placebo	10/76 (13.2%)			

Source: Statistical Reviewer's Analysis, CSR page 92-93

Adjusted odds ratio based on logistic regression with treatment and stratification factors as fixed effects
Patients with missing data are regarded as non-responders

While the Applicant's pre-specified significance level was 0.10, all further analyses and results are presented and discussed using an alpha of 0.05 to aid in interpretability. Further, as the Applicant did not pre-specify any multiplicity adjustments for the secondary endpoints and some analyses are post-hoc, if appropriate, results are referred to as nominally significant.

Table 21 below displays the results for the difference in proportions of SRI-4 + OCS tapering and the treatment policy strategy for handling the intercurrent events³⁸ of treatment discontinuation and excess use of immunosuppressants and OCS tapering requirements at week 24 in the whole population. The treatment policy strategy ignores excessive OCS medication and the OCS tapering requirement and uses the observed outcome data, i.e. patients that exceed OCS medication requirements and/or do not meet tapering OCS requirements are not necessarily considered treatment failures. Regardless of excessive OCS use or OCS tapering requirements, anifrolumab 300 mg was nominally significant when compared to placebo.

Table 21. Study 1013: SRI-4 response at week 24 in whole population

Handling of excess OCS	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
SRI-4 + OCS Tapering	Ani 1000mg	30/104 (28.8%)	10.4	(-1.29, 22.00)
	Ani 300mg	34/99 (34.3%)	14.8	(2.63, 26.98)
	Placebo	18/102 (17.6%)		
Treatment Policy	Ani 1000mg	63/104 (60.6%)	17.8	(4.16, 31.39)
	Ani 300mg	60/99 (60.6%)	17.5	(4.07, 30.96)
	Placebo	44/102 (43.1%)		

Source: Statistical Reviewer's Analysis

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Table 22 below displays the results for SRI-4 with OCS tapering and using the treatment policy strategy at week 24 in type I IFN test high patients, considering the difference in proportions. Regardless of excessive OCS use or OCS tapering, both doses were nominally significant when compared to placebo.

³⁸ <https://www.fda.gov/media/148473/download>

Table 22. Study 1013: SRI-4 response at week 24 in type I IFN test high patients

Handling of excess OCS	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
SRI-4 + OCS Tapering	Ani 1000mg	22/78 (28.2%)	13.9	(0.96, 26.83)
	Ani 300mg	27/75 (36.0%)	20.3	(6.61, 34.05)
	Placebo	10/76 (13.2%)		
Treatment Policy	Ani 1000mg	50/78 (64.1%)	23.5	(8.05, 38.97)
	Ani 300mg	48/75 (64.0%)	23.8	(8.14, 39.38)
	Placebo	31/76 (40.8%)		

Source: Statistical Reviewer's Analysis

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Table 23 below displays the results for SRI-4 without the requirement of OCS tapering (i.e., a patient does not need to satisfy the requirement to taper OCS to < 10 mg/day and ≤ Day 1 dose of prednisone or equivalent by Day 85 and maintain OCS doses < 10 mg/day and ≤ Day 1 dose until Day 169 (see primary endpoints section above)) and the treatment policy strategy at week 52, considering the difference in proportions using alpha of 0.05. We see that both doses are nominally significant for SRI-4 without OCS tapering and using the treatment policy strategy.

Table 23. Study 1013: SRI-4 response at week 52 in whole population

Handling of excess OCS	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
SRI-4 without OCS tapering	Ani 1000mg	56/104 (53.8%)	13.9	(0.67, 27.16)
	Ani 300mg	62/99 (62.6%)	24.0	(10.86, 37.18)
	Placebo	41/102 (40.2%)		
Treatment Policy	Ani 1000mg	62/104 (59.6%)	15.1	(1.71, 28.41)
	Ani 300mg	69/99 (69.7%)	26.4	(13.23, 39.65)
	Placebo	45/102 (44.1%)		

Source: Statistical Reviewer's Analysis, CSR page 100

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Table 24 below displays the results of BICLA without OCS tapering and the treatment policy at week 52, considering the difference of proportions. Therefore, both doses for BICLA without OCS tapering and the treatment policy estimand, are nominally significant.

Table 24. Study 1013: BICLA response at week 52 in whole population

Handling of excess OCS	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
BICLA without OCS tapering	Ani 1000mg	45/104 (43.3%)	16.8	(3.93, 29.71)
	Ani 300mg	54/99 (54.5%)	28.8	(15.73, 41.87)
	Placebo	27/102 (26.5%)		
Treatment Policy	Ani 1000mg	51/104 (49.0%)	18.0	(4.92, 31.03)
	Ani 300mg	60/99 (60.6%)	30.7	(17.46, 43.85)
	Placebo	31/102 (30.4%)		

Source: Statistical Reviewer's Analysis

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Study 05

Table 25 below displays the results of SRI-4 response at week 52 under the pre-specified restricted medication rules, post-hoc study 04 restricted medication rules, and the treatment policy strategy, where use of restricted medication is ignored and observed data is used, i.e. patients that use restricted medication are not necessarily considered treatment failures. In all comparisons, neither dose of anifrolumab was different from placebo.

Table 25. Study 05: SRI-4 response at week 52: Primary and post-hoc analyses

Handling of restructured medication	Treatment	n/N (%)	Diff	Anifrolumab vs. Placebo	
				95% CI	P-value
Pre-specified restricted medication rules	Ani 300mg	65/180 (36.1%)	-4.2	(-14.20, 5.82)	0.41
	Ani 150mg	35/93 (37.6%)	-2.6	(-14.71, 9.60)	0.68
	Placebo	74/184 (40.2%)			
Study 04 restricted medication rules	Ani 300mg	88/180 (48.9%)	6.0	(-4.18, 16.20)	
	Ani 150mg	45/93 (48.4%)	5.5	(-6.69, 17.75)	
	Placebo	79/184 (42.9%)			
Treatment Policy	Ani 300mg	107/180 (59.4%)	2.0	(-8.07, 12.13)	
	Ani 150mg	57/93 (61.3%)	3.8	(-8.14, 15.67)	
	Placebo	106/184 (57.6%)			

Source: Statistical Reviewer's Analysis, CSR page 109 (pre-specified rules), SCE errata page 101 (study 04 rules)

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

As the primary endpoint failed to reach significance, testing under multiplicity control does not continue, and any positive results of analyses from pre-specified secondary endpoints should

be interpreted with caution. In addition, any positive results of post-hoc analyses, which are derived under a different set of restricted medications, are considered supportive only.

Table 26 below displays the results for BICLA response at week 52 under the pre-specified restricted medication rules, post-hoc study 04 restricted medication rules, and the treatment policy strategy. Regardless of restricted medication rules, the anifrolumab 300 mg dose had more BICLA responders than placebo and the differences were nominally statistically significant. The confidence interval for the difference in BICLA response rate for the anifrolumab 150 mg dose compared to placebo did not rule out the null value regardless of restricted medication rules.

Table 26. Study 05: BICLA response at week 52

Handling of restructured medication	Anifrolumab vs. Placebo			
	Treatment	n/N (%)	Diff	95% CI
Pre-specified Restricted Medication Rules	Ani 300mg	67/180 (37.2%)	10.1	(0.59, 19.68)
	Ani 150mg	27/93 (29.0%)	2.4	(-9.03, 13.87)
	Placebo	49/184 (26.6%)		
Study 04 Restricted Medication Rules	Ani 300mg	85/180 (47.2%)	17.0	(7.17, 26.77)
	Ani 150mg	35/93 (37.6%)	7.8	(-4.04, 19.60)
	Placebo	55/184 (29.9%)		
Treatment Policy	Ani 300mg	100/180 (55.6%)	15.0	(4.94, 25.08)
	Ani 150mg	42/93 (45.2%)	5.0	(-7.08, 17.08)
	Placebo	74/184 (40.2%)		

Source: Statistical Reviewer's Analysis, CSR page 132 (pre-specified rules), SCE errata page 86 (analyses conducted using study 04 restricted medication rules)

Difference of proportions based of CMH weights adjusted for stratification factors. Patients with missing data are regarded as non-responders

Study 04

Table 27 below displays the results for BICLA at week 52 using the pre-specified restricted medication rules and the treatment policy strategy, where use of restricted medication is ignored. Regardless of handling restricted medication, results were consistently in favor of anifrolumab.

Table 27. Study 04: BICLA response at week 52: Primary analyses

Handling of restructured medication	Anifrolumab vs. Placebo				
	Treatment	n/N (%)	Diff	95% CI	P-value
Pre-specified restricted medication rules	Ani 300mg	86/180 (47.8%)	16.3	(6.35, 26.27)	0.001
	Placebo	57/182 (31.3%)			
Treatment Policy	Ani 300mg	102/180 (56.7%)	11.6	(1.34, 21.80)	
	Placebo	82/182 (45.1%)			

Source: Statistical Reviewer's Analysis, CSR page 105

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Table 28 below displays the results for SRI-4 at week 52 using the pre-specified restricted medication rules and the treatment policy estimand. Regardless of using restricted medication rules or not, results were consistently in favor of anifrolumab.

Table 28. Study 04: SRI-4 response at week 52

Handling of restructured medication	Anifrolumab vs. Placebo			
	Treatment	n/N (%)	Diff	95% CI
Pre-specified restricted medication rules	Ani 300mg	100/180 (55.6%)	18.2	(8.10, 28.32)
	Placebo	68/182 (37.4%)		
Treatment Policy	Ani 300mg	123/180 (68.3%)	12.9	(3.04, 22.85)
	Placebo	101/182 (55.5%)		

Source: Statistical Reviewer's Analysis, CSR page 127

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Site Inspection Concerns

Concern arose after site inspections over sites 7815 and 7834 in study 04. A sensitivity analysis was performed on the primary endpoint with patients from these sites excluded from the analysis. Site 7815 had 10 patients and site 7834 had 7 patients, so 17 patients were removed from the analysis. The results are summarized in Table 29 below. Excluding the sites had little impact and the conclusion remains unchanged. Therefore, there is no concern on the impact of removing the sites on the analysis of the primary endpoint.

Table 29. Study 04: BICLA response at week 52 excluding sites 7815 and 7834

Handling of restructured medication	Anifrolumab vs. Placebo			
	Treatment	n/N (%)	Diff	95% CI
Pre-specified	Ani 300mg	80/173 (46.2%)	15.2	(4.99, 25.35)
Restricted Medication Rules	Placebo	53/172 (30.8%)		

Source: Statistical Reviewer's Analysis

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Sensitivity Analyses

A tipping point analysis was performed to assess the impact of missing data. This analysis considered the number of patients on placebo and anifrolumab with missing data and varies the possible number of responses among these missing outcomes on the two treatment arms. The goal is to explore the plausibility of scenarios under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. For a fixed number of additional responders on anifrolumab, we consider how many additional responders on placebo it will take to observe a p-value less than 0.05 to greater 0.05. For example, if the assumption is that there is only 1 additional responder among the missing outcomes on anifrolumab 300mg, the analysis can be used to explore how many additional responders on placebo it would take to tip the results. The plausibility of the scenarios under which conclusions may be tipped can then be assessed.

Further, we make use of the knowledge of whether patients exceeded/initialized restricted medication before the endpoint. By definition of the primary endpoint, such patients were considered non-responders, regardless of how favorable the efficacy outcomes were. Likewise, patients with missing data, but who were known to have exceeded/initialized restricted medication are considered non-responders in the tipping point analysis. By taking this approach, this greatly reduced the number of patients with uncertain response status. However, it should be noted that targeting the treatment policy estimand, which would ignore prior use of excess/initialized restricted medication, would lead to a greater number of patients with unknown response status, and thus the results will be less robust.

Tipping point analyses were performed for all 3 studies on the analysis of SRI-4 and BICLA. As anifrolumab 150 mg and anifrolumab 1000 mg are not being considered for approval, the tipping point analyses only considered comparisons between the 300 mg arm and placebo. Further, to explore all potential effects of missing data, in these analyses, patients who were considered as having available week 52 data based on week 48 LOCF data, are considered as missing.

Study 1013

SRI-4 + OCS tapering at week 24

There were 9 patients on the anifrolumab 300mg arm and 20 on the placebo arm that had missing data at week 24. Of these, 19 of them failed to meet the no excess medication and OCS tapering criteria and are considered non-responders. Therefore, based on the definition of the primary endpoint which incorporates use of excess medication and OCS tapering, only 10 patients, 1 on anifrolumab 300 mg and 9 on the placebo arm, are considered as having missing data.

Table 30 below displays the number of additional placebo responders needed to tip results per additional number of added responders on anifrolumab. For example, if we consider the single patient on anifrolumab 300mg with missing data to remain a non-responder, the results do not tip, i.e., does not change the conclusion, until at least 6 of the 9 placebo patients with missing data are responders. If we consider the single patient in the anifrolumab 300mg arm to be a responder, the results do not tip until at least 7 of the 9 placebo patients are responders.

To consider if such scenarios are plausible, we note that among placebo completers at Week 24, the response rate is 20.7%, and the estimated response rate among anifrolumab completers is 37.8%. All scenarios that result in tipping the conclusions would require at least 67% of the placebo subjects with missing data to be responders. Such a response rate would represent almost a doubling of the estimated response rate of anifrolumab 300mg and over three times the response rate observed among placebo completers. Such an increase in response rates for placebo patients who do not have week 24 data seems implausible, and we therefore consider these results to be robust to missing data assumptions.

Table 30. Study 1013: Tipping point scenarios for SRI-4 + OCS tapering response at week 24

	# of added anifrolumab responders	
# of added placebo responders		0
	5	S
	6	NS
	7	NS
	8	NS
	9	NS

Source: Statistical Reviewer's Analysis

S: Nominally significant; NS: Not significant; alpha=0.05 was used

BICLA without OCS tapering at Week 52

There were 12 patients on the anifrolumab 300mg arm and 33 patients on the placebo arm that had missing week 52 data. Of these, 13 failed to meet the no excess medication requirements

and are considered non-responders. Therefore, the tipping point analysis only considers the 32 patients, 6 on anifrolumab 300 mg, and 26 on placebo, as having missing data.

Table 31 below displays the number of additional placebo responders needed to tip results per additional number of added responders on anifrolumab. For example, given 0 additional responders on anifrolumab 300mg, it would require at least 14 additional responders on placebo to tip the results. Likewise, given 1 additional responder on anifrolumab 300mg, it would require at least 15 additional responders on placebo.

In this study, the response rate at Week 52 is 39.1% among placebo completers, and the estimated response rate among anifrolumab completers is 60.9%. All scenarios that result in tipping the conclusions would require at least 54% of the placebo subjects with missing data to be responders. If we further consider that at least some additional anifrolumab 300mg responders could be expected, an even higher response rate would be required among missing placebo subjects to tip the results. Considering the higher proportion of missing placebo subjects required to be responders to tip the results relative to the observed rates among placebo completers, we consider this to be a relatively unlikely scenario.

Table 31. Study 1013: Tipping point scenarios for BICLA response without tapering at week 52

# of added placebo responders	# of added anifrolumab responders							
		0	1	2	3	4	5	6
13	S	S	S	S	S	S	S	S
14	NS	S	S	S	S	S	S	S
15	NS	NS	S	S	S	S	S	S
16	NS	NS	NS	S	S	S	S	S
17	NS	NS	NS	NS	S	S	S	S
18	NS	NS	NS	NS	NS	S	S	S
19	NS	NS	NS	NS	NS	NS	S	S
20	NS	NS	NS	NS	NS	NS	NS	S
21	NS	NS	NS	NS	NS	NS	NS	NS
22	NS	NS	NS	NS	NS	NS	NS	NS
23	NS	NS	NS	NS	NS	NS	NS	NS
24	NS	NS	NS	NS	NS	NS	NS	NS
25	NS	NS	NS	NS	NS	NS	NS	NS
26	NS	NS	NS	NS	NS	NS	NS	NS

Source: Statistical Reviewer's Analysis

S: Nominally significant; NS: Not significant; alpha=0.05 was used

Study 05

BICLA

Tipping point analyses were performed using the results for BICLA response under the post-hoc study 04 restricted medication rules, since it is considered to be more clinically relevant and what will appear on the label.

There were 41 patients on the anifrolumab 300mg arm and 45 patients on the placebo arm that had missing week 52 data. Of these, 35 initiated restricted medication (based on study 04 rules) and are considered non-responders for the tipping point analyses. Therefore, the tipping point analyses considers the 51 patients, 26 on anifrolumab 300mg, and 25 on placebo, as having missing data.

Table 32 below displays the number of additional placebo responders needed to tip results per additional number of added responders on anifrolumab. For example, given 0 additional responders on anifrolumab 300mg, it would require at least 13 additional responders on placebo.

Based on placebo completers, an estimated response rate is 36.0%, and the estimated response rate among anifrolumab completers in this study is 56.8%. All scenarios that result in tipping the conclusions would require at least 52% of the placebo subjects with missing data to be responders. If we further consider that at least some of the 26 missing anifrolumab 300mg subjects could be responders, based on these observed rates, an even higher response rate would be required among missing placebo subjects to tip the results. Considering the higher proportion of missing placebo subjects required to be responders to tip the results relative to the observed rates among placebo completers, we consider this to be a relatively unlikely scenario.

Table 32. Study 05: Tipping point scenarios for BICLA response at week 52

Table S27: Study 001: Tipping point scenarios for DLT response at week 02															
	# of added anifrolumab responders														
# of added placebo responders		0	1	2	3	4	5	6	7	8	9	10	11	12	13
	12	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	13	NS	S	S	S	S	S	S	S	S	S	S	S	S	S
	14	NS	NS	S	S	S	S	S	S	S	S	S	S	S	S
	15	NS	NS	NS	S	S	S	S	S	S	S	S	S	S	S
	16	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S	S
	17	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S
	18	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S
	19	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S
	20	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S
	21	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S
	22	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S
	23	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S
	24	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S
	25	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S

Source: Statistical Reviewer's Analysis

S: Nominally significant; NS: Not significant; alpha=0.05 was used

Study 04

BICLA

There were 34 patients on the anifrolumab 300mg arm and 50 patients on the placebo arm that had missing week 52 data. Of these, 31 initiated restricted medication, and are considered non-responders for the tipping point analyses. Therefore, the tipping point analyses considers the 53 patients, 25 on anifrolumab 300mg, and 28 on placebo, as having missing data.

Table 33 below displays the number of additional placebo responders needed to tip results per additional number of added responders on anifrolumab. For example, given 0 additional responders on anifrolumab 300mg, it would require at least 12 additional responders on placebo.

Based on placebo completers, an estimated response rate is 39.4%, and the estimated response rate among anifrolumab completers in this study is 55.5%. All scenarios that result in tipping the conclusions would require at least 43% of the placebo subjects with missing data to be responders. If we further consider that at least some additional anifrolumab 300mg responders could be expected based on these observed rates, an even higher response rate would be required among missing placebo subjects to tip the results, making such a scenario less likely.

Table 33. Study 04: Tipping point scenarios for BICLA response at week 52

# of added placebo responders	# of added anifrolumab responders																		
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
# of added placebo responders	11	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	12	NS	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	13	NS	NS	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	14	NS	NS	NS	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	15	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	16	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S	S	S	S	S
	17	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S	S	S	S
	18	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S	S	S
	19	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S	S
	20	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S	S
	21	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S	S
	22	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S	S
	23	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S	S
	24	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S	S
	25	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S	S
	26	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	S
27	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	S	
28	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	S	

Source: Statistical Reviewer's Analysis

S: Nominally significant; NS: Not significant; alpha=0.05 was used

Data Quality and Integrity

There were no issues with data quality and integrity

Efficacy Results – Secondary and other relevant endpoints

Study 1013

Testing of secondary endpoints was not pre-specified, hence the secondary endpoints presented in this section are considered exploratory and any reported p-values less than 0.05 are considered nominally significant. Table 34 below display the results of the following exploratory secondary endpoints: OCS reduction at week 52, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) response at week 12, joint reduction at week 52, and BICLA in IFN test high patients.

Among patients whose baseline OCS use was ≥ 10 mg/day, OCS reduction was measured by the ability to reduce OCS use from 10 mg/day at baseline to ≤ 7.5 mg/day by week 52. Note that in this analysis, a responder is defined by the last dose ≤ 7.5 mg/day and not having discontinued investigational product. The difference in proportions comparing anifrolumab 1000mg and 300mg to placebo is 10.8 and 30.1, respectively. We see that anifrolumab 300mg is nominally significant compared to placebo in the proportion of patients who achieve last known dose of OCS ≤ 7.5 mg by week 52.

Among patients with a CLASI activity score ≥ 10 at baseline, CLASI response was measured by the ability to achieve $\geq 50\%$ reduction in CLASI activity score at week 12. The difference in proportions comparing anifrolumab 1000mg and 300mg to placebo is 36.1 and 33.4,

respectively. Both doses were nominally significant in having more patients achieve $\geq 50\%$ reduction in CLASI activity score at week 12.

Among patients with at least 6 swollen and 6 tender joints at baseline, joint reduction response was measured by achieving $\geq 50\%$ reduction in joint counts at week 52. The difference in proportions comparing anifrolumab 1000mg and 300mg to placebo is 15.7 and 31.2, respectively. Anifrolumab 300mg was nominally significant in having more patients achieve $\geq 50\%$ reduction in joint counts compared to placebo.

The difference in proportions in BICLA response among patients in the type I IFN test high subgroup comparing anifrolumab 1000mg and 300mg to placebo was 19.9 and 29.1, respectively. We see that both doses were nominally significant in having more patients achieve BICLA response compared to placebo.

Table 34. Study 1013: Exploratory Secondary Endpoints

Endpoint	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
OCS reduction at week 52 ^a	Ani 1000mg	21/63 (33.3%)	10.8	(-5.10, 26.62)
	Ani 300mg	29/55 (52.7%)	30.1	(13.26, 46.97)
	Placebo	14/64 (21.9%)		
CLASI at week 12 ^a	Ani 1000mg	11/24 (45.8%)	27.9	(1.09, 54.64)
	Ani 300mg	14/27 (51.9%)	33.2	(7.43, 59.01)
	Placebo	5/26 (19.2%)		
Joint reduction at week 52 ^a	Ani 1000mg	37/60 (61.7%)	11.7	(-6.09, 29.42)
	Ani 300mg	45/58 (77.6%)	29.6	(12.68, 46.61)
	Placebo	28/58 (48.3%)		
BICLA without OCS tapering in type I IFN high at week 52 ^a	Ani 1000mg	34/78 (43.6%)	19.9	(5.22, 34.67)
	Ani 300mg	39/75 (52.0%)	29.1	(14.17, 44.04)
	Placebo	18/76 (23.7%)		

Source: Statistical Reviewer's Analysis

Difference of proportions based of CMH weights adjusted for stratification factors

a Patients with missing data are regarded as non-responders

Table 35 displays the results on BILAG flare rate through week 52. A flare is defined as either 1 or more new A or 2 or more new B items compared to the previous visit. The rate ratio comparing anifrolumab 1000mg and 300mg to placebo was 0.67 and 0.72, respectively. Since the rate ratio is defined as the ratio of the rate of anifrolumab over the rate of placebo, this means that a rate ratio of < 1 favors anifrolumab in reducing BILAG flares. However, since the 95% confidence intervals includes 1, we conclude that anifrolumab 1000mg and 300mg are not supportive in having more patients reduce annual flare rate compared to placebo.

Table 35. Study 1013: Annual flare rate through Day 365

Treatment	n	Total Follow-Up time (years)	Anifrolumab vs. Placebo	
			Rate Ratio	95% CI
Ani 1000mg	47	92.2	0.67	(0.40, 1.14)
Ani 300mg	50	93.8	0.72	(0.42, 1.21)
Placebo	61	85.1		

Source: Statistical Reviewer's Analysis, SCE errata indication page 137
Analysis performed irrespective of excess OCS use or tapering

Study 05

Original Restricted Medication Rules

This section presents the results for the pre-specified key secondary endpoints under the pre-specified set of restricted medication rules. Since the primary endpoint failed, any positive results were considered nominally significant.

Table 36 display the results of the following pre-specified secondary endpoints: maintain OCS reduction at week 52, CLASI response at week 12, SRI-4 response in type I IFN test high patients at week 52, and SRI-4 response at week 24.

Among patients whose baseline OCS use was ≥ 10 mg/day, maintaining OCS reduction was measured by the ability to reduce OCS use from 10 mg/day at baseline to ≤ 7.5 mg/day by week 40 and maintaining ≤ 7.5 mg/day through week 52. The difference in proportions comparing anifrolumab 300mg and 150mg to placebo was 8.9 and 4.5, respectively. Neither anifrolumab 300mg or 150mg were supportive in having more patients achieve OCS reduction compared to placebo.

Among patients with CLASI activity score ≥ 10 at baseline, CLASI response was measured by the ability to achieve $\geq 50\%$ reduction in CLASI activity score at week 12. The difference in proportions comparing anifrolumab 300mg and 150mg to placebo is 17.0 and 26.2, respectively. We see that anifrolumab 300mg is not supportive in having more patients achieve $\geq 50\%$ reduction in CLASI activity score at week 12 compared to placebo.

Among patients in the type I IFN test high subgroup, for SRI-4 response at week 52, the difference in proportions in responders comparing anifrolumab 300mg and 150mg to placebo is -3.4 and 0.4, respectively. We see that neither dose was supportive in having more patients achieve SRI-4 response compared to placebo.

For SRI-4 at week 24, the difference in proportions in responders comparing anifrolumab 300mg and 150mg to placebo is 0.1 and -4.7, respectively. We see that neither dose is supportive in having more patients achieve SRI-4 response at week 24 compared to placebo.

Table 36. Study 05: Pre-specified key secondary endpoints

Endpoint	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
OCS reduction at week 52	Ani 300mg	42/103 (40.8%)	8.9	(-4.11, 21.86)
	Ani 150mg	17/48 (35.4%)	4.5	(-11.89, 20.93)
	Placebo	33/102 (32.4%)		
CLASI at week 12	Ani 300mg	24/58 (41.4%)	17.0	(-0.26, 34.31)
	Ani 150mg	15/30 (50.0%)	26.2	(4.77, 47.63)
	Placebo	14/54 (25.9%)		
SRI-4 in type I IFN high at week 52	Ani 300mg	53/148 (35.8%)	-3.4	(-14.39, 7.65)
	Ani 150mg	30/76 (39.5%)	0.4	(-13.04, 13.92)
	Placebo	59/151 (39.1%)		
SRI-4 at week 24	Ani 300mg	74/180 (41.1%)	0.1	(-9.96, 10.09)
	Ani 150mg	34/93 (36.6%)	-4.7	(-16.81, 7.44)
	Placebo	76/184 (40.8%)		

Source: Statistical Reviewer's Analysis, CSR page 109

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Table 37 displays the results on BILAG flare rate, as defined in study 1013. The rate ratio comparing anifrolumab 300mg and 150mg to placebo is 0.83 and 0.86, respectively. We see that neither dose was supportive in having more patients reducing annual flare rate compared to placebo.

Table 37. Study 05: Annual flare rate through week 52

Treatment	n	Total Follow-Up time (years)	Anifrolumab vs. Placebo	
			Rate Ratio	95% CI
Ani 300mg	109	166.7	0.83	(0.60, 1.14)
Ani 150mg	58	87.1	0.86	(0.58, 1.27)
Placebo	133	170.8		

Source: Statistical Reviewer's Analysis, CSR page 110

Analysis performed irrespective of use of restricted medication

Study 04 Restricted Medication Rules

This section presents the results for study 05 for the secondary endpoints analyzed after applying the post-hoc set of restricted medication rules, i.e. the restricted medication rules used for study 04. As the primary endpoint failed in this study, and these analyses were implemented after unblinding the data, these analyses are considered exploratory. Table 38 display the results of the following secondary endpoints with the restricted medication rules

used for study 04: maintain OCS reduction at week 52, CLASI response at week 12, joint reduction at week 52, BICLA response in type I IFN test high patients at week 52.

Among patients whose baseline OCS use was ≥ 10 mg/day, the difference in proportions in maintaining OCS reduction comparing anifrolumab 300mg and 150mg to placebo is 17.5 and 19.9, respectively. Both doses were nominally significant in having more patients maintain OCS reduction compared to placebo.

Among patients with CLASI activity score ≥ 10 at baseline, the difference in proportions in CLASI response comparing anifrolumab 300mg and 150mg to placebo was 18.8 and 26.7, respectively. Both doses were nominally significant in having more patients achieve $\geq 50\%$ reduction in CLASI activity score at week 12 compared to placebo.

Among patients with at least 6 swollen and 6 tender joints at baseline, joint reduction response was measured by achieving $\geq 50\%$ reduction in joint counts at week 52. The difference in proportions comparing anifrolumab 300mg and 150mg to placebo is 19.3 and 25.9, respectively. Both doses were nominally significant in having more patients achieve $\geq 50\%$ reduction in joint counts compared to placebo.

Among patients in the type I IFN test high subgroup, for BICLA response the difference in proportions comparing anifrolumab 300mg and 150mg to placebo was 19.7 and 13.0, respectively. We see that anifrolumab 300mg was nominally significant in having more patients achieve BICLA response at week 52 compared to placebo.

Table 38. Study 05: Post-hoc analysis of secondary endpoints under study 04 rules

Endpoint	Treatment	n/N (%)	Anifrolumab vs. Placebo	
			Diff	95% CI
OCS reduction at week 52	Ani 300mg	51/103 (49.5%)	16.6	(3.39, 29.78)
	Ani 150mg	25/48 (52.1%)	19.9	(3.26, 36.50)
	Placebo	34/102 (33.3%)		
CLASI at week 12	Ani 300mg	25/58 (43.1%)	18.7	(1.41, 35.99)
	Ani 150mg	15/30 (50.0%)	26.7	(5.38, 47.93)
	Placebo	14/54 (25.9%)		
Joint reduction at week 52	Ani 300mg	51/93 (54.8%)	19.3	(5.43, 33.20)
	Ani 150mg	29/48 (60.4%)	25.9	(9.16, 42.61)
	Placebo	37/100 (37.0%)		
BICLA in type I IFN high at week 52	Ani 300mg	70/148 (47.3%)	19.0	(8.32, 29.75)
	Ani 150mg	31/76 (40.8%)	13.0	(-0.09, 26.15)
	Placebo	42/151 (27.8%)		

Source: Statistical Reviewer's Analysis, SCE errata page 122, 127

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Study 04

This section presents the results for the pre-specified key secondary endpoints. Since the primary endpoint of BICLA was significant, the testing of the secondary endpoints continued under the multiplicity control procedure and the unadjusted and adjusted (Weighted-Holm) p-values are presented. Table 39 display the results of the following key secondary endpoints: BICLA response in type I IFN test high patients at week 52, maintain OCS reduction at week 52, CLASI response at week 12, and joint reduction at week 52.

For BICLA response at week 52 among patients in the type I IFN test high subgroup, the difference in proportions is 17.3. Since the adjusted p-value is less than 0.01, anifrolumab 300mg had significantly more patients who achieved BICLA response at week 52 compared to placebo.

Among patients whose baseline OCS use was ≥ 10 mg/day, maintaining OCS reduction was measured by the ability to reduce OCS use from 10 mg/day at baseline to ≤ 7.5 mg/day by week 40 and maintaining ≤ 7.5 mg/day through week 52, the difference in proportions is 21.2. Since the adjusted p-value is 0.01, anifrolumab 300mg had significantly more patients who achieved OCS reduction compared to placebo.

Among patients with CLASI activity score ≥ 10 at baseline, CLASI response was measured by the ability to achieve $\geq 50\%$ reduction in CLASI activity score at week 12, the difference in

proportions 24.0. Since the adjusted p-value is 0.04, anifrolumab 300mg had significantly more patients who achieved $\geq 50\%$ reduction in CLASI activity score at week 12 compared to placebo.

Among patients with at least 6 swollen and 6 tender joints at baseline, joint reduction response was measured by achieving $\geq 50\%$ reduction in joint counts at week 52, the difference in proportions 4.7. Since the adjusted p-value is 0.55, anifrolumab 300mg did not have significant more patients who achieved $\geq 50\%$ reduction in joint counts compared to placebo.

Table 39. Study 04: Pre-specified key secondary endpoints

Endpoint	Treatment	n/N (%)	Diff	Anifrolumab vs. Placebo		
				95% CI	Unadjusted P-value	Adjusted P-value
BICLA in type I IFN high at week 52	Ani 300mg	72/150 (48.0%)	17.3	(6.46, 28.24)	< 0.01	< 0.01
	Placebo	46/151 (30.5%)				
OCS reduction at week 52	Ani 300mg	45/87 (51.7%)	21.2	(6.76, 35.71)	< 0.01	0.01
	Placebo	25/83 (30.1%)				
CLASI at week 12	Ani 300mg	24/49 (49.0%)	24.0	(4.32, 43.6)	0.02	0.04
	Placebo	10/40 (25.0%)				
Joint reduction at week 52	Ani 300mg	30/71 (42.6%)	4.7	(-10.61, 20.05)	0.55	0.55
	Placebo	34/90 (37.8%)				

Source: Statistical Reviewer's Analysis, CSR page 105

Difference of proportions based of CMH weights adjusted for stratification factors

Patients with missing data are regarded as non-responders

Table 40 displays the results on annual flare rate through week 52. The rate ratio was 0.67. Since the adjusted p-value = 0.08, anifrolumab 300mg was not significant in reducing annual flare rate compared to placebo.

Table 40. Study 04: Annual flare rate through week 52

Treatment	n	Total Follow-Up time (years)	Rate Ratio	Anifrolumab vs. Placebo		
				95% CI	Unadjusted P-value	Adjusted P-value
Ani 300mg	86	170.2	0.67	(0.48, 0.94)	0.02	0.08
Placebo	122	164.6				

Source: Statistical Reviewer's Analysis, CSR page 105

Analysis performed irrespective of use of restricted medication

Subgroups

This section summarizes results from various subgroup analyses for the primary endpoint, BICLA response at week 52 within subgroup levels. The subgroups and levels explored are:

- Sex (Male; Female)
- Age (<45 ; ≥45)
- Race (White; Non-White)
- Region (North America; Not North America)

BICLA response at week 52 is considered for each study. We further performed shrinkage analyses for sex, age, race, and region. Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. Below is the model used:

$$(\widehat{p_A - p_p})_i \sim N((p_A - p_p)_i, \sigma_i^2), i = 1, 2$$

$$(p_A - p_p)_i \sim N(p_A - p_p, \tau^{-2}), i = 1, 2$$

$$p_A - p_p \sim N(0, 2), \quad \tau^{-2} \sim \text{Gamma } N(0.001, 0.001)$$

We assume that before seeing data, the difference in proportions is 0, and we further place one-eighth of a response (BICLA) and one-eighth of a non-response on anifrolumab 300mg and placebo, which will not be very impactful in linking the groups together. Thus,

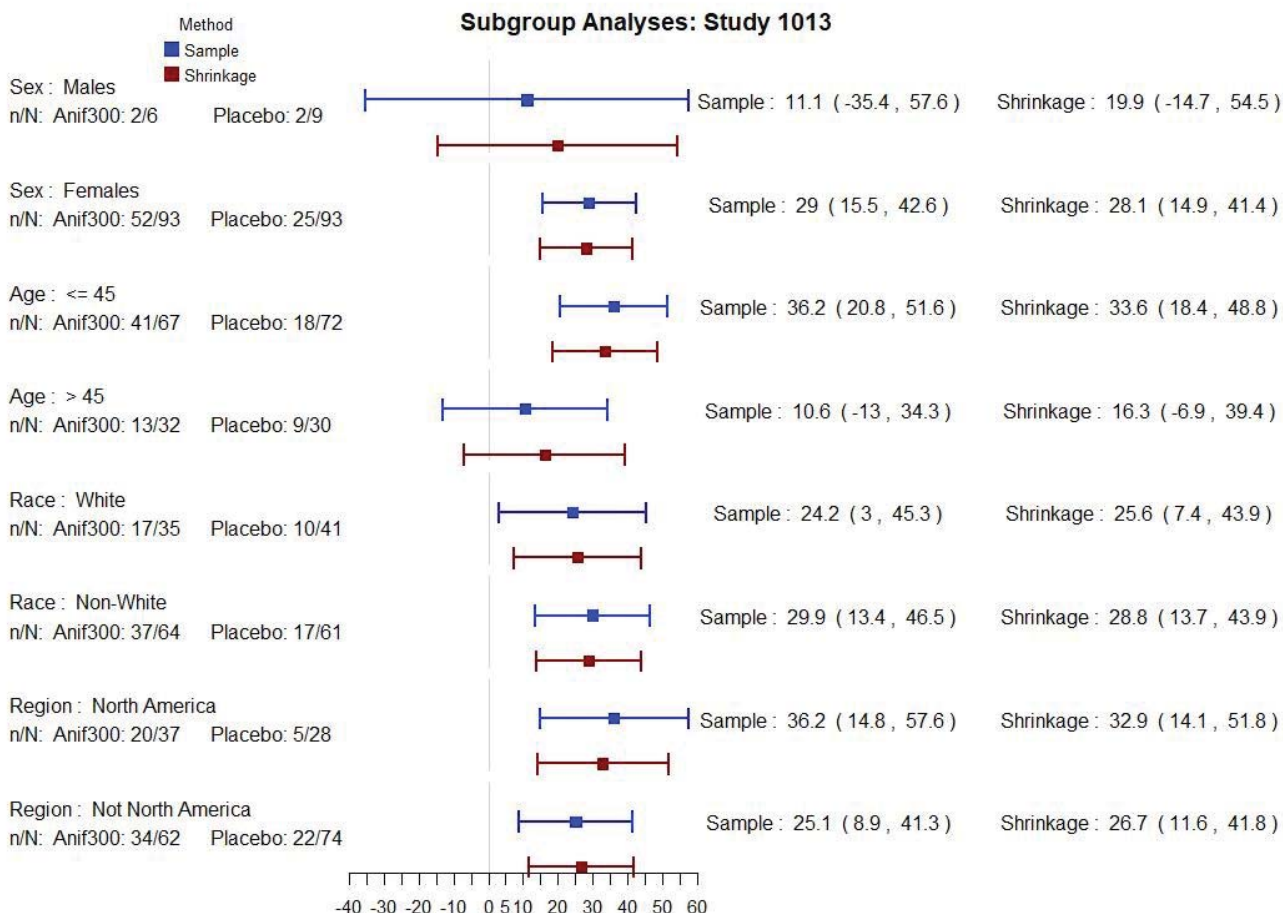
$$\text{Var}(p_A - p_p) = \frac{\tilde{p}(1 - \tilde{p})}{n_A} + \frac{\tilde{p}(1 - \tilde{p})}{n_p} = 2$$

Where $\tilde{p}$ is the common proportion

Study 1013

Figure 14 display the forest plots of the subgroup analyses (in isolation and shrinkage) for sex, age, race, and region. Consistent treatment effects were observed across each of the subgroups. Among males and patients over 45, the nominal 95% confidence intervals include 0 for both the sample and shrinkage analyses. This is not surprising since the study was not powered for any of the subgroup analyses and relatively few patients were males.

Figure 14. Forest plot of subgroup analyses for study 1013

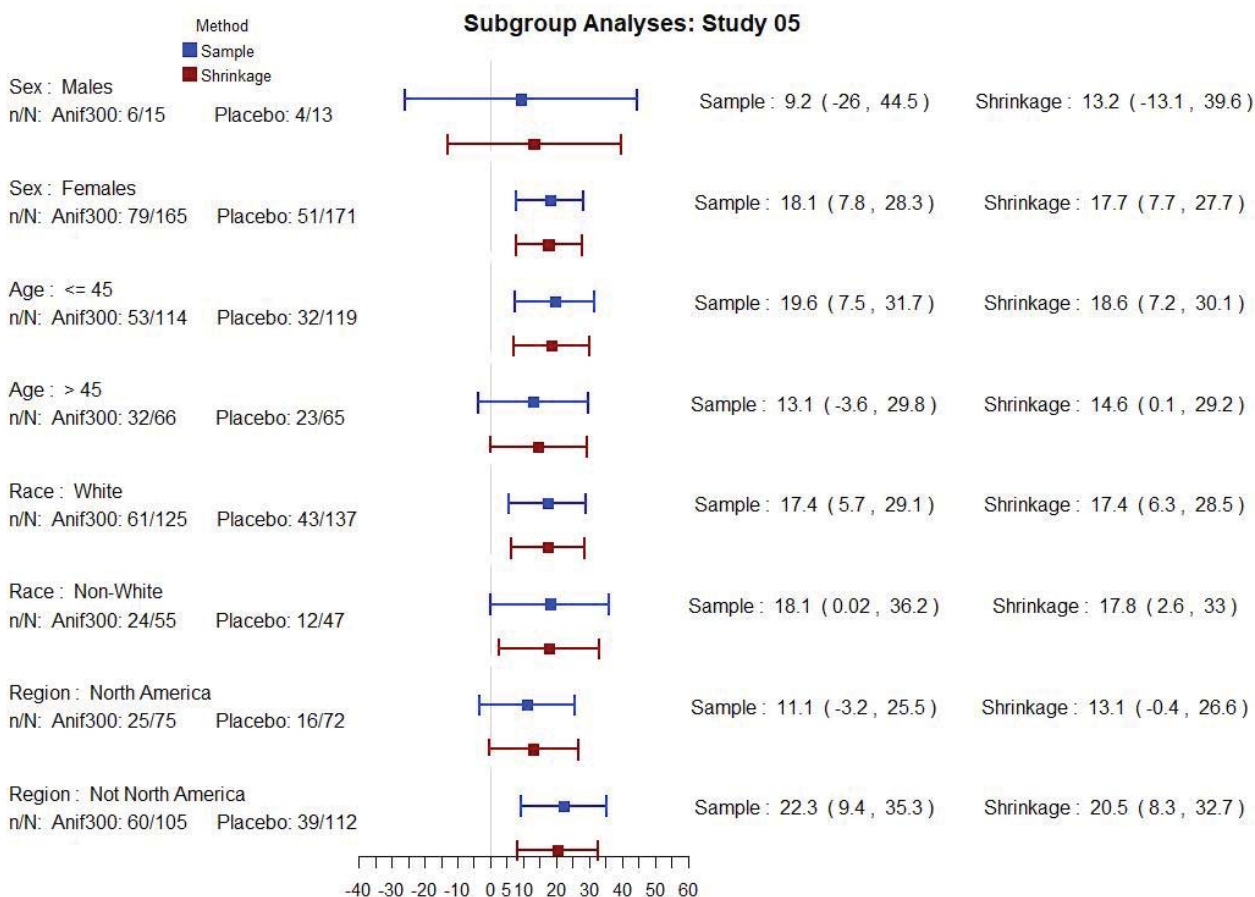


Source: Statistical Reviewer's Analysis
Treatment effects are measured by difference in proportions
Values greater than 0 favor anifrolumab

Study 05

Figure 15 displays the forest plot of the subgroup analyses (in isolation and shrinkage) for sex, age, race, and region for study 05 under the 04 rules. Consistent treatment effects were observed across each of the subgroups. When analyzed in isolation, among males, patients over 45, and North America, the nominal 95% confidence intervals include 0. This is not unexpected given the relatively small sample sizes and resulting uncertainty around the estimates. However, after performing the shrinkage analyses, among patients over 45, the confidence interval excludes 0.

Figure 15. Forest plot of subgroup analyses for study 05



Source: Statistical Reviewer's Analysis

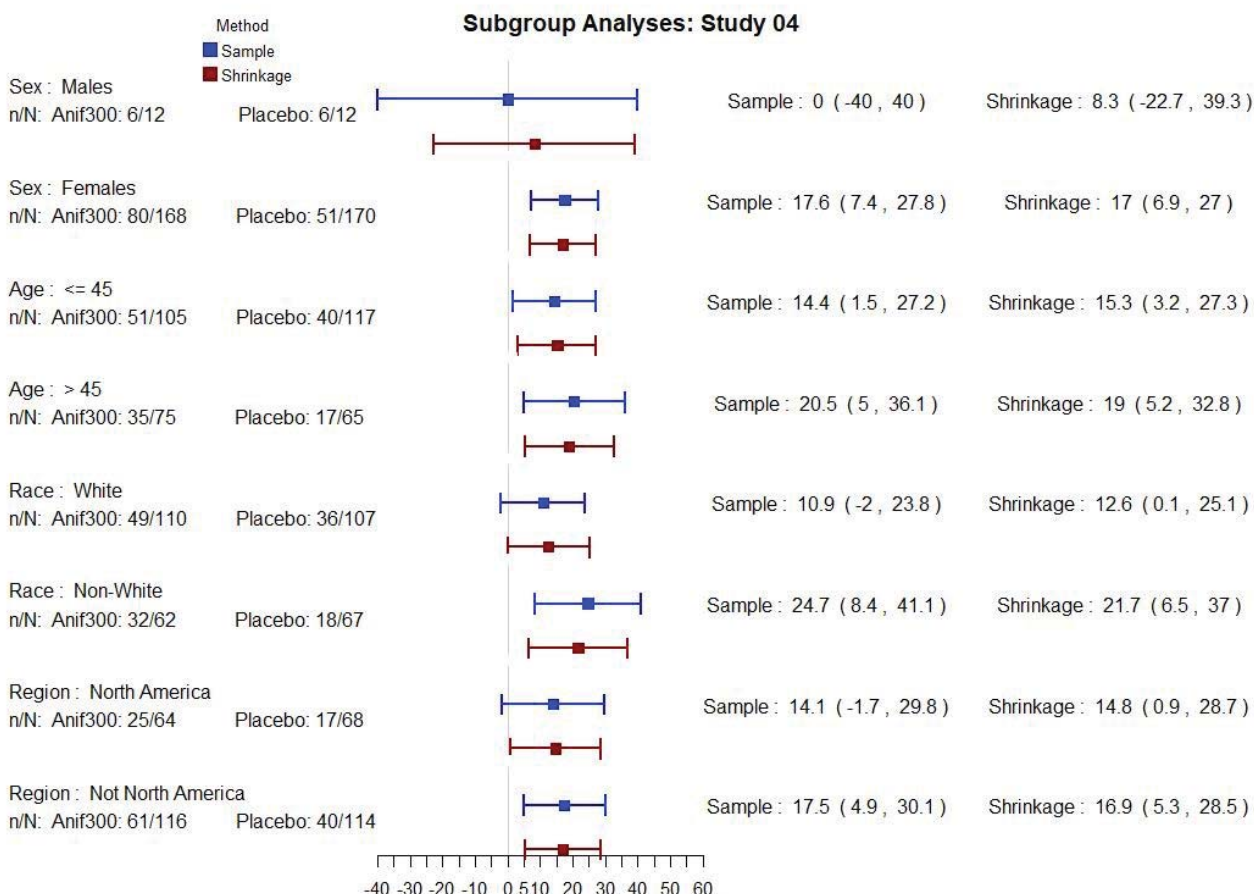
Treatment effects are measured by difference in proportions

Values greater than 0 favor anifrolumab

Study 04

Figure 16 display the forest plots of the subgroup analyses (in isolation and shrinkage) for sex, age, race, and region for study 04. Consistent treatment effects were observed across each of the subgroups, with the exception that among males, for which the difference in proportions between was 0. When analyzed in isolation, among males, whites, and in North America, the nominal 95% confidence intervals include 0. However, after performing the shrinkage analyses, among patients in the subgroup of white, and in North America, the confidence intervals exclude 0. The sample size for male subjects is extremely small in this study, making it challenging to draw conclusions based on the analysis of this subgroup alone.

Figure 16. Forest plot of subgroup analyses for study 04

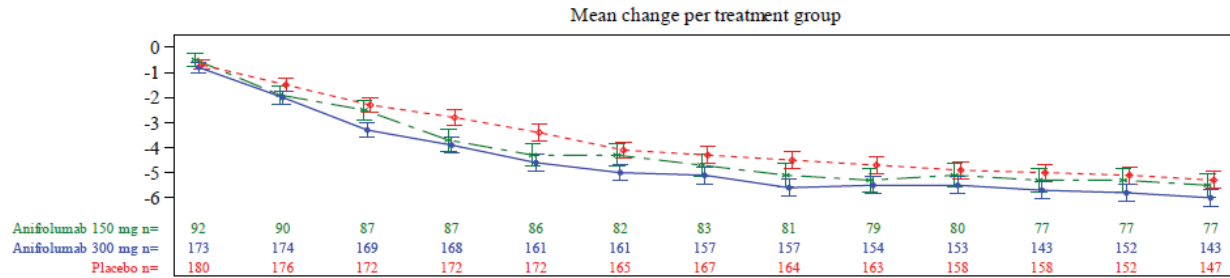


Source: Statistical Reviewer's Analysis
Treatment effects are measured by difference in proportions
Values greater than 0 favor anifrolumab

Dose/Dose Response

Figure 17 below shows the change in SLEDAI-2K, a measure of disease activity that is used to define both SRI-4 and BICLA, over time from baseline for study 05. The placebo group had the smallest reduction, followed by anifrolumab 150mg, while anifrolumab 300mg had the largest reduction throughout all timepoints beginning at week 8 throughout the remainder of the study. While study 05 failed on the primary endpoint of SRI-4, both under the original and revised set of study 04 restricted medication rules, and while the differences in SLEDAI-2K relative to placebo are not statistically significant, these results support a dose-dependent trend.

Figure 17. SLEDAI-2K over time in study 05

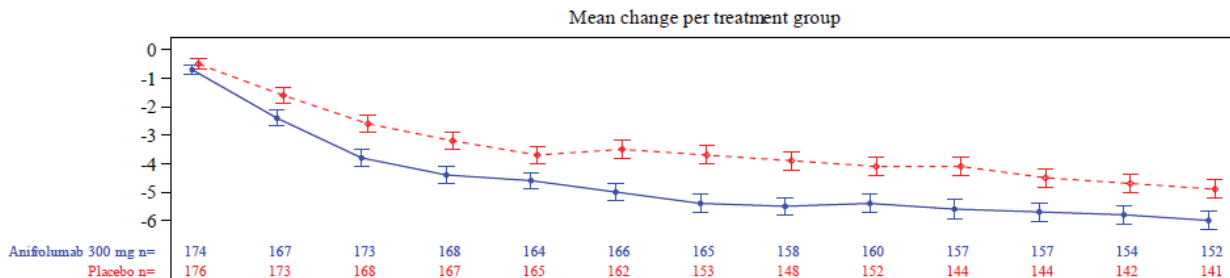


Estimates and standard errors from linear mixed effect model at weeks 4-52

Source: Integrated Summary of Efficacy (Efficacy Figures) page 1356

Similarly, in study 04, Figure 18 below shows the changes in SLEDAI-2K over time from baseline. There is clear separation favoring anifrolumab 300mg starting at week 8 and throughout the remainder of the study. As with study 05, while the separation is not statistically significant, the trend favors anifrolumab 300mg in SLEDAI-2K reduction compared to placebo. A similar trend is seen in Figure 19 below for study 1013, though the anifrolumab 1000 mg dose studied only in this study largely overlaps with the anifrolumab 300 mg dose. Also, see Section 6.3.1.

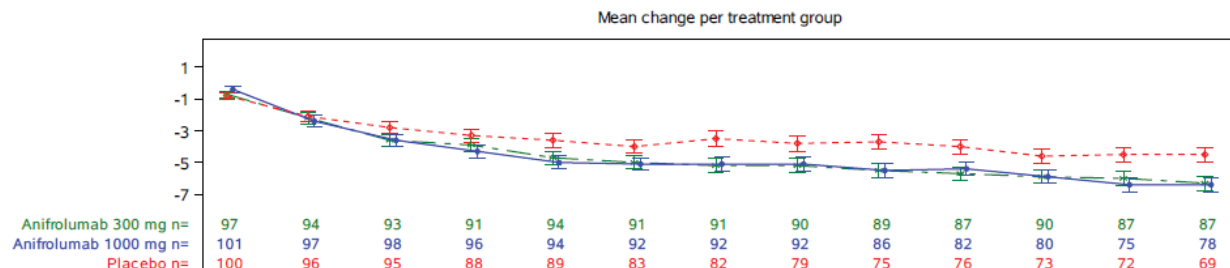
Figure 18. SLEDAI-2K over time in study 04



Estimates and standard errors from linear mixed effect model at weeks 4-52

Source: Integrated Summary of Efficacy (Efficacy Figures) page 1354

Figure 19. SLEDAI-2K over time in study 1013



Estimates and standard errors from linear mixed effect model at weeks 4-52

Source: Integrated Summary of Efficacy (Efficacy Figures) page 1651

8.1.3. Assessment of Efficacy Across Trials

Evaluation of efficacy was evaluated as stand-alone trials. Pooled efficacy analyses were not considered during this review.

Additional Efficacy Considerations

The Applicant was asked to provide an explanation for the apparent discrepancy between SRI-4 and BICLA responses within study 05 and between study 04 and study 05. These two studies were identical in design and enrolled patients had similar demographics, baseline SLE disease characteristics and background medication use (see above Table 12, Table 13, Table 14, and Table 16). However, while study 04 showed differences of anifrolumab over placebo for both BICLA and SRI-4 endpoints (Table 27 and Table 28), study 05 only showed differences using the BICLA endpoint (Table 25 and Table 26).

In order to further understand the discrepant result on SRI(4) in study 05, the Applicant performed an exploratory post-hoc analysis to compare each patient's outcome on SRI(4) and BICLA for each patient in the studies, with the following findings.

- The majority of patients in both studies (84% to 85%) had concordant outcomes on SRI(4) and BICLA (i.e., had a SRI[4] response and BICLA response, or a SRI[4] nonresponse and BICLA nonresponse), and the pattern of concordance was consistent across the studies.
 - In study 05, the difference in the proportion of patients who were both SRI[4] responders and BICLA responders ('dual responders') between anifrolumab 300 mg and placebo was 14.5% (95% CI (4.6, 24.0)), which is clinically meaningful and similar to that observed in study 04 [16.9%; 95% CI (7.2, 26.7)].
- A smaller proportion of patients in both studies had discordant outcomes on SRI(4) and BICLA (i.e., had a SRI[4] response and BICLA nonresponse, or a SRI[4] nonresponse and BICLA response). In one subset in study 05 (SRI[4] responders/BICLA nonresponders; 11.0% of the total patients in the study), more patients in the placebo group were able to achieve a SRI(4) response than patients in the anifrolumab group (15.2% vs 6.7%), and this appears to be driving the overall discrepant result on SRI(4) in the study.
 - In this discordant subset in study 05, patients in the placebo group had lower baseline disease severity, and greater steroid use during the study, compared with the anifrolumab 300 mg group. This may have led to more patients in the placebo group achieving complete resolution of arthritis, which alone meets the criteria for a SRI(4) response, leading to more SRI(4) responders in the placebo group compared with the anifrolumab 300 mg group.

- Despite achieving a SRI(4) response, all the patients in this discordant subset in study 05 were BICLA nonresponders. To be a BICLA responder, a patient must have improvement in all impacted organ systems at baseline and, as the patients in this subset had several involved clinical manifestations at baseline and none of them achieved improvement in all of them, they were all BICLA nonresponders.

We note that these results should be interpreted with caution as they are from exploratory analyses and in some cases based on a subgroup of patients defined by post-randomization variables. There was a clinically meaningful difference between the treatment groups in the proportion of patients who were both a SRI(4) responder and BICLA responder, in favor of anifrolumab, in both studies. These dual responders, based on 2 validated endpoints, confirm the beneficial effect of anifrolumab on overall disease activity in patients with SLE. One subset of patients in study 05 appears to be driving the overall discrepant result on SRI(4) in study 05. In this subset, more patients in the placebo group were able to achieve a SRI(4) response than patients in the anifrolumab group. This may be due to an imbalance between the treatment groups in baseline disease severity, and the degree of steroid use during the study, leading to more patients in the placebo group achieving complete resolution of arthritis, which alone meets the criteria for a SRI(4) response.

8.1.4. Integrated Assessment of Effectiveness

Study 04 represents an adequate and well-controlled trial showing favorable and statistically significant changes on the pre-specified, clinically meaningful primary and secondary endpoints when comparing anifrolumab 300 mg IV versus placebo. Because the phase 2 trial (1013) was designed only as a proof of concept and dose-ranging study with inadequate multiplicity control and study 05, the first phase 3 trial, failed on its primary endpoint, these cannot be considered additional successful adequate and well-controlled trials when considered independently. However, the review team feels that when these trials are considered in combination, the consistent results observed in studies 1013 and 05 do provide confirmatory evidence that support the effectiveness of anifrolumab 300 mg IV.

Across the three studies, there are three randomized comparisons, each with adequate duration (52 weeks), that support the claim that anifrolumab 300 mg IV yields higher BICLA response rates compared to placebo. Further, two of the three studies provide support that anifrolumab 300 mg IV yields higher SRI-4 response rates compared to placebo at week 52. While study 05 failed to show an effect on SRI-4, the study showed a numerically dose-dependent trend that is not statistically significant in SLEDAI-2K, a measure of disease activity that is used to define both SRI-4 and BICLA and for which there was relatively consistent evidence across all three studies. In all three studies, additional supportive evidence was noted in the analyses of the secondary endpoints, including a greater proportion of subjects on anifrolumab than placebo able to reduce oral corticosteroid use and a lower proportion of subjects on anifrolumab experiencing a flare of SLE disease activity, further supporting the effectiveness of anifrolumab 300 mg IV.

8.2. Review of Safety

8.2.1. Safety Review Approach

The application contained double-blind safety data from adult SLE patients collected over 52 weeks of 300 mg IV every 4 weeks anifrolumab dosing in studies 1013, 04 and 05. Safety data for all 3 doses of anifrolumab (150 mg IV every 4 weeks, 300 mg IV every 4 weeks, and 1000 mg IV every 4 weeks) from studies 1013, 04 and 05 plus study 1145 (open-label extension from study 1013) and for the 300 mg IV every 4 weeks dose in study 09 (placebo-controlled long-term extension from studies 04 and 05) were also included for completeness. The individual studies contributing safety data are summarized in (Table 41).

Table 41. Individual Studies Contributing to Safety Review

Study ID Study name Status	Study location	Study design	Study subjects	Anifrolumab IV Q4W dose	Number of subjects, total and by treatment group	Treatment duration
CD-IA-MEDI-546-1013 Study 1013 Completed	Global	Randomized (1:1:1), double-blind, placebo-controlled	Adults (18-65 years) with moderate to severe SLE receiving standard of care	300 mg, 1000 mg, or placebo	Safety population total: N = 305 99 (300mg) 105 (1000 mg) 101 (placebo)	52 weeks (13 doses) 12-week (85 days) follow-up after last dose
CD-IA-MEDI-546-1145 Study 1145 Completed	Global	Open-label extension	Patients who completed study 1013	Initially 1000 mg; then all patients switched to 300 mg ¹	As-treated population total: 218 (1000 mg); 191 switched to 300 mg	156 weeks (up to 40 doses) 12-week (85 days) follow-up after last dose
D3461C00005 Study 05 Completed	Global	Randomized (1:2:2), double-blind, placebo-controlled	Adults (18-65 years) with moderate to severe SLE receiving standard of care	150 mg, 300 mg, or placebo	Full analysis set, total: N = 456 ^a 93 (150 mg) 180 (300 mg) 183 (placebo)	52 weeks (13 doses) 12-week (84 days) follow-up after last dose for patients not entering the LTE
D3461C00004 Study 04 Completed	Global	Randomized (1:1) double-blind, placebo-controlled	Adults (18-65 years) with moderate to severe SLE receiving standard of care	300 mg or placebo	Full analysis set, total: N = 362 ^b 180 (300 mg) 182 (placebo)	52 weeks (13 doses) 12-week (84 days) follow-up after last dose for patients not entering the LTE
D3461C00009 Study 09 Ongoing	Global	Randomized, double-blind, placebo-controlled	Patients who completed study 04 or study 05	300 mg or placebo Patients on anifrolumab in study 04 and	Full analysis set, total: N = 556 ² 443 (300 mg) 113 (placebo)	156 weeks (39 doses) 12-week follow-up after last dose

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

				05 continued on 300 mg, placebo patients from study 04 and 05 randomized 1:1 to anifrolumab or placebo		
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¹ In OLE study 1145, initially, all patients were administered 1000 mg, which was later amended to 300 mg following the population modeling of study 1013 interim data.

² Interim data from study 09 (up to and including August 01, 2019) were submitted with the BLA.

^a Excludes 3 patients from 1 site, who were excluded from all analysis due to non-compliance

^b Excludes 8 patients due to sustained site non-compliance

The focus of this safety review is on the 52-week safety data for the 300 mg IV dose summarized in the clinical study reports for studies 1013, 04 and 05—52-week Safety Pool—including the Integrated Summary of Safety and electronic datasets for adverse events (AES), lab data, and vital signs. The safety review is also supported by a P3 Safety Pool, comprising 52-week 300 mg data for studies 04 and 05 only, a Phase 3 LTE Pool, consisting of up to 4 years of data for the 300 mg dose in the long-term extension study recruiting from studies 04 and 05, two 52-week dose-specific pools—150 mg Pool (from study 05) and 1000 mg Pool (from study 1013)—and an All Anifrolumab Pool, consisting of 52-week and long-term extension data for all 3 doses of anifrolumab. A summary of the Safety Pools is shown in Table 42.

Table 42. Summary of Safety Pools for Integrated Assessment of Safety

Treatments compared Pool/comparison	Phase III studies contributing data							Phase II studies contributing data			
	Study 05			Study 04		Study 09		Study 1013			Study 1145
	Ani 150 mg	Ani 300 mg	Placebo	Ani 300 mg	Placebo	Ani 300 mg	Placebo	Ani 300 mg	Ani 1000 mg	Placebo	Ani 300/1000 mg
300 mg vs placebo											
P3 Safety Pool		X	X	X	X						
52-week Safety Pool		X	X	X	X			X		X	
Phase III LTE Safety Pool		X	X	X	X	X	X				
150 mg vs placebo											
150 mg Safety Pool	X		X								
1000 mg vs placebo											

1000 mg Safety Pool									X	X	
All anifrolumab vs placebo											
All Anifrolumab Safety Pool	X	X	X	X	X	X	X	X	X	X	X

Source: Section 2.2 in Module 5.3.5.3

A summary of interim adverse events, including serious adverse event (SAE) data generated from the ongoing placebo-controlled, double-blind phase 3 long-term extension study (09) were also provided for the reporting period August 01, 2019 through March 26, 2020 in the 120-Day Safety Update submitted on November 02, 2020 and are included in the pertinent areas of the following discussion.

Event categories for adverse events of special interest (AESIs) were selected based on the mechanism of action of anifrolumab, non-clinical findings, factors related to biologic and infusion-based therapies, and based on the prevalence of a particular adverse event in the SLE population (as is the case for MACE). AESIs were protocol-specified and assessed by the investigator in the electronic case report form based on case definitions. For the integrated safety summary, AESIs were identified using the criteria detailed in the Integrated Safety Analysis Plan. The AESIs for the integrated safety analysis were:

- Non-opportunistic serious infections
- Opportunistic infections
- Herpes Zoster
- TB (including latent TB)
- Influenza
- Anaphylaxis/Hypersensitivity/Infusion-related reaction
- Malignancy
- MACE
- Vasculitis (non-SLE)

For each AESI, both the study-level protocol-specified case definitions and integrated safety analysis criteria for the primary safety pool are summarized in Table 43.

Table 43. Identification and definition of adverse events of special interest (AESIs)

AESI or AE category	Phase 3 study protocol case definitions or descriptions of events of interest	Summary of Clinical Safety AE identification criteria
Non-opportunistic serious infections	Any non-opportunistic infection that met the SAE criteria.	All SAEs in the SOC Infections and infestations, excluding AEs defined as opportunistic infections.
Opportunistic	An invasive infection caused by micro-organisms that are	All serious and non-serious AEs with

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

infections	normally non-pathogenic or rarely pathogenic in individuals with normal immune function or cause an infection of a type or severity not seen in the normal host. Investigators were asked to undertake appropriate microbiologic identification and report culture results for all patients who developed serious infections.	PTs included in a MedDRA custom PT grouping, developed with reference to Winthrop et al 2015 and the NIH Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.
Herpes Zoster	A viral infection characterized by a cutaneous vesicular eruption on an erythematous base presenting along dermatome(s) and usually associated with prodromal pain.	AEs of herpes zoster included serious and non-serious AEs identified by select PTs from the HLT Herpes viral infections.
TB (including latent TB)	An active TB infection could be either new or a reactivation of dormant disease and could be either bacteriologically confirmed or clinically diagnosed. Latent TB was defined as a mycobacterial infection without clinical, bacteriological findings, or radiologic findings consistent with active TB and a TB blood test using an IGRA or using purified protein derivative skin test that is positive both at the time of provisional diagnosis and on repeat assessment.	AEs of TB or latent TB were identified using a custom MedDRA PT grouping (PTs: latent tuberculosis, tuberculosis, and mycobacterium tuberculosis complex test positive).
Influenza	Where a patient reported a viral infection severe enough to be considered, a viral test should have been performed to confirm the diagnosis. However, if in the opinion of the investigator, the subject had influenza based on defined clinical symptoms, this was to be reported as influenza, whether or not a test to confirm the diagnosis had been performed.	AEs with the PT influenza. SAEs of influenza were also included in the AESI category non-opportunistic serious infection.
Anaphylaxis	A definition based on Sampson et al 2006 was detailed in Appendix Y to the study 04 and 05 CSPs as a simple and rapid means to make the diagnosis of anaphylaxis associated with the infusion of IP.	Custom MedDRA PT grouping (PTs: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock).
Hypersensitivity	An acute onset of an illness with involvement of the skin, mucosal tissue, or both during infusion of IP, but did not meet the definition of anaphylaxis (i.e., there was no respiratory compromise or reduced BP/associated symptoms of end organ dysfunction).	Custom MedDRA PT grouping (LLT hypersensitivity reaction and PT hypersensitivity).
Infusion-related reaction	Infusion-related reaction was defined as any other reaction (aside from anaphylaxis or hypersensitivity) occurring during infusion of IP or felt to be temporally related to the infusion within 24 hours of IP administration.	AEs with the PT infusion-related reaction.
Malignancy	A neoplasm characterized by cells with abnormal features and uncontrolled rapid growth with invasive and/or metastatic tendencies, diagnosed based on pathologic and clinical standards. Investigators were requested to additionally obtain biopsy results and pertinent biomarker and/or genetic testing results.	Four SMQs: hematological malignant tumors, non-hematological malignant tumors, malignant lymphomas (narrow), and skin malignant tumors (narrow).
MACE	An independent CV-EAC reviewed cases of interest to determine if they met accepted diagnostic criteria for MACE events.	For the phase III studies, MACE were those assessed by the CV-EAC. For study 1013, MACE were identified using a custom MedDRA term list.

Vasculitis (non-SLE)	An inflammatory disorder of blood vessels involving arteries and/or veins and characterized by characteristic clinical signs/symptoms and diagnosed by biopsy, imaging such as angiography, or blood tests such as findings of antineutrophil cytoplasmic antibodies consistent with the diagnosis. Underlying causes were to be identified, wherever possible. Only non-SLE-related vasculitis was to be reported as an AESI of vasculitis.	
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Source: Table 3, Summary of Clinical Safety

8.2.2. Review of the Safety Database

Overall Exposure

In the entire clinical development program for anifrolumab, which includes scleroderma and lupus nephritis in addition to SLE, more than 1,000 subjects have been exposed to at least one dose of anifrolumab (doses ranging from 150 mg to 1000 mg IV). For SLE specifically, 837 SLE patients (Table 44) have received at least one dose of anifrolumab (doses ranging from 150 mg to 1000 mg). The proposed dose for SLE is 300 mg IV every 4 weeks. For the proposed dose of 300 mg in SLE patients, a total of 639 subjects have received at least one dose (Table 45), of which 180 were initially treated with placebo during the 52-week placebo-controlled periods of studies 1013, 04, and 05 and then switched to anifrolumab 300 mg in study 1145 (open-label extension study from 1013) or study 09 (long-term extension study from studies 04 and 05).

Table 44. Safety Population, Size and Denominators for anifrolumab (any dose) in SLE

Safety Database for Anifrolumab (any dose) Individuals exposed to the study drug in this development program for the indication under review N=837 ¹			
Clinical Trial Groups	Anifrolumab (n= 837)	Active Control (n= 0)	Placebo (n= 466) ²
Controlled trials conducted for this indication	204+273+180+115 (studies 1013+04+05+09 PBO-->ANI)	n=0	101+183+182 (studies 1013+05+04)
All other than controlled trials conducted for this indication	65 (study 1145 PBO-->ANI)	n=0	n=0
Controlled trials conducted for other indications	n=0	n=0	n=0

¹ All Anifrolumab safety pool is comprised of all subjects exposed to any dose of anifrolumab in studies 1013, 04, 05, 1145 and 09

² All Anifrolumab safety pool placebo (n=286) is limited to subjects who received placebo in studies 1013, 04 and 05 and did not enter an extension study (466-(115+65))

Source: Reviewer derived from Summary of Clinical Safety Section 1.2.1.2

Table 45. Safety, Population, Size and Denominators for anifrolumab 300 mg in SLE

Safety Database for Anifrolumab 300 mg Individuals exposed to the study drug in this development program for the indication under review N=639 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	Anifrolumab 300 mg (n= 639) ^{1,2,3}	Active Control (n=0)	Placebo (n= 466)
Controlled trials conducted for this indication	99+180+180+115 (1013+04+05+09 PBO->ANI)	n=0	101+183+182 (1013+05+04)
All other than controlled trials conducted for this indication	65 (Placebo switched to OLE 1145 from study 1013)	n=0	n=0
Controlled trials conducted for other indications	n=0	n=0	n=0

¹ Primary safety pool is limited to the 360 subjects exposed to anifrolumab 300 mg in studies 04 and 05 and 365 in the placebo arm

² Supportive Safety pool is limited to the 459 subjects exposed to anifrolumab 300 mg in studies 1013, 04 and 05 and 466 in the placebo arm

³ Phase 3 LTE safety pool is limited to the 360 subjects exposed to anifrolumab 300 mg in studies 04, 05 and 09; 365 in the placebo arm is limited to the 52-week data from study 04 and 05

Duration of Exposure

In the primary safety pool (phase 3 studies only), patients in the anifrolumab 300 mg group (N = 360) had a total of 326.0 PY of exposure to IP (Table 46). The mean duration of exposure was 330.8 days (SD: 86.24, range: 3 to 419) in the anifrolumab 300 mg group and 319.1 days (SD: 93.41, range: 21 to 393) in the placebo group. Overall, 326 patients (90.6%) were treated with anifrolumab for ≥ 24 weeks and 299 patients (83.1%) were treated with anifrolumab for ≥ 48 weeks in the primary safety pool. In the supportive safety pool (studies 1013, 04 & 05), patients in the anifrolumab 300 mg group (N = 459) had a total of 419.4 PY of exposure to IP (Table 46). There were 420 patients (91.5%) treated with anifrolumab for ≥ 24 weeks and 387 patients (84.3%) treated with anifrolumab for ≥ 48 weeks.

Table 46. Duration of exposure in Primary (studies 04 & 05) and Supportive (1013, 04 & 05) pools

Exposure		Primary safety pool		Supportive safety pool	
		Anifrolumab 300 mg (N = 360)	Placebo (N = 365)	Anifrolumab 300 mg (N = 459)	Placebo (N = 466)
Duration of exposure (days)	n	360	365	459	466
	Mean (SD)	330.8 (86.24)	319.1 (93.41)	333.7 (83.89)	315.9 (96.50)
	Median	365.0	365.0	365.0	365.0
	Min, max	3, 419	21, 393	3, 419	21, 393
	Total PY of exposure	326.0	318.8	419.4	403.0
Cumulative exposure over time, n (%)	≥ 1 day	360 (100.0)	365 (100.0)	459 (100.0)	466 (100.0)
	≥ 12 weeks	346 (96.1)	351 (96.2)	441 (96.1)	446 (95.7)
	≥ 24 weeks	326 (90.6)	326 (89.3)	420 (91.5)	411 (88.2)
	≥ 36 weeks	311 (86.4)	300 (82.2)	403 (87.8)	379 (81.3)
	≥ 48 weeks	299 (83.1)	280 (76.7)	387 (84.3)	351 (75.3)
	≥ 52 weeks	238 (66.1)	224 (61.4)	315 (68.6)	286 (61.4)
Total follow-up time	n	360	365	459	466
	Mean (SD)	355.2 (75.49)	348.9 (78.40)	365.2 (78.81)	351.6 (87.50)
	Median	366.5	366.0	370.0	367.0
	Min, max	3, 549	21, 494	3, 549	21, 498

Source: Table 3.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3

Additional, longer-term exposure to anifrolumab 300 mg occurred in the placebo-controlled long-term extension study 09, which enrolled subjects who had completed studies 04 and 05. Study 09 is ongoing, and the Applicant provided data through August 01, 2020 for the initial BLA and through March 19, 2020 with the 120-day safety update. The long-term extension data provides significant exposure to anifrolumab 300 mg beyond 52 weeks. In addition, patients who received placebo in the phase 3 studies, were randomized to continue placebo or receive 300 mg of anifrolumab. As shown in Table 47, up to March 19 2020, the total exposure in the anifrolumab 300 mg group was 872.8 PY. Overall, 294 patients (81.7%) were exposed to

anifrolumab for ≥ 52 weeks, 237 patients (65.8%) were exposed for ≥ 104 weeks (~ 2 years), and 161 patients (44.7%) were exposed for ≥ 156 weeks (~ 3 years).

Table 47. Phase 3 PC Long-Term Safety Duration of Exposure (with 120-day safety update)

Exposure		Phase 3 long-term safety	
		Anifrolumab 300 mg (N = 360)	Placebo (N = 365)
Duration of exposure (days)	n	360	365
	Mean (SD)	885.6 (466.47)	526.2 (395.06)
	Median	1038.5	365.0
	Min, max	3, 1514	21, 1508
	Total PY of exposure	872.8	525.8
Cumulative exposure over time, n (%)	≥ 1 day	360 (100.0)	365 (100.0)
	≥ 12 weeks	346 (96.1)	351 (96.2)
	≥ 24 weeks	326 (90.6)	326 (89.3)
	≥ 36 weeks	311 (86.4)	300 (82.2)
	≥ 48 weeks	300 (83.3)	280 (76.7)
	≥ 52 weeks	294 (81.7)	242 (66.3)
	≥ 76 weeks	248 (68.9)	102 (27.9)
	≥ 104 weeks	237 (65.8)	91 (24.9)
	≥ 128 weeks	221 (61.4)	77 (21.1)
	≥ 156 weeks	161 (44.7)	53 (14.5)
	≥ 180 weeks	95 (26.4)	35 (9.6)
	≥ 208 weeks	32 (8.9)	10 (2.7)
Total follow-up time	n	360	365
	Mean (SD)	931.9 (445.22)	574.2 (394.16)
	Median	1072.0	373.0
	Min, max	3, 1689	21, 1690

Source: Table 3.1.1a in Appendix B

Adequacy of the safety database:

Regarding overall exposure for the assessment of safety, a total of 1029 subjects have been exposed to *any dose* of anifrolumab for periods of up to 4 years in the anifrolumab clinical development program. Of those 1029 subjects, at least 837 were SLE patients exposed to IV anifrolumab Q4W (150 mg, 300 mg, or 1000 mg). Of these, 688 patients with SLE were exposed to IV anifrolumab for at least one year and 263 patients were exposed for at least 3 years. 459 subjects were exposed to at least one dose of anifrolumab 300 mg during the 52-week, placebo-controlled periods of studies 1013, 04 and 05; of those, 420 (91.5%) of subjects were exposed to 300 mg IV anifrolumab for at least 6 months, and 315 (68.6%) were exposed to 300 mg IV anifrolumab for at least one year. Data from the ongoing long-term extension study (09) for > 150 subjects exposed to anifrolumab 300 mg for at least 3 years provides additional long-term safety information to support the BLA. Patients who received placebo in the phase 3 studies and enrolled in study 09 were randomized to either continue placebo or receive 300 mg of anifrolumab. The size of the safety database for this submission is adequate to provide sufficient basis for a risk/benefit assessment in the adult SLE population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality submitted was well-organized and adequate to perform a complete review of safety. Several information requests were sent to the Applicant during the review of safety for additional analyses which were satisfactory and received in a timely manner.

Categorization of Adverse Events

Verbatim terms of AEs and Disease Related Events (DRE) recorded in the case report forms (CRF) by investigators were coded by the Applicant using MedDRA dictionary Preferred Term (PT), High-Level Term (HLT), and System Organ Class (SOC) version 22.1. The MedDRA coding of the information generated from studies 1013, 1145, 04, 05, and 09 conducted by the Applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

Routine Clinical Tests

The following clinical and lab testing were included in studies 1013, 04, 05 and 09 in support of anifrolumab IV's safety profile:

- o Symptom driven physical exam, height, and weight
- o Vital signs: systolic and diastolic blood pressure, heart rate and temperature
- o Complete cell count (CBC) with differential and platelet count, hemoglobin, and hematocrit
- o Serum chemistries: albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, creatine kinase, glucose, gamma glutamyl transferase, potassium, sodium, total bilirubin, cholesterol, and fasting lipid profile (HDL, LDL, triglycerides)
- o Urinalysis: including specific gravity, spot urine protein, spot urine creatinine, and protein/creatinine ratio
- o Pregnancy test
- o TB blood test
- o Immunology profile: Anti-dsDNA, C3, C4, CH50
- o Immunogenicity test (pre-dose)
- o 12-lead ECG: baseline and end of study
- o Columbia-Suicide Severity Rating Scale (C-SSRS)

8.2.4. Safety Results

Deaths

Overall, there were 14 deaths during the anifrolumab clinical studies in the anifrolumab development program for SLE including all doses for 52 weeks (studies 1013, 05 and 04) and placebo controlled long-term extension study 09 (participants in studies 05 and 04 continuing

on either anifrolumab or placebo for greater than 52 weeks). Key patient data for patients with fatal AEs are summarized in Table 48, based on full patient narratives of all deaths in the CSRs for completed studies, in the 120-day safety update for the phase 3 long-term extension study (study 09, LTE), and in an April 2021 response to query regarding the DSUR covering January 2020-2021. No deaths occurred during the phase 2 studies 02 and 08 or during phase 1 studies (MI-CP180 and 06). Four deaths occurred during the phase 2 and 3 52-week placebo controlled studies (1013, 04 and 05)—one in the anifrolumab 1000 mg arm of study 1013, one in the anifrolumab 300 mg arm of study 04, one in the anifrolumab 300 mg arm of study 05, and one in the placebo arm of study 05. There was one death during the open-label extension (OLE) of the phase 2 study (1145) in a subject originally randomized to placebo in study 1013 and who received first 1000 mg anifrolumab (16 doses) and then 300 mg anifrolumab (16 doses) during the OLE period. For the phase 3 LTE through August 1, 2019 with the initial BLA filing, there were two deaths, both in the placebo group. Between August 2019 and March 19, 2020, two additional deaths were recorded in the 120-day safety update of the phase 3 LTE; both in the anifrolumab 300 mg arm, including one attributed to infection (pneumonia). Five additional deaths were reported for study 09 in an Annual Report/DSUR for study 09 covering January 2020 through January 2021, all in the anifrolumab 300 mg arm, four attributed to infections (1 pneumonia and 3 COVID-19) and one attributed to SLE exacerbation.

Table 48. Summary of all deaths occurring during the anifrolumab SLE development program

Demographics	STUDY	ARM	# DOSES	SAE/DAYS From last Dose To SAE	CAUSE OF DEATH/DAYS LD TO DEATH	RELATED/ UNRELATED
42/F/A	05 LTE 09	150 300	37	Influenza-Like Illness/29 [Neg Flu A/B tests] Myocarditis/34	Cardiogenic Shock related to Myocarditis/43	Both SAE and Death considered Unrelated
64/F/W	04 LTE 09	300 300	35	Pneumonia/6 Thrombocytopenia/21	Pneumonia/57	Both SAEs and Death considered Unrelated
54/F/H	05 LTE 09	300 300	35	Pneumonia/24	Pneumonia/29	Unrelated
28/F/H	04 LTE 9	300 300	50	COVID Pneumonia/6	COVID-19 Pneumonia/52	Unrelated
51/F/H	05 LTE 09	150 300	33	SLE exacerbation/54	SLE exacerbation/60	Unrelated
47/F/W	05 LTE 09	PBO 300	50	COVID-19/21	COVID-19/48	Unrelated
37/F/O	04 LTE 9	PBO 300	44	COVID-19/2 COVID-19 Pneumonia/6	COVID-19 Pneumonia/25	Unrelated
60/F/W	1013	1000	1	Colitis/27	Colitis complicated by MAS/34	Unrelated
54/F/O	1013 OLE 1145	PBO 1000 (16) 300 (16)	32	Pneumonia/20	Pneumonia complicated by Septic Shock/20	Related
53/F/W	04	300	8	Pneumonia/24	Pneumonia complicated by Septic Shock/26	Related
65/F/O	05	300	2	Possible Partial Bowel Obstruction/4 Nosocomial Pneumonia/22	Nosocomial Pneumonia/36	Unrelated
25/F/B	05	PBO	9	Encephalitis/36	Acute meningo- encephalitis/36	Unrelated
55/F/B	05 LTE 09	PBO PBO	22	Pulmonary HTN/128	Severe Pulm HTN/190	Unrelated
50/F/W	04 LTE 09	PBO PBO	35	MI/37	Possible Heart Attack/37	Unrelated

Source: CSR/narratives for studies 1013, 1145, 04, 05, and 09 (including 120-day safety update); response-to-query-fda-2021-patient-narratives (4/07/2021)

Overall, 11 patients in the all anifrolumab group and 3 patients in the placebo group had a fatal adverse event. Many of the deaths occurred during the long-term extension study from the two phase 3 studies (study 09), thus exposure time to anifrolumab was significantly greater than placebo, resulting in overall similar exposure-adjusted incidence rate (EAIR) for deaths. The mortality EAIR for anifrolumab was 0.3/100 PY compared to 0.6/100 PY (data not shown). A number of deaths in the all anifrolumab group were associated with a serious infection, including 5 due to pneumonia and 3 COVID-19, as compared to one (encephalitis) in the placebo group, as summarized in Table 49. Limiting the data to only subjects who were either on anifrolumab IV 300 mg vs placebo for 52+ weeks, there were 7 deaths attributable to infections (4 pneumonia and 3 COVID-19).

Table 49. Summary of Deaths by Cause and AE contributing to death

Cause of Death	Patient Population				
	AE Contributing to Death	PBO	Anifrolumab 150 mg	Anifrolumab 300 mg	Anifrolumab 1000 mg
Pneumonia				5 ^a	
COVID-19				3	
SLE exacerbation				1	
Cardiogenic Shock	Influenza-like Illness			1	
Colitis					1
Encephalitis		1			
Severe Pulm HTN		1			
Possible MI		1			

Source: CSR/narratives for studies 1013, 1145, 04, 05, and 09 (including 120-day safety update and 2021 DSUR)

^a One of the deaths on anifrolumab 300 mg occurred in a subject originally treated with 150 mg during the 52-week period of study 05 and one occurred in a subject originally treated with placebo during the 52-week period.

Serious Adverse Events

Serious adverse events: 52-week treatment period

In a pool of the three studies submitted to support approval (1013, 04 and 05), fewer patients in the anifrolumab 300 mg group had any Serious Adverse Event (SAE) than patients in the placebo group (Table 50; 11.8% vs 16.7%); the EAIR risk difference was -7.2 (95% CI -12.5, -1.9). Similarly, in a pool limited to the two phase 3 studies (04 and 05), fewer patients in the anifrolumab 300 mg group had any Serious Adverse Event (SAE) than patients in the placebo group (11.1% vs 16.4%); the EAIR risk difference was -7.3 (95% CI: -13.3, -1.4). Among patients with SAEs during the 52-week treatment period, in both treatment groups, the most common SAEs by PT were pneumonia and systemic lupus erythematosus.

There were 8 patients (1.7%) in the anifrolumab group and 9 patients (1.9%) in the placebo group who had an SAE of pneumonia (EAIR 1.9 vs 2.2; risk difference -0.3, 95% CI -2.5, 1.8). Among the 8 SAEs on pneumonia in the anifrolumab 300 mg group, two were fatal (see details above) and there were no fatal pneumonias in the placebo group.

As a safety variable, the PT of systemic lupus erythematosus included SLE flares, where subjects experienced increased disease activity with new or worsening clinical signs and symptoms. There were 7 patients (1.5%) in the anifrolumab group and 14 patients (3.0%) in the placebo group who had an SAE of systemic lupus erythematosus (EAIR 0.7 vs 3.5; risk difference -1.8, 95% CI (-4.3, 0.4).

One case of SAE-hypersensitivity and two cases of SAE-angioedema occurred during treatment with anifrolumab 300 mg for a total of 0.6% (3/459) of patients experiencing hypersensitivity events during the 52-week clinical trial periods of the three studies submitted for approval. There was one event of anaphylactic reaction reported in the SLE development program in a subject receiving anifrolumab 150 mg (study 05).

In the one reported case of anaphylaxis with anifrolumab - patient (b) (6) in study D3461C00005 - a 27year old white female from Argentina experienced a mild pruritic rash after the first dose of study treatment with anifrolumab 150 mg infusion. The patient was prophylactically administered one dose of diphenhydramine prior to the second infusion. On the day of Dose 2, during the post-dose flush infusion, the patient developed anaphylactic reaction with dyspnea, wheezing, flushing, and pruritis; was treated with hydrocortisone, diphenhydramine, and epinephrine; and was hospitalized for anaphylactic reaction. Both the initial pruritic rash and anaphylactic reaction were considered to be related to study treatment with anifrolumab.

Table 50. Serious Adverse Events during the 52-week treatment period by PT in ≥2 patients in the anifrolumab 300 mg group--Studies 1013, 04, & 05

Preferred Term	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference ^a (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Patients with any SAE	54 (11.8)	397.9	13.6	78 (16.7)	376.0	20.7	-7.2 (-12.5, -1.9)
Pneumonia	8 (1.7)	417.3	1.9	9 (1.9)	400.4	2.2	-0.3 (-2.5, 1.8)
Systemic lupus erythematosus	7 (1.5)	416.4	0.7	14 (3.0)	399.4	3.5	-1.8 (-4.3, 0.4)
Appendicitis	3 (0.7)	418.7	0.7	0	403.0	0	0.7 (-0.2, 2.1)

Angioedema	2 (0.4)	418.6	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Asthma	2 (0.4)	418.7	0.5	1 (0.2)	403.0	0.2	0.2 (-1.0, 1.5)
Chest pain	2 (0.4)	418.7	0.5	1 (0.2)	403.0	0.2	0.2 (-1.0, 1.5)
Gastroenteritis	2 (0.4)	419.0	0.5	3 (0.6)	401.3	0.7	-0.3 (-1.7, 1.1)
Gastroenteritis viral	2 (0.4)	418.4	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Herpes Zoster	2 (0.4)	418.5	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Influenza	2 (0.4)	418.3	0.5	1 (0.2)	402.2	0.2	0.2 (-1.0, 1.5)
Urinary Tract Infection	2 (0.4)	418.2	0.5	1 (0.2)	402.2	0.2	0.2 (-1.0, 1.5)

Source: Table 3.4.1.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3

^a Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group-placebo group). If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group.

Serious adverse events: Phase 3 long-term extension treatment period (data not shown)

The phase 3 LTE group (study 09, including 120-day safety update) was similar to the 52-week treatment period, where SAEs were lower in the anifrolumab 300 mg group than the placebo group: 21.7% vs 22.2%; EAIR 10.1 vs 17.2 (risk difference -7.1; 95% CI -11.2, -3.2). Also consistent with the 52-week safety pool, the most common SAEs in both treatment groups in the phase 3 LTE period were pneumonia and systemic lupus erythematosus. Pneumonia was balanced between the two groups (9 (2.5%) in anifrolumab vs 10 (2.7%) in placebo (EAIR 1.0 vs 1.9; difference -0.9, 95% CI -2.6, 0.4)). Systemic lupus erythematosus flare/worsening SAE was less common in the anifrolumab group as compared to the placebo group (6 (1.7%) in anifrolumab vs 15 (4.1%) in placebo (EAIR 0.7 vs 2.9; difference -2.2, 95% CI -4.1, -0.9)). During up to 4 years of treatment, the EAIR of systemic lupus erythematosus SAEs was lower in the anifrolumab 300 mg group than the placebo group.

The evaluation of SAEs by yearly intervals did not suggest any change in overall SAE incidence of the course of long-term treatment. Evaluation of the most common SAEs in the anifrolumab 300 mg group by yearly intervals showed similar event rates over time (Table 51).

Table 51. Phase 3 Long-Term Extension—Serious Adverse Events During Treatment by Time Interval

Preferred Term	Time Interval	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)		
		n/N' (%) patients	Exposure years	EAIR (per 100 PY)	n/N' (%) patients	Exposure years	EAIR (per 100 PY)
Patients with and SAE	Total	78/360 (21.7)	772.8	10.1	81/365 (22.2)	471.6	17.2
	Year 1	40/360 (11.1)	310.3	12.9	60/365 (16.4)	296.6	20.2
	Year 2	29/277 (10.5)	234.8	12.3	15/174 (8.6)	97.0	15.5
	Year 3	24/237 (10.1)	198.3	12.1	11/90 (12.2)	69.5	15.8
	Year 4+	1/157 (0.6)	91.2	1.1	2/51 (3.9)	31.7	6.3

Source: Table 3.4.5.2a, 4-Month Safety Update
N' is the number at risk for outcome of interest

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, in the 52-week treatment period in the three studies submitted to support approval as well as in the phase 3 long-term extension data, there was low incidence of discontinuation from investigational product (IP) due to adverse event/s that was similar across treatment groups (Table 52). The proportion of patients with an adverse event leading to discontinuation of IP (DAEs) was low and favored the anifrolumab 300 mg group (4.1%) over the placebo group (5.2%); EAIR 4.5 vs 6.0 (risk difference -1.4 (95% CI -4.7, 1.7)). The most commonly reported DAEs by SOC in the anifrolumab group were Infections and Infestations with no PT predominating; the most commonly reported DAEs by SOC in the placebo group were Musculoskeletal and connective tissue disorders all in PT of systemic lupus erythematosus (flare). There was no evidence for an increase in rate of discontinuations over time in the phase 3 long-term safety data. As observed during the 52-week treatment period, rates of DAEs in the phase 3 long-term safety data (including 120-day safety update) were low and similar between the anifrolumab 300 mg group (EAIR 2.6/100 PY) and placebo group (4.2/100 PY) (data not shown).

Table 52. Adverse Events leading to discontinuation of IP during treatment by SOC and PT—52-week safety (studies 1013, 04, and 05)

System Organ Class Preferred Term	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95% CI)
	n (%) patients	Exposure Years	EAIR per 100 PY	n (%) patients	Exposure Years	EAIR per 100 PY	
Patients with any DAE	19 (4.1)	418.1	4.5	24 (5.2)	401.3	6.0	-1.4 (-4.7, 1.7)
Infections and infestations	7 (1.5)	419.0	1.7	3 (0.6)	402.7	0.7	0.9 (-0.7, 2.8)
Herpes Zoster	2 (0.4)	419.3	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Acute sinusitis	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Bronchitis	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Diverticulitis	1 (0.2)	419.3	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Mycobacterium avium complex infection	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Pneumonia	1 (0.2)	419.4	0.2	2 (0.4)	403.0	0.5	-0.3 (-1.6, 0.9)
Upper respiratory tract infection	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Gastroenteritis	0	419.3	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)
Nervous system disorders	5 (1.1)	419.2	1.2	1 (0.2)	402.7	0.2	0.9 (-0.3, 2.5)
Headache	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Migraine	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Myasthenia gravis	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Myelitis transverse	1 (0.2)	419.3	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Syncope	1 (0.2)	419.3	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Optic neuritis	0	419.4	0	1 (0.2)	402.7	0.2	-0.2 (-1.4, 0.7)
Skin and subcutaneous tissue disorders	2 (0.4)	419.3	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Angioedema	1 (0.2)	419.3	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Ecchymosis	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Eye disorders	1 (0.2)	419.2	0.2	0	403.0	0	0.2 (-0.7, 1.3)

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Retinal disorder	1 (0.2)	419.2	0.2	0	403.0	0	0.2 (-0.7, 1.3)
General disorders and administration site conditions	1 (0.2)	419.2	0.2	2 (0.4)	402.9	0.5	-0.3 (-1.6, 0.9)
Face edema	1 (0.2)	419.2	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Influenza like illness	0	419.4	0	2 (0.4)	402.9	0.5	0.5 (-1.8, 0.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.2)	419.4	0.2	1 (0.2)	402.9	0.2	-0.0 (-1.2, 1.1)
B-cell lymphoma	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Uterine cancer	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Renal and urinary disorders	1 (0.2)	419.2	0.2	1 (0.2)	402.9	0.2	-0.0 (-1.2, 1.1)
Nephritis	1 (0.2)	419.2	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Lupus nephritis	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Reproductive system and breast disorders	1 (0.2)	419.3	0.2	3 (0.6)	402.7	0.7	-0.5 (-2.0, 0.7)
Cervical dysplasia	1 (0.2)	419.3	0.2	2 (0.4)	402.7	0.5	-0.3 (-1.6, 0.9)
Adnexa uteri cyst	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Cardiac disorders	0	419.4	0	2 (0.4)	403.0	0.5	-0.5 (-1.8, 0.4)
Atrial fibrillation	0	419.4	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)
Myocardial ischemia	0	419.4	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)
Immune system disorders	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Hypersensitivity	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Injury, poisoning and procedural complications	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Infusion related reaction	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Musculoskeletal and connective tissue disorders	0	419.4	0	6 (1.3)	402.6	1.5	-1.5 (-3.2, -0.6)
Systemic lupus erythematosus	0	419.4	0	6 (1.3)	402.6	1.5	-1.5 (-3.2, -0.6)
Respiratory, thoracic, and mediastinal disorders	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Pulmonary alveolar hemorrhage	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Vascular disorders	0	419.4	0	2 (0.4)	403.0	0.5	-0.5 (-1.8, 0.4)
Hypertensive emergency	0	419.4	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)
Varicose vein	0	419.4	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)

Source: Table 3.5.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3

Increased Incidence in anifrolumab 300 mg of DAEs in the SOC group nervous system disorders

The second most commonly reported DAE by SOC in the anifrolumab group were Nervous system disorders with no PT predominating (Table 52)—5 (1.1%) cases in the anifrolumab 300 mg group vs 1 (0.2%) case in the placebo group; EAIR 1.2 vs 0.2 (risk difference 0.9; 95% CI -0.3, 2.5). In the phase 3 long-term extension pool (including 120-day safety update), which included only subjects receiving anifrolumab 300 mg or placebo for both their initial 52-week treatment period as well as long-term extension period up to 4 years, there was a similar imbalance of DAEs with 6 DAEs in the SOC of nervous system disorders in the anifrolumab group and 0 in the placebo group, again with no PT predominating (**Table 53**).

Table 53. Phase 3 LTE (including 120-day safety update) for DAE Nervous system disorders

System Organ Class Preferred Term	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			EAIR Risk difference (95% CI)
	n (%) patients	Exposure Years	EAIR per 100 PY	n (%) patients	Exposure Years	EAIR per 100 PY	
Nervous system disorders	6 (1.7)	872.6	0.7	0	525.8	0	0.7 (-0.0, 1.5)
Post herpetic neuralgia	2 (0.6)	872.8	0.2	0	525.8	0	0.2 (-0.5, 1.5)
Headache	1 (0.3)	872.8	0.1	0	525.8	0	0.1 (-0.6, 0.6)
Migraine	1 (0.3)	872.8	0.1	0	525.8	0	0.1 (-0.6, 0.6)
Myasthenia gravis	1 (0.3)	872.8	0.1	0	525.8	0	0.1 (-0.6, 0.6)
Syncope	1 (0.3)	872.7	0.1	0	525.8	0	0.1 (-0.6, 0.6)

Two of the 3 studies submitted to support approval provide potential data on dose-relatedness for DAEs. In study 05, the 150 mg dose of anifrolumab was studied in parallel to the 300 mg dose in addition to the placebo arm. One patient in the placebo arm of study 05 was recorded with a DAE for SOC of nervous system disorders (PT neuropsychiatric lupus), while 3 were recorded in the anifrolumab 300 mg arm (no PT predominating) and 0 recorded in the anifrolumab 150 mg arm. In the phase 2 study/1013, 1 DAE for SOC of nervous system disorders was recorded in the placebo arm (optic neuritis) and 1 DAE for SOC of nervous system disorders was recorded in the anifrolumab 300 mg arm (transverse myelitis); 0 DAE for SOC of nervous system disorders recorded in the anifrolumab 1000 mg arm.

For total treatment-emergent adverse events, the SOC of nervous system disorders was common in both placebo and anifrolumab treatment arms (ranging from 14-31%), with headache as the predominating PT. 52-week data from studies 1013, 04 and 05 showed an imbalance with SOC nervous system disorders occurring in 19.4% (EAIR 23.9) of anifrolumab 300 mg subjects and 16.7% (EAIR 21.7) of placebo subjects. The phase 3 LTE data (including 120-day safety update) also showed an imbalance with SOC nervous system disorders occurring in 31.1% of anifrolumab 300 mg subjects (EAIR 16.6) and 18.1% of placebo subjects (EAIR 14.5). In study 05, TEAE for SOC nervous system disorders was higher in the anifrolumab 300 mg arm (23.3%; EAIR 26.1) than the anifrolumab 150 mg arm (14%; EAIR 15.6); placebo arm was lower than anifrolumab 300 mg arm but higher than the anifrolumab 150 mg arm (14%, EAIR 19.7). Study 1013 did not show an imbalance between study arms for SOC nervous system disorders—24% (EAIR 34.3) in the placebo group; 21% in the anifrolumab 300 mg arm; 20% in the anifrolumab 1000 mg arm (EAIR 26.2).

Serious adverse events (SAE) for the SOC of nervous system disorders were uncommon (<2%) for any of the anifrolumab treatment doses during the 52-week treatment period. For the 300 mg dose of anifrolumab during 52-weeks, SAEs were balanced between anifrolumab and placebo groups—4 (0.9%)/EAIR 1.0 vs 5 (1.0%)/EAIR 1.3. A higher number of SAE for SOC nervous system disorders occurred in the anifrolumab 300 mg group than the placebo group in the phase 3 long-term safety data—7 (1.9%)/EAIR 0.8 vs 1 (0.3%)/EAIR 0.2. The 7 SAEs included 2 cases of post-herpetic neuralgia and 1 case each of hypoesthesia, intracranial aneurysm, ischemic stroke, myasthenia gravis, and syncope.

The SAE/DAE of myasthenia gravis occurred during study 05 in a 67 year old female 22 days after her fifth dose of anifrolumab 300 mg. The SAE/DAE of transverse myelitis occurred during study 1013 in a 51 year old female 3 days after her second dose of anifrolumab 300 mg; this patient was found to have positive CSF PCR for varicella and the transverse myelitis was ultimately attributed to Herpes Zoster (and resolved after treatment with steroids and acyclovir). Two cases of SAE/DAE post-herpetic neuralgia occurred during the long-term extension study. Thus, 3 SAE/DAE cases for anifrolumab 300 mg in the SOC of nervous system disorders were directly associated with Herpes Zoster infection (1 in 52-week data, 2 in long-term extension data).

Significant Adverse Events

Table 54 is a tabular listing of adverse events observed during the 52-week study period (studies 1013, 04 and 05) by treatment group that were rated as severe by study investigators. A slightly higher proportion of subjects in the anifrolumab 300 mg group experienced severe treatment emergent adverse events as compared to the placebo group—9.2% vs 7.9%; EAIR 10.5 vs 9.5. The most common severe AEs during the 52-week period by SOC were infections and infestations, with no particular PT predominating. Similar overall results were observed in the long-term extension data (Table 55), with a higher proportion of severe AEs in the anifrolumab arm as compared to placebo (15.3% vs 9.3%), but an equivalent exposure-adjusted incidence rate in both arms (EAIR 6.8 for anifrolumab 300mg and EAIR 6.7 for placebo). Infections and infestations remained the most common severe SOC with PTs of pneumonia and herpes zoster being the most common: Anifrolumab 300 mg group had 6 cases of severe pneumonia and 4 cases of severe herpes zoster as compared to 3 cases of severe pneumonia and 0 cases of severe herpes zoster in the placebo group.

Table 54. Severe AEs by SOC/PT for common AEs (>5%) reported during 52-week study period (studies 1013, 04 and 05)

Severe TEAEs System Organ Class Preferred Term	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)		
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)
Subjects with any severe TEAE*	42 (9.2)	401.7	10.5	37 (7.9)	388.9	9.5
Infections and infestations*	22 (4.8)	410.1	5.4	10 (2.1)	398.6	2.5
Nasopharyngitis	1 (0.2)	418.9	0.2	0	403.0	0
Upper respiratory tract infection	0	419.4	0	0	403.0	0
Urinary tract infection	2 (0.4)	418.2	0.4	0	403.0	0
Bronchitis	3 (0.7)	418.5	0.7	3 (0.6)	402.6	0.7
Herpes Zoster	2 (0.4)	419.3	0.5	0	403.0	0
Sinusitis	0	419.4	0	1 (0.2)	402.3	0.2
Musculoskeletal and connective tissue disorders	4 (0.9)	418.3	1.0	9 (1.9)	401.3	2.2
Back pain	0	415.8	0	1 (0.2)	402.9	0.2
Injury, poisoning and procedural complications	2 (0.4)	418.5	0.5	2 (0.4)	402.3	0.5
Infusion related reaction	0	419.4	0	0	403.0	0
Nervous system disorders	6 (1.3)	417.1	1.4	5 (1.1)	399.7	1.3

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Headache	0	419.4	0	0	403.0	0
Post herpetic neuralgia†	0	419.4	0	0	403.0	0
Respiratory, thoracic, and mediastinal disorders	4 (0.9)	418.4	1.0	4 (0.9)	402.9	1.0
Cough	0	419.4	0	0	403.0	0

Source: Table 3.2.5.1, Appendix 2.7.4.7.1 in Module 5.3.5.3

*Any severe TEAE includes all AEs; Any severe SOC includes all AEs in that SOC; Specific PT data is limited to common AEs (≥5%)

†Post herpetic neuralgia included as an important sequela of herpes zoster infection; 3 total cases in anifrolumab 300 mg group—2 mild, 1 moderate—and 0 cases in placebo group

Table 55. Severe AEs by SOC/PT for common AEs (>5%) reported during phase 3 LTE (including 120-day safety update)

Severe TEAEs System Organ Class Preferred Term	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)		
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)
Subjects with any severe TEAE*	55 (15.3)	810.3	6.8	34 (9.3)	506.2	6.7
Infections and infestations*	27 (7.5)	839.7	3.2	10 (2.7)	519.2	1.9
Nasopharyngitis	0	872.8	0	0	525.8	0
Upper respiratory tract infection	0	872.8	0	0	525.8	0
Urinary tract infection	1 (0.3)	872.6	0.1	0	525.8	0
Bronchitis	2 (0.6)	869.2	0.2	2 (0.5)	525.7	0.4
Herpes Zoster	4 (1.1)	869.4	0.5	0	525.8	0
Sinusitis	0	827.8	0	1 (0.3)	524.8	0.2
Pneumonia	6 (1.7)	866.7	0.7	3 (0.8)	524.4	0.6
Influenza	2 (0.6)	870.7	0.2	1 (0.3)	525.1	0.2
Latent tuberculosis	0	872.8	0	0	525.8	0
Musculoskeletal and connective tissue disorders	7 (1.9)	867.8	0.8	8 (2.2)	522.4	1.5
Back pain	0	872.8	0	1 (0.3)	525.7	0.2
Injury, poisoning and procedural complications	4 (1.1)	867.4	0.5	3 (0.8)	524.4	0.6
Infusion related reaction	0	872.8	0	0	525.8	0
Nervous system disorders	8 (2.2)	867.2	0.9	1 (0.3)	524.9	0.2
Headache	0	872.8	0	0	525.8	0
Post herpetic neuralgia†	2 (0.6)	872.8	0.2	0	525.8	0
Respiratory, thoracic, and mediastinal disorders	4 (1.1)	867.7	0.5	6 (1.6)	525.5	1.1
Cough	1 (0.3)	870.7	0.1	0	525.8	0

Source: Table 3.2.5.1a, Appendix 2.7.4.7.1 in Module 5.3.5.3

*Any severe TEAE includes all AEs; Any severe SOC includes all AEs in that SOC; Specific PT data is limited to common AEs (≥5%)

†Post herpetic neuralgia included as an important sequela of herpes zoster infection; 8 total cases in anifrolumab 300 mg group—1 mild, 5 moderate, 2 severe—and 0 cases in placebo group

Treatment Emergent Adverse Events and Adverse Reactions

Most subjects experienced a treatment emergent adverse event (TEAE) during the 52-week period of studies 1013, 04 and 05. Adverse events were reported in 87% of patients receiving anifrolumab 300 mg and 79% of patients receiving placebo (Source: Table 3.2.1.1.1). Table 56

lists the frequency of the TEAEs observed during the 52-week period of studies 1013, 04, and 05 by SOC and treatment group. For the most commonly occurring TEAEs ($\geq 5\%$), the proportion of subjects who had a TEAE were somewhat higher in the anifrolumab group than the placebo group for PTs of nasopharyngitis, upper respiratory tract infection, bronchitis, infusion related reaction, herpes zoster, back pain, and cough (Table 56). Overall, the types and incidences of common TEAEs were consistent with what would be expected for patients with active SLE who had been exposed to immunosuppressive therapies and are similar to what has been observed in other SLE clinical trials.

Table 56. Adverse events reported in > 2% of patients during treatment, by PT—52 week safety period (studies 1013, 04, and 05)

Preferred Term	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)		
	n (%) Patients	Exposure Years	EAIR per 100 PY	n (%) Patients	Exposure Years	EAIR per 100 PY
Patients with any AE above reporting threshold of 2%	339 (73.9)	NC	NC	294 (63.1)	NC	NC
Nasopharyngitis	75 (16.3)	377.4	19.9	44 (9.4)	379.5	11.6
Upper respiratory tract infection	71 (15.5)	380.2	18.7	45 (9.7)	376.4	12.0
Urinary tract infection	55 (12.0)	391.7	14.0	63 (13.5)	370.0	17.0
Bronchitis	45 (9.8)	396.7	11.3	20 (4.3)	395.1	5.1
Infusion related reaction	43 (9.4)	385.9	11.1	33 (7.1)	377.6	8.7
Headache	37 (8.1)	398.3	9.3	45 (9.7)	379.6	11.9
Herpes zoster	75 (16.3)	377.4	19.9	44 (9.4)	379.5	11.6
Back pain	24 (5.2)	407.4	5.9	20 (4.3)	391.5	5.1
Sinusitis	24 (5.2)	406.3	5.9	24 (5.2)	393.5	6.1
Cough	23 (5.0)	405.0	5.7	15 (3.2)	396.4	3.8
Arthralgia	22 (4.8)	405.1	5.4	9 (1.9)	399.7	2.3
Pharyngitis	21 (4.6)	407.2	5.2	17 (3.6)	393.7	4.3
Vomiting	18 (3.9)	411.0	4.4	12 (2.6)	396.5	3.0
Nausea	17 (3.7)	410.7	4.1	25 (5.4)	389.5	6.4
Oral herpes	17 (3.7)	409.1	4.2	12 (2.6)	395.5	3.0
Pneumonia	15 (3.3)	413.9	3.6	13 (2.8)	399.3	3.3
Diarrhea	14 (3.1)	411.3	3.4	25 (5.4)	391.7	6.4
Respiratory tract infection	14 (3.1)	411.2	3.4	2 (0.4)	401.5	0.5
Depression	13 (2.8)	411.9	3.2	8 (1.7)	398.8	2.0
Gastroenteritis	13 (2.8)	412.5	3.2	14 (3.0)	397.6	3.5
Hypersensitivity	13 (2.8)	410.5	3.2	3 (0.6)	401.6	0.7
Influenza	12 (2.6)	414.0	2.9	9 (1.9)	398.6	2.3
Gastroenteritis viral	11 (2.4)	412.3	2.7	7 (1.5)	400.5	1.7
Gastroesophageal reflux disease	11 (2.4)	413.9	2.7	12 (2.6)	396.9	3.0
Pain in extremity	11 (2.4)	414.5	2.7	3 (0.6)	402.8	0.7
Anxiety	10 (2.2)	413.8	2.4	8 (1.7)	398.9	2.0
Dizziness	10 (2.2)	413.7	2.4	12 (2.6)	395.0	3.0
Fatigue	10 (2.2)	411.0	2.4	9 (1.9)	399.6	2.3
Edema peripheral	10 (2.2)	414.1	2.4	4 (0.9)	401.1	1.0
Systemic lupus erythematosus	10 (2.2)	414.8	2.4	14 (3.0)	399.4	3.5
Insomnia	9 (2.0)	415.4	2.2	19 (4.1)	394.5	4.8
Abdominal pain upper	8 (1.7)	413.3	1.9	11 (2.4)	397.7	2.8
Migraine	8 (1.7)	415.8	1.9	10 (2.1)	397.5	2.5
Hypertension	7 (1.5)	414.7	1.7	16 (3.4)	395.2	4.0
Pyrexia	7 (1.5)	416.2	1.7	13 (2.8)	398.0	3.3

Gastritis	5 (1.1)	416.6	1.2	11 (2.4)	398.5	2.8
Myalgia	5 (1.1)	416.3	1.2	10 (2.1)	398.2	2.5

Source: Table 3.2.3.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3

Laboratory Findings

Hematology

Patients with treatment-emergent changes in clinical hematology and chemistry tests (TELVC) that fell outside predefined criteria are considered clinically meaningful. The mean hematology values were generally similar between the anifrolumab 300 mg and placebo groups at baseline and at Week 52 in the phase 3 studies (data not shown). There were no clinically meaningful differences noted between the treatment groups in categorical shifts (data not shown). During the phase 3 52-week study period, there were no notable differences among treatment groups in the incidence of any potentially clinically important hematology abnormalities based on prespecified criteria (Table 57). The most frequently observed potentially clinically important hematology abnormalities were for lymphocytes, with values ≤ 0.5 GI/L below extended reference range observed in 10.4% of patients in the anifrolumab mg group versus 22.4% in the placebo group. There were also no significant differences in the frequency or pattern of potentially clinically significant treatment-emergent changes from baseline in hematology variables during the phase 3 long-term safety data (Table 57). Similar results were seen in the phase 2 study (1013) 52-week study period (data not shown), including a lower number of subjects in the anifrolumab 300 mg than placebo group with below normal lymphocyte count at week 52—5.5% for anifrolumab 300 mg vs 26.8% for placebo.

Table 57. Hematology variables, potentially clinically meaningful treatment-emergent laboratory changes in phase 3 52-week data and phase 3 long-term safety (including 120-day safety update)

Laboratory variable	SI unit	Category	52-week safety pool		Phase 3 long-term safety	
			Anifrolumab 300 mg (N = 360) n (%)	Placebo (N = 365) n (%)	Anifrolumab 300 mg (N = 360) n (%)	Placebo (N = 365) n (%)
Hemoglobin	g/L	n	357	357	357	357
		$\leq 60^a$	0	0	0	0
		$\geq 200^a$	0	0	0	0
		TELVC (≤ 70 and decrease from BL ≥ 15) ^b	1 (0.3)	0	1 (0.3)	0
Hematocrit	%	n	357	357	357	357
		$\leq 0.18^a$	0	0	0	0
		$\geq 0.64^a$	0	0	0	0
		TELVC (≤ 0.21 and decrease from BL $\geq 15\%$) ^b	0	0	0	0
Leukocytes	GI/L	n	357	357	357	357
		$< 1^a$	0	0	0	0
		$\leq 2^a$	6 (1.7)	15 (4.2)	8 (2.2)	15 (4.2)
		$\geq 20^a$	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

Basophils	GI/L	n	357	357	357	357
		≥ 1.0 ^a	0	0	0	0
		≥ 2.0 ^a	0	0	0	0
Eosinophils	GI/L	n	357	357	357	357
		≥ 1.5 ^a	0	0	1 (0.3)	0
		≥ 5 ^a	0	0	0	0
Monocytes	GI/L	n	357	357	357	357
		≥ 1.4 ^a	3 (0.8)	0	3 (0.8)	0
		≥ 5 ^a	0	0	0	0
Lymphocytes	GI/L	n	357	357	357	357
		≤ 0.25 ^a	3 (0.8)	13 (3.6)	3 (0.8)	13 (3.6)
		≤ 0.5 ^a	37 (10.4)	80 (22.4)	39 (10.9)	85 (23.8)
		≥ 10 ^a	0	0	0	0
Neutrophils	GI/L	n	357	357	357	357
		< 0.5 ^a	2 (0.6)	1 (0.3)	3 (0.8)	1 (0.3)
		≥ 20 ^a	1 (0.3)	0	1 (0.3)	0
		TELVC (< 1 and decrease from BL ≥ 0.5) ^b	7 (2.0)	8 (2.2)	9 (2.5)	8 (2.2)
Platelets	GI/L	n	357	357	357	357
		≤ 20 ^a	0	0	0	0
		≥ 600 ^a	2 (0.6)	1 (0.3)	3 (0.8)	1 (0.3)
		TELVC (≤ 50 and decrease from BL ≥ 25) ^b	1 (0.3)	0	3 (0.8)	0

Derived from: Table 3.9.3 and 3.9.3a, Appendix 2.7.4.7.1 in Module 5.3.5.3.

^a Patients with baseline laboratory values within extended reference limits and any post-baseline laboratory value outside extended reference limits (increase and decrease, respectively).

^b Patients with baseline laboratory values within extended reference limits and with any post-baseline laboratory value outside criteria for treatment-emergent change.

Clinical Chemistry

In the phase 3 safety pool, no significant differences in mean clinical chemistry values were noted between anifrolumab 300 mg and placebo and no clinically meaningful trends in change from baseline values over time were detected (data not shown). Renal function as assessed by serum creatinine remained stable from baseline to week 52. There were generally no differences noted between the treatment groups in the frequency and pattern of potentially clinically significant changes or categorical shifts from baseline in clinical chemistry variables during the phase 3 studies at 52 weeks or in the phase 3 long-term safety data (Table 58). Two exceptions were: 1) a slight increase in incidence of elevated gamma glutamyl transferase during both the 52-week safety period (2.8 % for anifrolumab 300 mg vs 1.1% for placebo) and phase 3 long-term safety period (3.1% for anifrolumab 300 mg vs 1.4% for placebo: and 2) a slight increase in incidence of elevated glucose during the phase 3 long-term safety study (7.7% for anifrolumab 300 mg vs 5.5 % for placebo in phase 3 LTE vs 4.9% and 4.1%, respectively, during the 52-week study period). 52-week safety data from the phase 2 study (1013) showed no significant changes in chemistry values that were different between anifrolumab 300 mg and placebo (data not shown).

Table 58. Clinical Chemistry variables, potentially clinically meaningful treatment-emergent laboratory changes in phase 3 52-week data and phase 3 long-term safety (including 120-day safety update)

Laboratory variable	SI unit	Category	52-week safety pool		Phase 3 long-term safety	
			Anifrolumab 300 mg (N = 360) n (%)	Placebo (N = 365) n (%)	Anifrolumab 300 mg (N = 360) n (%)	Placebo (N = 365) n (%)
Gamma Glutamyl Transferase	U/L	N	358	357	358	357
		≥ 5 x ULN ^a	10 (2.8)	4 (1.1)	11 (3.1)	5 (1.4)
Alanine Aminotransferase	U/L	N	358	357	358	357
		≥ 3 x ULN ^a	8 (2.2)	17 (4.8)	9 (2.5)	21 (5.9)
		≥ 5 x ULN ^a	1 (0.3)	3 (0.8)	1 (0.3)	4 (1.1)
Aspartate Aminotransferase	U/L	N	358	357	358	357
		≥ 3 x ULN ^a	4 (1.1)	8 (2.2)	4 (1.1)	9 (2.5)
		≥ 5 x ULN ^a	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)
Alkaline Phosphatase	U/L	N	358	357	358	357
		≥ 3 x ULN ^a	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Albumin	g/L	N	358	357	358	357
		≤ 20 ^a	0	0	0	0
		≥ 100 ^a	0	0	0	0
		TELVC (≤ 25 and decrease from BL ≥ 10) ^b	0	1 (0.3)	1 (0.3)	1 (0.3)
		TELVC (≥ 70 and decrease from BL ≥ 10) ^b	0	0	0	0
Bilirubin	μmol/L	N	358	357	358	357
		≥ 2 x ULN ^a	2 (0.6)	0	2 (0.6)	0
Sodium	mmol/L	N	358	357	358	357
		≤ 132 ^a	16 (4.5)	22 (6.2)	19 (5.3)	23 (6.4)
		≥ 152 ^a	0	2 (0.6)	0	2 (0.6)
Potassium	mmol/L	N	358	357	358	357
		≤ 3 ^a	14 (3.9)	13 (3.6)	15 (4.2)	14 (3.9)
		≥ 5.5 ^a	1 (0.3)	4 (1.1)	2 (0.6)	7 (2.0)
Chloride	mmol/L	N	358	357	358	357
		≤ 90 ^a	2 (0.6)	6 (1.7)	2 (0.6)	6 (1.7)
		≥ 120 ^a	0	0	0	0
Glucose	mmol/L	N	287	271	297	274
		≤ 2.5 ^a	0	0	0	0
		≥ 7.0 ^a	14 (4.9)	11 (4.1)	23 (7.7)	15 (5.5)
		≥ 11.1 ^a	1 (0.3)	1 (0.4)	3 (1.0)	2 (0.7)
Urea Nitrogen	mmol/L	N	358	357	358	357
		≥ 18 ^a	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Creatinine	μmol/L	N	358	357	358	357
		≥ 140 ^a	7 (2.0)	6 (1.7)	9 (2.5)	8 (2.2)
		≥ 190 ^a	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
Cholesterol	mmol/L	N	279	269	289	273
		≥ 7.25 ^a	12 (4.3)	9 (3.3)	14 (4.8)	12 (4.4)
HDL Cholesterol	mmol/L	N	278	267	289	272
		≤ 0.8 ^a	10 (3.6)	18 (6.7)	14 (4.8)	20 (7.4)
LDL Cholesterol	mmol/L	N	272	263	284	268
		≥ 5.2 ^a	7 (2.6)	6 (2.3)	8 (2.8)	8 (3.0)
Triglycerides	mmol/L	N	277	268	289	273
		≥ 3.6 ^a	8 (2.9)	9 (3.4)	10 (3.5)	9 (3.3)
		≥ 5.4 ^a	1 (0.4)	4 (1.5)	3 (1.0)	4 (1.5)

Data derived from Table 3.9.3, Appendix 2.7.4.7.1 in Module 5.3.5.3.

^a Patients with baseline laboratory values within extended reference limits and any post-baseline laboratory value outside extended reference limits (increase and decrease, respectively).

^b Patients with baseline laboratory values within extended reference limits and with any post-baseline laboratory value outside criteria for treatment-emergent change.

In the two phase 3 studies, the change from baseline to week 52 in mean specific gravity was similar in the anifrolumab 300 mg and placebo groups (data not shown). Urine protein/creatinine ratio (UPCR) values remained stable from baseline to week 52 (data not shown). There was also no difference noted between the treatment groups in the frequency and pattern of potentially clinically significant changes in UPCR over 52 weeks of treatment. In the phase III long-term safety data, the change from baseline to the end of treatment in mean specific gravity was similar in the anifrolumab 300 mg and placebo groups (data not shown). From baseline to end of treatment, the change in median UPCR values was -0.12 and 0.46 mg/mmol in the anifrolumab 300 mg and placebo groups, respectively (data not shown). In the phase III long-term safety data, 2.2% and 2.8% of patients had a UPCR value categorized as a potentially meaningful increase (≥ 395 mg/mmol creatinine) in the anifrolumab 300 mg group and placebo group, respectively (data not shown).

Additional safety data available from study 05 comparing two doses of anifrolumab (150 mg vs 300 mg) may indicate if there were any dose-related patterns for clinically meaningful changes in hematology and chemistry parameters. There were no notable differences among treatment groups in the incidence of any potentially clinically important hematology abnormalities based on prespecified criteria. The most frequently observed potentially clinically important hematology abnormalities were for lymphocytes, with values ≤ 0.5 GI/L below extended reference range observed in 20.4% and 11.7% of patients in the anifrolumab 150 mg and 300 mg groups, respectively, versus 20.8% in the placebo group (Table 59). These results are similar to what was observed in the combined phase 3 52-week and long-term safety data (Table 57) and were not unexpected for this patient population; the majority of these changes were assessed to be not clinically important. For other hematology parameters (hemoglobin, hematocrit, leukocytes, monocytes, neutrophils, and platelets), few patients had potentially clinically important abnormalities.

Table 59. Study 05 (compare 150 mg to 300 mg dose) Potentially Clinically Important Changes in Laboratory Parameters--Hematology

Parameter/Criteria	x/n Number (%) of patients		
	Anifrolumab 150 mg N=93 n/N (%)	Anifrolumab 300 mg N=180 n/N (%)	Placebo N=184 n/N (%)
Hemoglobin (g/L) (≤ 70 and decrease from BL ≥ 15)	1/93 (1.1)	1/179 (0.6)	0
Hematocrit (≤ 0.21 and decrease from BL $\geq 15\%$)	1/93 (1.1)	0	0
Leukocytes (GI/L) (≤ 2 GI/L)	3/93 (3.2)	5/179 (2.8)	6/183 (3.3)
Leukocytes (GI/L) (≥ 20 GI/L)	2/93 (2.2)	0	1/183 (0.5)
Monocytes (GI/L) (≥ 1.4 GI/L)	0	2/179 (1.1)	0
Lymphocytes (GI/L) (≤ 0.25 GI/L)	5/93 (5.4)	3/179 (1.7)	8/183 (4.4)

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Lymphocytes (GI/L) (≤ 0.5 GI/L)	19/93 (20.4)	21/179 (11.7)	38/183 (20.8)
Neutrophils (GI/L) (≥ 20 GI/L)	2/93 (2.2)	0	0
Neutrophils (GI/L) (< 0.5 GI/L)	0	2/179 (1.1)	0
Neutrophils (GI/L) (< 1 and decrease from BL ≥ 0.5)	3/93 (3.2)	5/179 (2.8)	3/183 (1.6)
Platelets (GI/L) (≥ 600 GI/L)	0	3/179 (1.7)	0
Platelets (GI/L) (≤ 50 and decrease from BL ≥ 25)	NA	1/179 (0.6)	1/182 (0.5)

Data derived from study 05 Clinical study Report Table 11.3.7.1.2

^a x Number of subjects with any post-baseline laboratory value outside extended reference limits or outside criteria for treatment emergent change. n Subjects with a measurement at baseline and at least 1 subsequent measurement of the variable.

Percentages are based upon all subjects with a measurement at baseline and at least 1 subsequent measurement of the variable (at the respective timepoint).

Comparing two doses of anifrolumab—150 mg and 300 mg—to placebo, there were no clinically meaningful trends in the mean change from baseline for any clinical chemistry parameter (Table 60). One exception was a slight increase in incidence of elevated gamma glutamyl transferase during both the 52-week safety period for anifrolumab 300 mg (3.4%) vs anifrolumab 150 mg and placebo (1.1% and 1.6%, respectively).

Table 60. Study 05 (compare 150 mg to 300 mg dose) Potentially Clinically Important Changes in Laboratory Parameters—Chemistry

Parameter/Criteria	n/N (%) of patients		
	Anifrolumab 150 mg N=93 n/N (%)	Anifrolumab 300 mg N=180 n/N (%)	Placebo N=184 n/N (%)
Gamma glutamyl transferase (U/L) ($\geq 5 \times$ ULN)	1/93 (1.1)	6/179 (3.4)	3/183 (1.6)
Alanine aminotransferase (U/L) ($\geq 3 \times$ ULN)	2/93 (2.2)	5/179 (2.8)	10/183 (5.5)
Alanine aminotransferase (U/L) ($\geq 5 \times$ ULN)	1/93 (1.1)	1/179 (0.6)	2/183 (1.1)
Aspartate aminotransferase (U/L) ($\geq 3 \times$ ULN)	2/92 (2.2)	2/179 (1.1)	4/183 (2.2)
Aspartate aminotransferase (U/L) ($\geq 5 \times$ ULN)	0	0	1/183 (0.5)
Alkaline phosphatase (U/L) ($\geq 3 \times$ ULN)	0	0	1/183 (0.5)
Albumin (g/L) (≤ 25 and decrease from BL ≥ 10)	0	1/179 (0.6)	1/183 (0.5)
Bilirubin ($\mu\text{mol/L}$) ($\geq 2 \times$ ULN)	0	1/179 (0.6)	0
Sodium (mmol/L) (≤ 132 mmol/L)	6/93 (6.5)	8/179 (4.5)	15/183 (8.2)
Sodium (mmol/L) (≥ 152 mmol/L)	0	0	1/183 (0.5)
Potassium (mmol/L) (≤ 3 mmol/L)	5/93 (5.4)	8/179 (4.5)	8/183 (4.4)
Potassium (mmol/L) (≥ 5.5 mmol/L)	3/93 (3.2)	1/179 (0.6)	5/183 (2.7)
Chloride (mmol/L) (≤ 90 mmol/L)	2/93 (2.2)	3/179 (1.7)	1/183 (0.5)
Glucose, serum, fasted (mmol/L) (≥ 7.0 mmol/L)	2/75 (2.7)	9/154 (5.8)	13/149 (8.7)
Glucose, serum, fasted (mmol/L) (≥ 11.1 mmol/L)	1/75 (1.3)	2/154 (1.3)	2/149 (1.3)
Urea nitrogen (mmol/L) (≥ 18 mmol/L)	0	1/179 (0.6)	2/183 (1.1)
Creatinine ($\mu\text{mol/L}$) (≥ 140 $\mu\text{mol/L}$)	2/93 (2.2)	5/179 (2.8)	6/183 (3.3)
Creatinine ($\mu\text{mol/L}$) (≥ 190 $\mu\text{mol/L}$)	0	1/179 (0.6)	2/183 (1.1)
Creatine kinase (U/L) (≥ 500 U/L)	6/93 (6.5)	6/179 (3.4)	11/183 (6.0)
Creatine kinase (U/L) (≥ 2000 U/L)	1/93 (1.1)	1/179 (0.6)	1/183 (0.5)
Cholesterol (mmol/L) (≥ 7.25 mmol/L)	3/75 (4.0)	8/151 (5.3)	10/149 (6.7)

HDL Cholesterol (mmol/L) (≤ 0.8 mmol/L)	0	7/151 (4.6)	7/149 (4.7)
LDL Cholesterol (mmol/L) (≥ 5.2 mmol/L)	1/73 (1.4)	5/150 (3.3)	8/146 (5.5)
Triglycerides (mmol/L) (≥ 3.6 mmol/L)	2/74 (2.7)	8/151 (5.3)	7/149 (4.7)
Triglycerides (mmol/L) (≥ 5.4 mmol/L)	1/74 (1.4)	2/151 (1.3)	2/149 (1.3)

Data derived from study 05 Clinical study Report Table 11.3.7.1.2

Vital Signs

During the 52-week study period in the two phase 3 studies, no differences in mean blood pressure or heart rate were noted between anifrolumab 300 mg and placebo. There were also no clinically meaningful trends in change from baseline values at 52 weeks (data not shown). There were also patients with clinically significant treatment-emergent changes in diastolic blood pressure, systolic blood pressure, or heart rate (data not shown). Similar results were seen in the phase 2 52-week data (data not shown). In studies 1013, 04 and 05, there were no clinically important differences among treatment groups in mean changes from baseline in body weight to week 52.

Electrocardiograms (ECGs)

In all three studies submitted to support approval (1013, 04 and 05), there were no shifts in ECG parameters from normal to abnormal that were clinically significant and the proportions of patients with abnormal (not clinically significant) ECG findings were balanced between the anifrolumab 300 mg group and the placebo group (data not shown). Very few patients in either treatment group had ECG results fulfilling potentially clinically significant criteria.

QT

QTc data not reported. Data on PR, RR and QRS intervals showed very few subjects with prolongation or shortened intervals and there were no meaningful differences between treatment arms (data not shown).

Immunogenicity

In the phase 2 study (1013), 1 patient was positive to anti-drug-antibody (ADA) prior to the first dose of anifrolumab 300 mg and 5 patients were post dose ADA positive in the anifrolumab 300 mg group. Only one patient had persistent positive ADA for > 16 weeks. Similarly, in study 04, only one patient had persistent, treatment-induced ADA and in study 05 there were 3 subjects with persistently positive, treatment-induced ADA. In all phase 3 data, including the long-term extension study, there were similar proportions of subjects with any ADA or persistent ADA in both anifrolumab 300 mg and placebo groups, indicating little or no specific induction of ADA response to anifrolumab. Overall, based on only a limited number of ADA-positive patients, there was not trend or pattern suggesting an association between the presence of anifrolumab ADA and the occurrence of AEs, SAEs, DAEs or AESIs. A small number of mild infusion reactions occurred in both anifrolumab 300 mg and placebo subjects who were ADA positive (data not shown).

8.2.5. Analysis of Submission-Specific Safety Issues

The following sections address the potential adverse events of special interest (AESIs) specified in the integrated analysis of safety plan (summarized above in Section 8.2.1, Safety Review Approach). For ease of review, AESIs will be grouped by Organ System.

8.2.6. Infections

Infections were identified as a topic of interest in the anifrolumab program due to the immunomodulatory mechanism of action of anifrolumab. Serious non-opportunistic infections, opportunistic infections, herpes zoster, tuberculosis (TB) including latent TB, and influenza were analyzed as individual AESI categories. Overall infections were not a category of AESI but are discussed here as an additional supportive analysis.

Infections overall during treatment, as assessed by the system-organ-class (SOC) Infections and infestations, were reported in a greater proportion of patients in the anifrolumab 300 mg group than the placebo group (69.7% vs 57.4%) (Table 61). Most infections in both treatment groups were mild or moderate in intensity, were not considered serious, and did not result in discontinuation from treatment. The difference between the overall rates of infection in the 300 mg anifrolumab group versus placebo group was driven by differences in the incidence rates of mild and moderate infections involving the respiratory tract, excluding pneumonia (comparable in both treatment groups), and separately, herpes zoster.

The incidence of serious infections during the 52-week treatment periods of the three studies submitted for approval was similar between the treatment groups: 24/459 patients (5.2%; EAIR 5.4) in the anifrolumab 300 mg group and 32/466 patients (6.9%; EAIR 7.3) in the placebo group.

Table 61. Infections and infestations during treatment, overall and by intensity—52-week data for studies 1013, 04 and 05

System organ class	Maximum reported intensity	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)		
		n (%) Patients	Exposure years	EAIR (per 100 PY)	n (%) Patients	Exposure years	EAIR (per 100 PY)
Infections and infestations	All	320 (69.7)	225.7	141.8	258 (55.4)	258.2	99.9
	Mild	181 (39.4)	243.6	74.3	156 (33.5)	263.7	59.1
	Moderate	117 (25.5)	351.4	33.3	92 (19.7)	350.2	26.3
	Severe	22 (4.8)	410.1	5.4	10 (2.1)	398.6	2.5

Source: Derived from Table 3.2.2.1.1 and Table 3.2.5.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

Limiting 52-week data to phase 3 data (primary safety pool), the incidence of infections during treatment (any AE in the SOC Infections and infestations) was greater in the anifrolumab 300 mg group (71.7%; EAIR 151.8) than the placebo group (57.8%; EAIR 105.4) (data not shown). Similar to the safety pool of all 3 studies submitted to support approval, this difference was

driven by differences in the incidence rates of mild and moderate infections involving the respiratory tract, excluding pneumonia (comparable in both treatment groups), and, separately, herpes zoster (data not shown).

In the phase 3 long-term safety data, including the 120-day safety update through 19 March 2020, the EAIRs of patients with any AE during treatment in the SOC of Infections and infestations were 107.6/100 PY in the anifrolumab 300 mg group and 91.6/100 PY in the placebo group. In both treatment groups, among patients with an infection AE, most patients' events had a maximum reported intensity of mild or moderate. Overall, up to 19 March 2020, the incidence rates of patients with any infection in the phase III long-term safety data were consistent with the rates reported in the initial BLA filing.

8.2.7. Non-opportunistic serious infections

During the 52-week study pool (studies 1013, 04 and 05), the proportions of subjects with a non-opportunistic serious infection were similar in the study arms (Table 62): 4.8% (22/459; EAIR 5.4) in the anifrolumab 300 mg group and 5.6% (26/466; EAIR 6.6) in the placebo group. In the placebo group, most non-opportunistic infections were of moderate severity, while in the anifrolumab 300 mg group, there were a greater number of severe events (11/459 (2.4%) in anifrolumab 300 mg vs 8/466 (1.7%) in the placebo group. In the anifrolumab 300 mg group, events reported in > 2 patients by PT were pneumonia (1.7%, 8/459) and appendicitis (0.7%, 3/459). In the placebo groups, events reported in > 2 patients by PT were pneumonia (1.9%, 9/466) and gastroenteritis (0.6%, 3/466).

Table 62. Non-opportunistic serious infections during treatment during 52-week study period (studies 1013, 04 and 05)

AESI AE category or PT	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Non-opportunistic serious infections							
Any SAE (including fatal events)	22 (4.8)	411.2	5.4	26 (5.6)	393.2	6.6	-1.3 (-4.7, 2.1)
Any DAE	2 (0.4)	419.3	0.5	2 (0.4)	402.9	0.5	-0.0 (-1.4, 1.3)
Any AE by maximum reported intensity							
Mild	1 (0.2)	411.4	0.2	0	393.2	0	NC
Moderate	10 (2.2)	412.2	2.4	18 (3.9)	393.2	4.6	NC
Severe	11 (2.4)	415.8	2.6	8 (1.7)	398.9	2.0	NC
Any AE by PT:							
Pneumonia	8 (1.7)	417.3	1.9	9 (1.9)	400.4	2.2	-0.3 (-2.5, 1.8)
Appendicitis	3 (0.7)	418.7	0.7	0	403.0	0	0.7 (-0.2, 2.1)
Gastroenteritis	2 (0.4)	419.0	0.5	3 (0.6)	401.3	0.7	-0.3 (-1.7, 1.1)
Gastroenteritis viral	2 (0.4)	418.4	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Herpes Zoster	2 (0.4)	418.5	0.5	0	403.0	0	0.5 (-0.5, 1.7)

BLA 761123 Multi-disciplinary Review and Evaluation
Saphnelo (anifrolumab-fnia) for adults with SLE

Influenza	2 (0.4)	418.3	0.5	1 (0.2)	402.2	0.2	0.2 (-1.0, 1.5)
Urinary tract infection	2 (0.4)	418.2	0.5	1 (0.2)	402.8	0.2	0.2 (-1.0, 1.5)
Abscess limb	1 (0.2)	418.8	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Bronchitis	1 (0.2)	419.0	0.2	1 (0.2)	402.9	0.2	-0.0 (-1.2, 1.1)
Cellulitis	1 (0.2)	418.8	0.2	1 (0.2)	402.9	0.2	-0.0 (-1.2, 1.1)
Diverticulitis	1 (0.2)	419.3	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Genital herpes	1 (0.2)	418.9	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Hematoma infection	1 (0.2)	419.3	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Meningitis viral	1 (0.2)	419.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Peritonitis	1 (0.2)	419.2	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Pyelonephritis acute	1 (0.2)	418.6	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Abscess	0	419.4	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)
Epididymitis	0	419.4	0	1 (0.2)	402.7	0.2	-0.2 (-1.4, 0.7)
Large intestine infection	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Meningitis	0	419.4	0	1 (0.2)	402.7	0.2	-0.2 (-1.4, 0.7)
Otitis media chronic	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Pelvic infection	0	419.4	0	1 (0.2)	403.0	0.2	-0.2 (-1.4, 0.7)
Periodontitis	0	419.4	0	1 (0.2)	402.0	0.2	-0.2 (-1.4, 0.7)
Postoperative wound infection	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Sepsis	0	419.4	0	2 (0.4)	401.5	0.5	-0.5 (-1.8, 0.4)
Septic shock	0	419.4	0	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Sialadenitis	0	419.4	0	1 (0.2)	402.6	0.2	-0.2 (-1.4, 0.7)
Sinusitis	0	419.4	0	1 (0.2)	402.3	0.2	-0.2 (-1.4, 0.7)
Subcutaneous abscess	0	419.4	0	1 (0.2)	402.8	0.2	-0.2 (-1.4, 0.7)
Upper respiratory tract infection	0	419.4	0	1 (0.2)	402.1	0.2	-0.2 (-1.4, 0.7)

Derived from: Table 3.6.8.1.1 and Table 3.6.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

Consistent with the 52-week data, the phase 3 long-term safety data demonstrated that patients in the anifrolumab 300 mg group (9.8 %; EAIR 4.2) had a similar risk for non-opportunistic serious infections compared with patients in the placebo group (8.2%; EAIR 6.0). In the phase 3 long-term safety data, the most common non-opportunistic serious infection by PT was pneumonia and similar proportions of patients experienced a serious pneumonia event in the anifrolumab 300 group (2.5%, 9 patients) and the placebo group (2.7%, 10 patients). In the anifrolumab 300 mg group, other non-opportunistic serious infections reported in > 2 patients were: herpes zoster (1.7%, 6 patients) and pyelonephritis (0.8%, 3 patients). No other non-opportunistic SAE, by PT, was reported in > 2 patients in either treatment group. In the long-term safety data, non-opportunistic serious infections were reported at rates of 4.2/100 PY in the anifrolumab 300 mg and 6.0/100 PY in the placebo group, with no trend in either treatment group by yearly intervals.

8.2.8. Opportunistic infections

During the 52-week study period (studies 1013, 04 and 05), one patient in the anifrolumab 300 mg group had a non-serious opportunistic infection with PT mycobacterium avium complex infection after 12 doses of anifrolumab that led to discontinuation of IP. The subject was treated with ethambutol, isoniazid, pyrazinamide, and rifampicin. The event was considered by the investigator to be moderate in intensity and related to study treatment. Two opportunistic

infections were reported in the placebo group. One patient had a non-serious AE of oropharyngeal candidiasis (the same placebo subject also experienced a post-operative wound infection counted as a treatment emergent serious AESI of non-opportunistic infection). One patient had a SAE of cryptococcal meningitis with an onset date 32 days after the last dose of IP (the same placebo subjects also experienced an SLE flare and vasculitis with digital ischemia that led to discontinuation of IP).

Two additional opportunistic infections occurred during the phase 3 long-term safety period; one each in the anifrolumab 300 mg group and one in the placebo group. A patient in the anifrolumab 300 mg group experienced an event of non-serious ophthalmic herpes simplex. A patient in the placebo group experienced an event of non-serious respiratory moniliasis (candida albicans).

8.2.9. Herpes Zoster

During the 52-week study period (studies 1013, 04 and 05), patients in the anifrolumab 300 mg group had an increased risk for herpes zoster infection (Table 63). 28 subjects (6.1%; EAIR 6.9) experienced a herpes zoster event in the anifrolumab 300 mg group and 6 patients (1.3%; EAIR 1.5) experienced a herpes zoster event in the placebo group.

Table 63. Herpes zoster events during the 52-week study period (studies 1013, 04 and 05)

Herpes zoster AEs	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95 % CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Any AE	28 (6.1)	406.9	6.9	6 (1.3)	399.5	1.5	5.4 (2.8, 8.4)
Any AE with outcome of death	0	419.4	0	0	403.0	0	0
ANY SAE (including events with outcome of death)	2 (0.4)	418.5	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Any DAE	2 (0.4)	419.3	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Any AE by maximum reported intensity							
Mild	9 (2.0)	406.9	2.2	1 (0.2)	399.5	0.3	NC
Moderate	17 (3.7)	411.0	4.1	5 (1.1)	400.2	1.2	NC
Severe	2 (0.4)	419.3	0.5	0	403.0	0	NC
Any cutaneous (localized) herpes zoster ^{a, d}	18 (5.0)	316.6	5.7	5 (1.4)	316.0	1.6	NC
Any cutaneous disseminated herpes zoster ^{b, d}	2 (0.6)	324.7	0.6	0	318.8	0	NC
Any visceral disseminated herpes zoster ^{c, d}	0	326.0	0	0	318.8	0	NC

Derived from: Table 3.6.7.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

^a Cutaneous is defined as ≤ 3 contiguous dermatomes (unilateral).

^b Cutaneous disseminated is defined as > 3 contiguous dermatomes (unilateral) OR “Skip lesions” –

involving noncontiguous dermatomes OR bilateral distribution rather than unilateral.

^c Visceral disseminated is defined as visceral complications, including pneumonitis, hepatitis, and meningoencephalitis.

^d The classification of cutaneous (localized/disseminated) and visceral was not collected for study 1013.

Of the 28 patients in the anifrolumab 300 mg group with a herpes zoster event during treatment, 19 patients had cases that were moderate or severe in intensity (Table 63). In the anifrolumab 300 mg group, 2 patients had a SAE of herpes zoster and 2 patients discontinued IP due to a herpes zoster AE. In the phase 2 study (1013), one patient in the anifrolumab 300 mg group experienced SAEs of herpes zoster as well as transverse myelitis with positive CSF PCR for varicella-zoster virus (study 1013 narratives). In the placebo group, none of the 6 herpes zoster events were serious or resulted in discontinuation of IP. All herpes zoster cases in both treatment groups resolved; in the anifrolumab 300 mg group 9 cases resolved with sequelae (most commonly post-herpetic neuralgia) and in the placebo group 1 case resolved with sequelae. Most patients received antiviral treatment: all patients in the anifrolumab 300 mg group and 3 of the 6 patients in the placebo group. Approximately half of the events had an onset during the first 12 weeks of treatment.

In the phase 3 long-term safety data, a greater proportion of patients in the anifrolumab 300 mg group (42; 11.7%) had a herpes zoster event during treatment than patients in the placebo group (11; 3.0%) (Table 64). Over up to 4 years of treatment, the EAIR was 5.2/100 PY in the anifrolumab 300 mg group and 2.2/100 PY in the placebo group, a risk difference of 3.0 (95% CI: 0.9, 5.0) (see Table 3.6.1.1a in Appendix B). Of the 42 events in the anifrolumab 300 mg group, 30 of the events were of moderate to severe intensity. None of the events in the placebo group were serious or resulted in discontinuation of treatment; in the anifrolumab 300 mg group, 8 were serious and 3 resulted in discontinuation of IP. The EAIR of herpes zoster AEs in the anifrolumab 300 mg group was highest in Year 1 of treatment (7.3/100 PY) and decreased in Years 2 through Year 4 (4.1, 3.9, and 2.2 per 100 PY, respectively).

Table 64. Herpes zoster events during the phase 3 long-term study period

Herpes zoster AEs	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95 % CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Any AE	42 (11.7)	814.1	5.2	11 (3.0)	511.5	2.2	3.0 (0.9, 5.0)
Any AE with outcome of death	0	872.8	0	0	525.8	0	0
ANY SAE (including events with outcome of death)	8 (2.2)	864.3	0.9	0	525.8	0	0.9 (0.2, 1.8)
Any DAE	3 (0.8)	872.7	0.3	0	525.8	0	0.3 (-0.4, 1.0)
Any AE by maximum reported intensity							
Mild	12 (3.3)	814.1	1.5	1 (0.3)	511.5	0.3	NC
Moderate	25 (6.9)	831.7	3.0	10 (2.7)	511.9	2.0	NC

Severe	5 (1.4)	869.4	0.6	0	525.8	0	NC
Any cutaneous (localized) herpes zoster ^{a, d}	30 (8.3)	829.1	3.6	10 (2.7)	511.8	2.0	NC
Any cutaneous disseminated herpes zoster ^{b, d}	3 (0.8)	866.2	0.3	1 (0.3)	525.4	0.2	NC
Any visceral disseminated herpes zoster ^{c, d}	0	872.8	0	0	525.8	0	NC

Derived from: Table 3.6.7.1.1a, Appendix B.

Two of the three studies submitted to support approval (1013 and 05) included doses of anifrolumab other than 300 mg (see overview discussion in Section 8.2.8 below). For herpes zoster, specifically, there appears to be a dose-related increase in the frequency and severity of herpes zoster events. In the phase 3 study 05, a similar frequency AE of herpes zoster occurred in the anifrolumab 300 mg arm (10/180 subjects; 5.6%) as compared to the anifrolumab 150 mg arm (5/93 subjects; 5.4%). All 5 events in the 150 mg dose arm were mild (1) or moderate (4); in the 300 mg dose arm, 2 of the events were mild, 7 were moderate and 1 was severe (disseminated cutaneous, recovered with sequelae of post-herpetic neuralgia). For the 150 mg dose, herpes zoster events occurred with equal frequency with different study duration, while half of the events in the 300 mg arm occurred within the first 24 weeks of treatment (data from study 05 derived from the CSR, Table 11.3.2.2.5). In the phase 2 study 1013, twice as many AE of herpes zoster occurred in the 1000 mg arm (10/105 subjects; 9.5%) as occurred in the 300 mg arm (5/99 subjects; 5.1%). In the 300 mg arm, herpes zoster events were labeled as grade 1 (1), grade 2 (3), and grade 3 (1); in the 1000 mg arm, herpes zoster events were labeled as grade 1 (1), grade 2 (7), and grade 3 (2). In summary, herpes zoster AE occurred earlier, with greater severity, and with greater frequency in a dose-dependent fashion.

8.2.10. Tuberculosis (TB) including latent TB

In the anifrolumab clinical program, there were no cases of active TB reported during any study. To be eligible for the controlled phase II and III studies (studies 1013, 04, and 05), patients were to have no evidence of active TB or latent TB, unless the latent TB was documented to have been appropriately treated or active treatment had been initiated (see Section 5.3.1 of the study 04 and study 05 CSRs and Section 9.3.1 of the study 1013 CSR, in Module 5.3.5.1). The QFT-G, an interferon gamma release assay (IGRA), is a blood test to aid the diagnosis of Mycobacterium tuberculosis infection; both latent TB infection and active TB disease. All patients in the controlled phase II and III studies underwent TB testing at screening and at week 52. If a patient had a positive or indeterminate test during screening, the patient had to meet additional criteria (e.g., repeat testing, chest x-ray, etc.) prior to the first administration of IP.

In the interim between the screening test and the week 52 test, investigators were asked to evaluate patients for signs and symptoms of TB at every visit and complete a TB surveillance questionnaire (studies 04 and 05) or clinical evaluation questionnaire (study 1013) prior to administration of IP (see sample eCRF in Appendix 12.1.2 to the study 04 CSR in Module 5.3.5.1 and Section 5.2.16 of the study 1013 CSP v3, Appendix 16.1.1 of the CSR in Module 5.3.5.1). In

the phase III studies, a positive IGRA during the study was recorded as an AESI of latent TB, provided the patient did not have any signs and symptoms of active TB.

During the 52-week study period (studies 1013, 04 and 05), the number of AEs reported as latent TB were 6 subjects (1.3%; EAIR 1.3/100 PY) in the anifrolumab 300 mg group (of which 4 occurred in the two phase 3 studies) as compared to 3 subjects (0.6%; EAIR 0.7/100 PY) in the placebo group (of which 2 occurred in the two phase 3 studies).

During the phase 3 long-term safety study, one additional case of latent TB occurred beyond the first year of study in the placebo arm for a total of 3 cases over 4 years (EAIR 0.6/100 PY); 14 additional cases of latent TB occurred beyond the first year of study in the anifrolumab 300 mg arm for a total of 18 cases over 4 years (EAIR 2.1/100 PY; risk difference 1.5, 95% CI 0.3, 2.8).

8.2.11. Influenza

During the 52-week study period (studies 1013, 04 and 05), the number of AEs reported as influenza were 12 subjects (2.6%; EAIR 2.9/100 PY) in the anifrolumab 300 mg group and 9 subjects (1.9%; EAIR 2.3/100 PY) in the placebo group.

During the phase 3 long-term safety study, three additional cases of influenza occurred beyond the first year of study in the placebo arm for a total of 11 cases over 4 years (EAIR 2.1/100 PY); 14 additional cases of influenza occurred beyond the first year of study in the anifrolumab 300 mg arm for a total of 20 cases over 4 years (EAIR 2.4/100 PY; risk difference 0.2, 95% CI -1.6, 1.8).

8.2.12. Anaphylaxis, hypersensitivity, and infusion-related reactions

In the placebo-controlled phase II and III studies (studies 1013, 04, and 05), patients did not receive premedication unless they had a prior infusion-related reaction to anifrolumab. If a prior infusion-related reaction was documented, the investigator could elect to administer prophylactically an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the patient prior to subsequent infusions. Prophylactic use of corticosteroids prior to subsequent infusions was not permitted.

8.2.13. Anaphylaxis

There were no cases of anaphylaxis in any patient treated with anifrolumab 300 mg in the primary safety pool, supportive safety pool, or phase III long-term safety data (data not shown). However, in study 05, one patient in the anifrolumab 150 mg group had an anaphylactic reaction during the second dose. In the one reported case of anaphylaxis with anifrolumab - patient (b) (6) in study D3461C00005 - a 27 year old white female from Argentina experienced a mild pruritic rash after the first dose of study treatment with anifrolumab 150 mg infusion. The patient was prophylactically administered one dose of diphenhydramine prior

to the second infusion. On the day of Dose 2, during the post-dose flush infusion, the patient developed anaphylactic reaction with dyspnea, wheezing, flushing, and pruritis; was treated with hydrocortisone, diphenhydramine, and epinephrine; and was hospitalized for anaphylactic reaction. Both the initial pruritic rash and anaphylactic reaction were considered to be related to study treatment with anifrolumab. There were no other anaphylaxis events reported in the anifrolumab development program.

A possible role for galactose- α -1,3-galactose (alpha-gal) glycan³⁹ contributing to the potential hypersensitivity and infusion-related reactions was taken into consideration for anifrolumab. Glycosylation analysis of anifrolumab showed that it contains (b) (4) % alpha-gal on the product Fc domain. It is concluded that alpha-gal glycan in anifrolumab has low risk to contribute to these events because of the following considerations (provided by the Applicant in response to an Information Request): 1) anifrolumab does not have any glycosylation sites in the Fab region, and the α -Gal is present in the conserved glycosylation site in the Fc domain, whereas monoclonal antibodies for which pre-formed anti-IgE contribute to anaphylaxis have alpha-gal in both the Fab and Fc domains; 2) none of the anaphylaxis/hypersensitivity cases happened during the 1st infusion, and 3) There was no distinct regional pattern (tick area). Therefore, testing for alpha-gal IgE in the single anaphylaxis case with 150 mg anifrolumab is not needed.

8.2.14. Hypersensitivity

During the 52-week study period (studies 1013, 04 and 05), there were more AEs categorized as hypersensitivity reactions in the anifrolumab 300 mg group than the placebo group: 13 patients (2.8%) and 3 patients (0.6%), respectively (Table 65). In the primary safety pool, all hypersensitivity AEs were mild or moderate in intensity, and all events in the anifrolumab 300 mg group resolved spontaneously or with symptomatic treatment. One patient in the anifrolumab 300 mg group had a hypersensitivity SAE, was treated, and continued with the IP dosing schedule with prophylaxis given for subsequent infusions (data not shown). One patient in the placebo group had a hypersensitivity AE that led to discontinuation of IP. During the 52-week treatment period, all hypersensitivity AEs occurred in the first 24 weeks of treatment (data not shown).

Table 65. Hypersensitivity events during the 52-week study period (studies 1013, 04 and 05)

	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95 % CI)
	n (%) patients	Exposur e years	EAIR per 100 PY	n (%) patients	Exposur e years	EAIR per 100 PY	
Hypersensitivity AEs ^a							

³⁹ Platts-Mills TAE et. al. On the cause and consequences of IgE to galactose- α -1,3-galactose: A report from the National Institute of Allergy and Infectious Diseases Workshop on Understanding IgE-Mediated Mammalian Meat Allergy. J Allergy Clin Immunol. 2020 Apr;145(4):1061-1071.

Any AE	13 (2.8)	410.5	2.9	3 (0.6)	401.6	0.7	NC
Any AE with outcome of death	0	419.4	0	0	403.0	0	0
ANY SAE (including events with outcome of death)	1 (0.2)	418.4	0.2	0	403.0	0	0.2 (-0.7, 1.3)
Any DAE	0	419.4	0	1 (0.2)	402.9	0	-0.2 (-1.4, 0.7)
Any AE by maximum reported intensity							
Mild	8 (1.7)	410.5	1.9	2 (0.4)	401.6	0.5	NC
Moderate	4 (0.9)	417.3	1.0	1 (0.2)	402.4	0.2	NC
Severe	0	419.4	0	0	403.0	0	NC

Derived from: Table 3.6.5.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

^a Hypersensitivity excludes those events meeting anaphylaxis criteria.

During the phase 3 long-term safety study, no additional cases of hypersensitivity occurred beyond the first year of study in the placebo arm for a total of 3 cases over 4 years (EAIR 0.6/100 PY); 4 additional cases of hypersensitivity occurred beyond the first year of study in the anifrolumab 300 mg arm for a total of 16 cases over 4 years (EAIR 1.9/100 PY).

8.2.15. Infusion-related reactions

During the 52-week study period (studies 1013, 04 and 05), there were more AEs categorized as infusion-related reactions in the anifrolumab 300 mg group than the placebo group: 43 patients (9.4%) and 33 patients (7.1%), respectively (Table 66). All infusion-related reaction AEs were mild or moderate in intensity, and there were no serious infusion-related reactions. One patient in the placebo group had an infusion-related reaction that led to discontinuation of IP. During the 52-week treatment period, most infusion-related reaction AEs occurred in the first 24 weeks of treatment (data not shown).

Table 66. Infusion related reactions during the 52-week study period (studies 1013, 04 and 05)

Infusion related reaction AEs ^a	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95 % CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Any AE	43 (9.4)	385.9	11.1	33 (7.1)	377.6	8.7	NC
Any AE with outcome of death	0	419.4	0	0	403.0	0	0
ANY SAE (including events with outcome of death)	0	419.4	0	0	403.0	0	0
Any DAE	0	419.4	0	1 (0.2)	402.9	0	-0.2 (-1.4, 0.7)
Any AE by maximum reported intensity							
Mild	29 (6.3)	386.2	7.5	27 (5.8)	377.7	7.1	NC

Moderate	14 (3.1)	409.3	3.4	6 (1.3)	398.3	1.5	NC
Severe	0	419.4	0	0	403.0	0	NC

Derived from: Table 3.6.5.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

Data on specific infusion related reaction (IRR) symptoms is provided for the two phase 3 studies, in which a total number of 79 IRR events occurred in the anifrolumab 300 mg group (39 subjects) as compared to 59 IRR events in the placebo group (26 subjects). Among the events in the anifrolumab 300 mg group, the most common symptoms (reported in $\geq 5\%$ of events) were headache (45.6% of events), nausea (22.8% of events), vomiting (7.6% of events), and fatigue (5.1% of events) (data not shown).

During the phase 3 long-term safety study, 3 additional cases of IRR occurred beyond the first year of study in the placebo arm for a total of 30 cases over 4 years (EAIR 6.3/100 PY); 11 additional cases of IRR occurred beyond the first year of study in the anifrolumab 300 mg arm for a total of 52 cases over 4 years (EAIR 1.9/100 PY).

8.2.16. Malignancies

According to the Summary of Clinical Safety, malignancies were identified in the anifrolumab clinical studies based on the MedDRA SMQs listed in Section 1.1.4.3. Across the phase II and III SLE controlled and uncontrolled studies of IV anifrolumab (studies 02, 04, 05, 09, 1013, and 1145), there were 14 malignancies reported in patients who received any dose of anifrolumab (see Listing 1, Appendix 2.7.4.7.3 in Module 5.3.5.3). Only non-melanoma skin cancers ($n = 7$) and breast cancers ($n = 3$) were reported in more than 1 patient. Among 6 total malignancies reported in anifrolumab-treated patients in the 52-week phase studies, there were 4 malignancies reported within 180 days of the first exposure to anifrolumab, which may have been pre-existing: 2 cases of squamous cell carcinoma in the anifrolumab 300 mg group (31 days and 51 days after the patient's first dose, respectively), an invasive breast carcinoma in the anifrolumab 150 mg group (113 days after the first dose), and a B-cell lymphoma in the anifrolumab 300 mg group (12 days after the first dose) (data not shown).

During the 52-week study period (studies 1013, 04 and 05), there were a total of 6 subjects (1.3%; EAIR 1.3) with any malignancy in the anifrolumab 300 mg group and 3 subjects (0.6%; EAIR 0.7) with any malignancy in the placebo group (Table 67). The risk difference between the anifrolumab 300 mg group and the placebo group was 0.6 (95% CI -0.8, 2.2).

Table 67. Malignancy by type during the 52-week study period (studies 1013, 04 and 05)

Type of malignancy Preferred Term	Anifrolumab 300 mg (N = 459)			Placebo (N = 466)			Risk difference (95 % CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Any Malignancy	6 (1.3)	456.3	1.3	3 (0.6)	447.0	0.7	0.6 (-0.8, 2.2)
Non-hematological							

malignant tumors							
Invasive ductal breast carcinoma	2 (0.4)	458.8	0.4	0	448.6	0	0.4 (-0.4, 1.6)
Lip squamous cell carcinoma	1 (0.2)	458.8	0.2	0	448.6	0	0.2 (-0.6, 1.2)
Squamous cell carcinoma	1 (0.2)	458.0	0.2	0	448.6	0	0.2 (-0.6, 1.2)
Carcinoid tumor	0	459.0	0	1 (0.2)	448.4	0.2	-0.2 (-1.3, 0.6)
Squamous cell carcinoma of the cervix	0	459.0	0	1 (0.2)	348.4	0.2	-0.2 (-1.3, 0.6)
Uterine cancer	0	459.0	0	1 (0.2)	347.8	0.2	-0.2 (-1.3, 0.6)
Malignant lymphomas							
B cell lymphoma	1 (0.2)	458.6	0.2	0	348.7	0	0.2 (-0.6, 1.2)
Skin malignant tumors							
Squamous cell carcinoma of skin	1 (0.2)	457.9	0.2	0	348.7	0	0.2 (-0.6, 1.2)

Derived from: Table 3.6.9.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

A malignancy during study is defined as a malignancy with a date of onset $\geq$ day of first dose of IP and $\leq$ end of study day.

During the phase 3 long-term safety study, 2 additional cases of malignancy occurred beyond the first year of study in the placebo arm for a total of 5 cases over 4 years (EAIR 0.9/100 PY); 1 additional case of malignancy occurred beyond the first year of study in the anifrolumab 300 mg arm for a total of 7 cases over 4 years (EAIR 0.7/100 PY; risk difference -0.2, 95% CI -1.4, 0.7). The phase 3 long-term safety data did not suggest any change in the rate of malignancies with long-term exposure to anifrolumab, with no temporal patterns observed by yearly intervals of malignancies during treatment (data not shown).

8.2.17. MACE

Major adverse cardiovascular events (MACE) events were identified in the two phase 3 studies (04 and 05) by an independent committee adjudicating cardiovascular events. As the phase 2 study (1013) did not include an independent cardiovascular adjudication committee, the events included in the pool of all three 52-week studies were identified by a custom MedDRA term list.

Only four MACE events were recorded. One patient in the anifrolumab 300 mg group had an AE of acute coronary syndrome (study 04). Three patients with MACE events occurred in the placebo group of study 1013—two of the patients had an ischemic stroke and one had a cerebral infarction.

8.2.18. Vasculitis (non-SLE)

Vasculitis has been evaluated because of findings of focal arteritis in a non-clinical study. However, non-SLE vasculitis was not observed in any anifrolumab-treated patient in any of the integrated safety pools.

8.2.19. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

N/A

8.2.20. Safety Analyses by Demographic Subgroups

Study 1013 was analyzed for AE by subgroup separately from the two phase 3 studies and is included in the study 1013 CSR. Of the subjects who were ≤ 45 years old at baseline, the proportion who had at least one TEAE was 85.3% (116/136) in the total anifrolumab group and 76.1% (54/71) in the placebo group. Similarly, of the subjects who were > 45 years old at baseline, the proportion who had at least one TEAE was 85.3% (58/68) in the total anifrolumab group and 80.0% (24/30) in the placebo group (Section 14, Table 14.3.1.31). Of the female subjects, the proportion who had at least one TEAE was 84.5% (163/193) in the total anifrolumab group and 78.3% (72/92) in the placebo group. The number of male subjects who had at least one TEAE at baseline was too low to analyze (Section 14, Table 14.3.1.33).

Data pooled from the two phase 3 study 52-week studies is presented for subgroup analysis. For baseline demographics, refer to Table 12. Overall, the AE profile was consistent across all pre-defined subgroups, including gender, age ($<$ or ≥ 65 years old), race, underlying renal or hepatic function, BMI at baseline ($<$ or ≥ 28 kg/m²), baseline disease-related factors (SLEDAI-2K $<$ or ≥ 10 points; IFN gene signature high or low), and based on anti-drug antibody (ADA) status. Additional analysis for the effect of geographic region, and subgroups based on concomitant medication use at baseline is also presented.

1. Gender

The majority ($>90\%$) of subjects were female. Although based on a limited sample size of males, the safety profile of anifrolumab was generally similar between men and women with no clinically meaningful differences observed in the frequency or pattern of AEs.

2. Age

The proportion of patients in the program over the age of 65 was small (3.2%). Based on limited data, the safety profile appears to be similar in patients ≥ 65 years compared to those < 65 years of age. No clinically meaningful differences were observed in the frequency or pattern of AEs. Anifrolumab has not been studied in pediatric subjects < 18 years of age.

3. Race

Although the primary safety pool study population was predominantly White (65.9% of patients), the AE profile of anifrolumab was generally similar across racial groups for up to 52 weeks of treatment. No clinically meaningful differences were observed in the frequencies or patterns of AEs.

4. Underlying renal and hepatic function

Patients with mild and moderate renal impairment were enrolled, but the phase 3 studies did not include patients with severe renal impairment. Most patients had normal kidney function ($\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$)—65.8% and 67.9% in the anifrolumab 300 mg group and placebo group, respectively. About one third of patients in each group had eGFR values characterized as mild disease (60 to 89 mL/min/1.73 m^2). Few (~4% in each group) had eGFR values categorized as moderate disease (30 to 59 mL/min/1.73 m^2).

Anifrolumab clearance is target-mediated and the primary clearance mechanism is neither hepatic nor renal; it binds to the IFNAR receptors, is internalized and subsequently cleared. Based on the population PK analysis, the clearance of anifrolumab in patients with mild, moderate decrease in eGFR was comparable to those with normal eGFR values (see Section 6.9.2.4 of the Population PK Report in Module 5.3.5.3). Similarly, based on the population PK analysis, baseline hepatic function tests (AST, ALT, and total bilirubin) had no clinically relevant impact on the clearance of anifrolumab (see Section 6.9.2.5 of the Population PK Report in Module 5.3.5.3).

5. Body mass index

The safety profile by BMI at baseline (< 28 , $\geq 28 \text{ kg/m}^2$) is summarized for the primary safety pool in data displays of AEs by category in Tables 3.8.7.1 and 3.8.7.2, Appendix 2.7.4.7.1 in Module 5.3.5.3. Summaries of most common AEs and SAEs by BMI are presented in Tables 3.8.18, 3.8.27.1, and 3.8.27.2, Appendix 2.7.4.7.1 in Module 5.3.5.3. The safety profile of anifrolumab is generally similar in patients with BMI $\geq 28 \text{ kg/m}^2$ compared with those $< 28 \text{ kg/m}^2$ for up to 52 weeks of treatment. No clinically meaningful differences were observed in the frequency or pattern of AEs.

6. Baseline disease-related factors (SLEDAI-2K and IFN gene signature)

In the phase 3 52-week safety pool, 71.6% of patients had baseline SLEDAI-2K ≥ 10 points. The safety profile of anifrolumab is generally similar in patients with SLEDAI-2K ≥ 10 points compared with those < 10 points for up to 52 weeks of treatment. No clinically meaningful differences were observed in the frequency or pattern of AEs.

Approximately 82.6% of patients in the phase 3 52-week safety pool were IFN gene signature high at screening. The safety profile of anifrolumab is generally similar in patients with IFN gene signature high compared with low for up to 52 weeks of treatment. No clinically meaningful differences were observed in the frequency or pattern of AEs.

7. ADA status

There was no apparent trend or pattern suggesting a correlation between the presence of anifrolumab ADA and occurrence of AEs, SAEs, DAEs, or AESIs, including hypersensitivity or anaphylaxis events. However, given that few patients were positive for ADA in the phase 3 52-week safety pool (25 patients in the anifrolumab 300 mg group and 35 patients in the placebo group), no definitive conclusions can be drawn.

8. Geographic region

The safety profile by geographic region (Asia Pacific/Europe/Latin America/North America) in the primary safety pool is summarized in data displays of AEs by category in Tables 3.8.9.1 and 3.8.9.2, Appendix 2.7.4 in Module 5.3.5.3. The safety profile of anifrolumab was generally similar in patients across geographic regions in the phase 3 52-week data. No clinically meaningful differences were observed in the frequency or pattern of AEs.

9. Baseline concomitant medications—steroids and immunosuppressant therapy

In the phase 3 52-week safety pool, 51.7% of patients were taking a daily dose of oral corticosteroids (OCS) of ≥ 10 mg/day, and 48.1% of patients were on other immunosuppressant therapy at baseline. The overall safety profile of anifrolumab was generally similar in subjects across baseline OCS dose and in patients taking or not taking immunosuppressant therapy at baseline.

General infection risk in individuals with SLE is higher in subjects on steroids and immunosuppressant therapy.⁴⁰ Subjects with underlying autoimmune disease may be at increased risk for infections. As an example, herpes zoster is more common in individuals with rheumatoid arthritis and SLE.⁴¹ In SLE patients, the risk of herpes zoster is higher in patients being treated with steroids and immunosuppressants.⁴² As the anifrolumab 300 mg group had a significantly higher rate of herpes zoster as compared to the placebo group, it would be helpful to know if individuals in either group who developed herpes zoster were also taking either steroids ≥ 10 mg/day or other immunosuppressant therapy. This may provide information regarding a possible additive effect (increased risk) of herpes zoster in subjects prescribed anifrolumab who are also taking OCS or immunosuppressants. The overall risk for herpes zoster for the phase 3 52-week safety data is shown with additional data according to baseline OCS use in Table 68 and with additional data according to baseline immunosuppressant use in Table 69.

Table 68. Comparison for infectious SAE and AESI in the phase 3 52-week safety pool for different baseline use of OCS and anifrolumab treatment

AE category	Placebo (N = 365)		Anifrolumab 300 mg (N = 360)		Placebo OCS < 10 (N = 180)		Placebo OCS ≥ 10 (N = 185)		Anifrolumab 300 mg OCS < 10 (N = 170)		Anifrolumab 300 mg OCS ≥ 10 (N = 190)	
	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR

⁴⁰ Yuan Q, Xing X, Lu Z, Li X. Clinical characteristics and risk factors of infection in patients with systemic lupus erythematosus: A systematic review and meta-analysis of observational studies. *Semin Arthritis Rheum*. 2020 Oct;50(5):1022-1039.

⁴¹ Kawai K, Yawn BP. Risk Factors for Herpes Zoster: A Systematic Review and Meta-analysis. *Mayo Clin Proc*. 2017 Dec;92(12):1806-1821.

⁴² Hu SC, Yen FL, Wang TN, Lin YC, Lin CL, Chen GS. Immunosuppressive medication use and risk of herpes zoster (HZ) in patients with systemic lupus erythematosus (SLE): A nationwide case-control study. *J Am Acad Dermatol*. 2016 Jul;75(1):49-58.

	pa- tients	(per 100 PY)	patie nts	(per 100 PY)	pa- tients	(per 100 PY)	pa- tients	(per 100 PY)	pa- tients	(per 100 PY)	pa- tients	(per 100 PY)
Non-opportunistic Serious Infections	22 (6.0)	7.1	16 (4.4)	5.0	12 (6.7)	7.6	10 (5.4)	6.5	6 (3.5)	3.9	10 (5.3)	6.0
Herpes Zoster	5 (1.4)	1.6	23 (6.4)	7.3	2 (1.1)	1.2	3 (1.6)	1.9	11 (6.5)	7.3	12 (6.3)	7.3
Pneumonia SAE	8 (2.2)	2.5	6 (1.7)	1.8	1 (0.6)	0.6	7 (3.8)	4.5	1 (0.6)	0.6	5 (2.6)	3.0

Reviewer compiled; Source: Tables 3.2.1.1.1, 3.2.2.1.1, 3.8.2.1, 3.8.13, and 3.8.22.1

Table 69. Comparison for infectious SAE and AESI in the phase 3 52-week safety pool for different baseline use of Immunosuppressant and anifrolumab treatment

AE category	Placebo (N = 365)		Anifrolumab 300 mg (N = 360)		Placebo No Imm. (N = 189)		Placebo Any Imm. (N = 176)		Anifrolumab 300 mg No Imm. (N = 187)		Anifrolumab 300 mg Any Imm. (N = 173)	
	n (%) pa- tients	EAIR (per 100 PY)	n (%) patie nts	EAIR (per 100 PY)	n (%) pa- tients	EAIR (per 100 PY)	n (%) pa- tients	EAIR (per 100 PY)	n (%) pa- tients	EAIR (per 100 PY)	n (%) pa- tients	EAIR (per 100 PY)
Non-opportunistic Serious Infections	22 (6.0)	7.1	16 (4.4)	5.0	12 (6.3)	7.6	10 (5.7)	6.6	7 (3.7)	4.2	9 (5.2)	5.8
Herpes Zoster	5 (1.4)	1.6	23 (6.4)	7.3	2 (1.1)	1.2	3 (1.7)	1.9	6 (3.2)	3.6	17 (9.8)	11.3
Pneumonia SAE	8 (2.2)	2.5	6 (1.7)	1.8	6 (3.2)	3.7	2 (1.1)	1.3	3 (1.6)	1.8	3 (1.7)	1.9

Reviewer compiled; Source: Tables 3.2.1.1.1, 3.2.2.1.1, 3.8.8.1, 3.8.19, and 3.8.28.2

For OCS use, there does not appear to be an increased (additive) risk of herpes zoster since the number of subjects who developed herpes zoster is similar between low and high dose OCS for both the anifrolumab (11 vs 12) and the placebo group (2 vs 3). However, for concomitant immunosuppressant use, there were a higher number of subjects taking any immunosuppressant who developed herpes zoster than subjects not on any immunosuppressant in the anifrolumab group (17 vs 6). This suggests that there may be an increased (additive) risk of herpes zoster in SLE subjects who are treated with both anifrolumab and immunosuppressant therapy. A similar conclusion has been recently presented in a published summary of the safety profile of anifrolumab--the authors found that subgroup analysis of pooled data from studies 04 and 05 did not suggest any clear trends in herpes zoster cases based on demographics, baseline disease characteristics or concomitant medication use. However, a greater number of herpes zoster events occurred in patients receiving anifrolumab together with concomitant immunosuppressants (9.8%, n=17) than in those not receiving immunosuppressants (3.2%, n=6); the risk difference for subjects on immunosuppressants is

reported as 8.1 (95% CI 2.6, 13.7) comparing those treated with anifrolumab (9.8%, n=17) to those on placebo (1.7%, n=3).⁴³

For comparison, there appears to be an increased (additive) risk for serious pneumonia when combining anifrolumab with higher dose steroids (5 vs 1) but not for concomitant immunosuppressant use (3 vs 3). These observations are based on small subgroups of patients in the phase 3 studies and should be interpreted with caution. Additional safety data is required to determine how concomitant use of higher dose steroids and other immunosuppressant therapy may increase the risk of herpes zoster and other serious infections in SLE subjects treated with anifrolumab.

8.2.21. Specific Safety Studies/Clinical Trials

N/A

8.2.22. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Due to the limited species specificity of anifrolumab, there are no animal models to evaluate the quantitative or dose-dependent risk of carcinogenicity associated with anifrolumab administration. The direct carcinogenic risks associated with anifrolumab administration are not known. Administration of murine IFN- α/β enhanced antitumor effects in mice that contained transplanted tumors. In IFNAR1- and IFNAR2-deficient mice or mice treated with analogous murine anti- IFNAR1 or IFN- α/β antibodies, decreased host defense to tumors was observed. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

Human Reproduction and Pregnancy

Overall, in the anifrolumab SLE clinical program there were 31 patients with one or more pregnancy as of 01 August 2019. Of those 31 patients, 20 patients were randomized to receive anifrolumab. Among the patients who received anifrolumab and reported a pregnancy, no congenital anomalies associated with IP or no drug-associated AEs were observed.

Pediatrics and Assessment of Effects on Growth

Pediatric studies were deferred until after completion of phase 3 studies in adults.

⁴³ Tummala R, Abreu G, Pineda L, et al. Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials. *Lupus Science & Medicine* 2021;8:e000464. doi:10.1136/ lupus-2020-000464

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Doses of up to 1000 mg IV in clinical studies in patients with SLE are associated with an acceptable safety profile. There was no event of overdose reported during clinical development with anifrolumab and, when administered IV, there is low potential for overdose. There is no specific treatment for an overdose with anifrolumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring and symptomatic treatment as necessary.

There is no evidence for and no anticipation of patient abuse or dependence potential with anifrolumab.

In study 1013, all patients were to be followed from the last dose of IP (week 48) through the end of the safety follow-up period (week 60). An analysis of those patients did not identify any adverse effects of drug withdrawal after stopping anifrolumab treatment (see study 1013 CSR addendum in Module 5.3.5.1).

Suicidality and depression

During phase 3 studies 04 and 05 (52-week treatment period), The eight-item Patient Health Questionnaire depression scale (PHQ-8) scores were similar across all treatment groups at baseline with no clinically meaningful changes from baseline to week 52; small and similar decreases in PHQ-8 scores were observed in all treatment arms from baseline to week 52. There were few AEs related to depression as assessed by the MedDRA SMQ depression (excluding suicide and self-injury) with balanced events between the treatment groups (Table 70). Few patients had AEs related to suicidality; no patients in the anifrolumab 300 mg arms; 2 patients in placebo (PTs: suicide attempt and suicidal ideation). There was no evidence of increased risk in suicidal ideation or behavior based on Columbia-Suicide Severity Rating Scale (C-SSRS)—5 subjects in the anifrolumab arms vs 10 in placebo arms. Depression (PT) in anifrolumab 300 mg vs placebo was 18 (5.0%)/EAIR 2.0 vs 13 (3.6%) EAIR 2.3.

Table 70. Phase 3 (studies 04 and 05) 52-week treatment period data on depression SMQ (narrow)

Preferred Term	Anifrolumab 300 mg (N = 360) n (adjusted cumulative proportion [%])	Placebo (N = 365) n (adjusted cumulative proportion [%])	Adjusted difference in cumulative proportion (%), anifrolumab 300 mg – placebo (95% CI)
Depression	11 (3.1)	9 (2.5)	0.6 (-2.2, 3.4)
Mixed anxiety and depressive disorder	1 (0.3)	0	0.3 (-1.3, 1.9)
Depressed mood	0	1 (0.3)	-0.3 (-1.9, 1.3)
Persistent depressive disorder	0	1 (0.3)	-0.3 (-1.9, 1.3)

8.2.23. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Not applicable.

8.2.24. Integrated Assessment of Safety

Overall, the safety profile of anifrolumab IV assessed at a dose of 300 mg IV every 4 weeks in the adult SLE population that participated in the three studies submitted to support approval (1013, 04 and 05) appeared to be similar to placebo, with the exception of certain infections and infusion related reactions.

There were only 2 deaths in the anifrolumab 300 mg IV group during the 52-week study period. No patients randomized to the placebo plus standard of care group died during the 52-week study period. In the entire anifrolumab IV clinical development program, including doses of 150 mg and 1000 mg IV during a 52-week period and ongoing, long-term, phase 3 extension study of 300 mg (up to a total of 3 years), there were 11 deaths in the anifrolumab IV group and 3 deaths in the placebo group. In long-term, placebo controlled assessment of subjects on anifrolumab 300 mg, a total of seven deaths were attributed to infections (4 pneumonia and 3 COVID-19) in anifrolumab-treated subjects as compared to none on placebo. Deaths in the anifrolumab group were more closely associated with infections, particularly pneumonias.

There were only 6 malignancies in the anifrolumab 300 mg IV group during the 52-week study period and 3 malignancies in the placebo group. Adding data from the ongoing phase 3 long-term extension study of 300 mg, there were 2 additional malignancies in the placebo group for a total of 5, as compared to 6 in the anifrolumab 300 mg IV group.

Many of the serious adverse events and withdrawals from study treatment in the anifrolumab IV safety database were related to underlying disease activity or infections. The number of subjects with any infection was higher in the anifrolumab IV group (69.7%) than the placebo group (55.4%) with increased rates of Nasopharyngitis (anifrolumab 300 16.3% vs placebo 9.4%); Upper Respiratory Infection (15.5% vs 9.7%); Bronchitis (9.8% vs 4.3%); Herpes Zoster (6.1% vs 1.3%); Influenza (2.6% vs 1.9%); and Latent TB (0.9% vs (0.2%).

Herpes zoster infections occurred in a higher proportion (6.9%) of anifrolumab IV patients than placebo (1.9%) during the 52-week study period.

There were no cases of active tuberculosis. An increased rate of latent TB occurred in the anifrolumab arms, in particular during the long-term extension study. The relationship between

tuberculosis and SLE is unclear, although a high suspicion of TB and planned monitoring for active and latent TB should be considered, in particular in SLE patients from endemic countries and with high cumulative steroid exposure.⁴⁴

MACE events were rare and balanced between anifrolumab and placebo arms.

There were no cases of suicide/self-injury.

There was one case of anaphylaxis with the anifrolumab 150 mg IV dose and no cases of anaphylaxis with the anifrolumab 300 mg IV dose. There were more infusion related reactions (9.4% vs 7.1%) and hypersensitivity reactions (2.6% vs 0.6%) in the anifrolumab 300 mg IV group, including two cases of angioedema, as compared to the placebo group.

Limitations associated with the anifrolumab IV safety database include the lack of concomitant IV cyclophosphamide or other biologics including those that target B cells (e.g., rituximab or belimumab), and the lack of patients with severe renal lupus and central nervous system disease. The small numbers of patients available for subgroup analysis of gender (males), age (≥ 65 years of age as well as children ≤ 18 years of age), and race precludes determination of the product's safety profile in these subgroups.

As reviewed above, there may be an increased (additive) risk for herpes zoster with the concomitant use of immunosuppressive therapies and anifrolumab. There may also be an increased risk for pneumonia with the concomitant use of steroids and anifrolumab. The data suggests an increased risk of potentially fatal infections associated with anifrolumab use. There is a possible increased risk of nervous system disorders that requires further assessment. Similarly, additional long-term data is required to determine possible associations between anifrolumab and chemistry abnormalities such as increased serum glucose and gamma glutamyl transferase.

In conclusion, the overall safety profile of anifrolumab is acceptable given the adequate demonstration of benefit in SLE patients.

8.3. Statistical Issues

There were two primary statistical issues that arose during this review; missing data and the question of whether the submission provided substantial evidence of efficacy.

The amount of missing data for the three studies was moderate to high. It was pre-specified

⁴⁴ Balbi GGM, Machado-Ribeiro F, Marques CDL, Signorelli F, Levy RA. The Interplay Between Tuberculosis and Systemic Lupus Erythematosus. *Curr Opin Rheumatol* 2018 Jul;30(4):395-402.

that missing week 52 data would be imputed by available week 48 data. Considering these patients as missing, in study 1013, there was approximately 14% missing data at week 24, and 23% at week 52. Similarly, study 05 and 04 had roughly 23% missing data at week 52.

Use of such a last observation carried forward (LOCF) approach is generally not recommended as the underlying missingness mechanisms are generally not scientifically justified. In particular, LOCF imputation makes the strong assumption that the outcome of a participant does not change after drop out⁴⁵. Additionally, LOCF is a single imputation approach, which generally results in underestimation of the uncertainty of the estimated treatment effect due to the failure to specifically account for the lack of knowledge of the values that are missing. The approach to handling missing data should (1) properly capture the statistical uncertainty in parameter estimation due to data missingness; and (2) reflect what is considered to be most clinically plausible.

In order to evaluate the potential impact of all missing data, including those subjects whose data would be imputed based on available week 48 data, we evaluated the potential impact of these patients having different outcomes on the primary endpoint for study 1013 and 04, and additionally on BICLA at week 52 for study 1013 and study 05. These sensitivity analyses showed that the missing data were relatively unlikely to impact the results and conclusions. The results are further supported by the consistent treatment effects in BICLA at week 52 across studies.

The *Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*⁴⁶ describes two possible approaches to demonstrating substantial evidence: (1) two adequate and well-controlled trials or (2) one adequate and well-controlled trial plus confirmatory evidence. Study 04 represents an adequate and well-controlled trial as a large, multicenter, randomized, double-blind, placebo-controlled, phase 3 study which was successful on its primary and key secondary endpoints. Though the primary endpoint was changed after the results of study 05 were made known, this change was made before study unblinding. After a review of the DSMB meeting minutes, there were no concerns over the integrity of the trial or the impact on the estimated treatment effect due to the change to the primary endpoint.

Study 1013 was a dose-ranging, phase 2, multicenter, randomized, double-blind, placebo-controlled trial. The primary endpoint of SRI-4 + OCS tapering at week 24 was significant using the pre-specified alpha=0.10. However, the study did not specify an appropriate multiplicity procedure for the testing of multiple populations and multiple doses, and therefore study 1013 is not considered to be an adequate and well-controlled trial. Nevertheless, the results of BICLA and SRI-4 at week 52, and other exploratory secondary endpoints were nominally significant

⁴⁵ National Research Council. The prevention and treatment of missing data in clinical trials. National Academies Press, 2010.

⁴⁶ <https://www.fda.gov/media/133660/download>

and notably consistent with the results of study 04, providing evidence that anifrolumab is effective.

Additional support for effectiveness comes from study 05. Although study 05 failed on the primary endpoint of SRI-4 at week 52 and as such, efficacy results are considered exploratory, the results of BICLA at week 52, both under the original protocol-specified rules and under the post-hoc set of restricted medication rules as defined in study 04, demonstrated a similar treatment effect of anifrolumab 300mg to the treatment effect in study 04.

Results on secondary endpoints, though considered exploratory, were also consistent with results observed in study 04 and study 1013. Thus, while there are limitations to the evidence provided by a study which failed to win on its primary endpoint, when considering these results in combination with those observed in study 04 and study 1013, we consider this further evidence of effectiveness.

8.4. Conclusions and Recommendations

To support the proposed indication, the Applicant provided the results from three trials, that evaluated anifrolumab IV 300 mg every 4 weeks as well as two additional doses (150 mg every 4 weeks and 1000 mg every 4 weeks) versus placebo in a total of 1,123 adults with active systemic lupus erythematosus (SLE) on stable immunosuppressive background medications. These were international, multicenter, randomized, double-blind, placebo-controlled, 52-week trials that evaluated the efficacy, safety, and immunogenicity of anifrolumab 300 mg IV every 4 weeks versus placebo in 925 adult subjects with active SLE receiving standard therapy.

Study 04 achieved statistically significant and clinically meaningful results using primary endpoints incorporating either SRI-4 or BICLA composite endpoints at week 52. Study 1013 demonstrated nominally significant results in favor of anifrolumab on BICLA and SRI-4 at week 52, and in study 05, there was an observed improved clinical outcome in anifrolumab compared to placebo in the pre-specified and post-hoc analysis for BICLA at week 52. In study 04, a higher proportion of anifrolumab IV subjects (47.8%) achieved the 52-week BICLA primary endpoint as compared to the placebo group (31.3%)[risk difference (95% CI): 16.3 (6.3, 26.3)]. In study 1013, a higher proportion of anifrolumab IV subjects (53.5%) achieved the 52-week BICLA secondary endpoint as compared to the placebo group (25.7%)[risk difference (95% CI): 28.4 (15.3, 41.5)]. In study 05 post-hoc analysis, a higher proportion of anifrolumab IV subjects (47.2%) achieved the 52-week BICLA endpoint as compared to the placebo group (29.9%)[risk difference (95% CI): 17.0 (7.2, 26.8)]; however, for its primary 52-week SRI-4 endpoint, study 05 did not demonstrate statistically significant superiority of anifrolumab IV over placebo. Additional supportive evidence for efficacy is provided by the SRI-4 composite 52-week endpoint achieved in study 04 by a higher proportion of anifrolumab IV subjects (55.6%) as compared to the placebo group (37.4%)[risk difference (95% CI):18.2 (8.1, 28.3)] and in study 1013 by a higher proportion of anifrolumab IV subjects (62.6%) as compared to the placebo group (40.2%)[risk

difference (95% CI):24.0 (10.9, 37.2)]. The proposed dose of 300 mg IV every 4 weeks demonstrated consistent benefit both for primary BICLA and SRI-4 endpoints as well as for secondary endpoints of maintaining steroid tapering and reduction in rate of SLE flare. There was also a qualitative improvement with 300 mg anifrolumab vs placebo for reduction in inflammatory joint symptoms and SLE skin disease severity.

Based on the above considerations, study 04 is considered an adequate and well controlled trial and provides the primary basis of substantial evidence of effectiveness of anifrolumab. The study showed favorable and statistically significant changes on the pre-specified, clinically meaningful primary and secondary endpoints when comparing anifrolumab 300 mg IV versus placebo. Specifically, a favorable and statistically significant BICLA response rate compared to placebo at week 52 was achieved with anifrolumab 300 mg IV.

These results were consistent with those from study 1013; however, study 1013 is not considered an adequate and well controlled since an appropriate method for controlling multiplicity was not pre-specified. While study 05 did not show statistically significant improvement in the prespecified primary endpoint (SRI-4), study 05 did show nominally significant changes in the key secondary BICLA endpoint in favor of anifrolumab 300 mg IV dose. Also, disease activity measured by the SLE disease activity index (updated in 2000), (SLEDAI-2K), showed a dose-dependent separation in favor of anifrolumab in study 05. In all three trials, additional confirmatory evidence was noted in the analyses of the secondary endpoints, including steroid-use reduction, and improvement in mucocutaneous disease activity. There was also a reduction in annualized flare rate in study 04 and a reduction in arthritis in studies 1013 and 05 when anifrolumab 300 mg IV was compared to placebo, providing additional supportive evidence of efficacy.

The safety of anifrolumab in the SLE clinical program was consistent with expected increased risk of infection due to immunosuppression, in particular for viral infections in which Type I IFN is a central part of the immune response. While the 52-week incidence of serious infections between placebo and anifrolumab arms in all three trials submitted to support approval was balanced between anifrolumab and placebo arms—anifrolumab 4.8% (22/459) vs placebo 5.6% (26/466)—the proportion of subjects with any infections was higher in subjects treated with anifrolumab 300 mg (69.7%; 320/459) as compared to subjects in the placebo arms (55.4%; EAIR 99.9/100 PY). Herpes zoster infections, in particular, occurred at a higher rate in anifrolumab-treated subjects compared to placebo (6.1% vs 1.3%). In the 52-week controlled study period, fatal infections occurred in 0.4% of patients receiving anifrolumab and 0.2% of patients receiving placebo. In long-term, placebo controlled assessment of subjects on anifrolumab 300 mg beyond 52 weeks, a total of seven deaths were attributed to infections in anifrolumab-treated subjects (four pneumonia and three COVID-19) as compared to none on placebo. Certain infections occurred more frequently in patients treated with anifrolumab, including Nasopharyngitis (anifrolumab 300 16.3% vs placebo 9.4%); Upper Respiratory Infection (15.5% vs 9.7%); Bronchitis (9.8% vs 4.3%); Herpes Zoster (6.1% vs 1.3%); Influenza (2.6% vs 1.9%); and Latent TB (0.9% vs 0.2%).

There was one case of anaphylaxis with the anifrolumab 150 mg IV dose and no cases of anaphylaxis with the anifrolumab 300 mg or 1000 mg IV doses. There were more infusion related reactions (9.4% vs 7.1%) and hypersensitivity reactions (2.6% vs 0.6%), including 2 cases of angioedema, in the anifrolumab 300 mg IV group as compared to the placebo group.

In summary, the increased risk for infections, in particular respiratory infections and herpes zoster, the increased risk for potentially fatal outcome from serious infections, and increased risk of hypersensitivity and infusion-related reactions for anifrolumab 300 mg is similar to the only other approved targeted therapy for SLE and represents an acceptable safety profile for this indication.

Lower SLE disease activity as well as a decrease in the risk for severe SLE flares and a reduction in daily steroid dose may result in less long-term end-organ damage from patients' underlying disease, less treatment with immunosuppressive agents commonly used to treat SLE with their own inherent toxicities, as well as fewer hospitalizations with less loss of absent work days and ultimately less morbidity and mortality associated with this disease.

In summary, the efficacy and safety data generated from one adequate and well-controlled study—04—as well as confirmatory evidence from studies 1013 and 05, result in a favorable benefit-risk assessment for approval of the 300 mg dosing regimen of anifrolumab IV as add-on treatment for adult patients with active SLE while receiving standard therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants.

If approved, anifrolumab, a first-in-class biologic with a unique mechanism of action, will provide a new treatment option for patients with SLE.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not deemed necessary for this BLA.

10. Pediatrics

Regulatory History

- iPSP submitted Oct 2013
- Agreed PSP (April 2014)
- Requests a waiver for SLE children under 5 years of age
 - SLE is difficult to diagnose in the pediatric age range
 - Scarcity of pSLE
- Request deferral for SLE age 5 to <18 years of age
- The proposed study includes:

(b) (4)

The pediatric study plan for anifrolumab was discussed at a PeRC meeting on May 25th, 2021,
(b) (4)

The following was communicated to the Applicant in the May 19th, 2021 Late Cycle meeting:

Anifrolumab is a first in class drug to treat SLE (b) (4)

(b) (4)

Since there are uncertainties (b) (4)

(b) (4) for this first-in-class product, the pediatric study plan should be revised (b) (4)

(b) (4) for the PREA PMR.

The PREA assessment template includes the following:

The Agreed iPSP (April 2014) is (b) (4)

(b) (4) PK/PD/safety study in pSLE (age 5 to <18). As the Applicant

was advised at the time of the Agreed iPSP (2014), the proposal (b) (4)
(b) (4) is acceptable, however, the study design should be revised (b) (4)

(b) (4)
(b) (4)
Pediatric Study Plan should be revised (b) (4)
for the PREA PMR.

Proposed language for PREA PMR:

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

Conduct a study to evaluate the safety, efficacy, and pharmacokinetics of anifrolumab-fnia plus background standard therapy in pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE).

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Proposed package labeling was included in this submission; however, a line-by-line labeling review is not included since negotiations with the Applicant are on-going. The following is a high-level summary of major changes to the originally submitted Prescribing Information based on review of the data submitted in support of this application:

- 1) The tradename SAPHNELO® is acceptable. It has been deemed acceptable by both DMETS and the Division.
- 2) The indication under Section 1 Indications and Usage is the following: “SAPHNELO (anifrolumab-fnia) is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy [see *Clinical Studies (14)*].” The review team concluded that it is important to include the statement “receiving standard therapy” rather than (b) (4) to clarify that anifrolumab is an ad-on to background therapy.
- 3) The description of the mechanism of action of anifrolumab is the following: “SAPHNELO is a type I interferon (IFN) receptor antagonist.” Anifrolumab is not included in the FDA Established Pharmacological Class (EPC) Term List. The review team has provided the recommended EPC term for SAPHNELO based on its mechanism of action.
- 4) Limitations of Use included under Section 1 Indications and Usage is the following: “The efficacy of SAPHNELO has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Use of SAPHNELO is not recommended in these situations.” The review team concluded that it is important to include a statement on the limitations of use as the efficacy of anifrolumab in patients with severe active lupus nephritis or severe active CNS lupus is uncertain.
- 5) Section 4 Contraindications was added as follows: “SAPHNELO is contraindicated in patients with a history of anaphylaxis (b) (4) with anifrolumab-fnia [see *Warnings and Precautions (5.2)*].” The review team concluded that it is appropriate to include a statement on a contraindication in patients with known hypersensitivity since severe hypersensitivity reactions have been observed with anifrolumab.
- 6) Section 5 Warnings and Precautions—subsection 5.1 Serious Infections was added and included the following language:

“Serious and sometimes fatal infections have occurred in patients receiving immunosuppressive agents, including SAPHNELO.

(b) (4)

Overall, the incidence of serious infections in controlled trials was similar in patients receiving SAPHNELO compared with placebo, whereas fatal infections occurred more frequently in patients receiving SAPHNELO [see *Adverse Reactions* (6.1)].

Consider the benefit and risk of administering SAPHNELO in patients with a chronic infection, a history of recurrent infections, or known risk factors for infection. Avoid initiating treatment with SAPHNELO in patients with any clinically significant active infection until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms of clinically significant infection occur. If a patient develops an infection, or is not responding to standard anti-infective therapy, monitor the patient closely and consider interrupting SAPHNELO therapy until the infection resolves.”

In addition to communicating that anifrolumab is associated with overall increased risk of infections, the review team concluded that it was important to provide information to healthcare providers regarding the increased risk of potentially fatal infections associated with anifrolumab based on observations in both the 52-week dataset and Phase III long-term extension dataset as detailed in Section 6.

- 7) Section 5 Warnings and Precautions—subsection 5.2 Hypersensitivity Reactions Including Anaphylaxis was added and included the following language:

“Serious hypersensitivity reactions including anaphylaxis have been reported following SAPHNELO administration.

(b) (4)

SAPHNELO should be administered by healthcare providers prepared to manage (b) (4) hypersensitivity (b) (4). If a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis) occurs, immediately interrupt the administration of SAPHNELO and initiate appropriate therapy.”

The review team concluded that it was important to provide information to healthcare providers on the potential risk of anaphylaxis as well as angioedema and other hypersensitivity and infusion-related reactions as detailed in Section 6.

- 8) Section 5 Warnings and Precautions—subsection 5.5 Not Recommended for Concomitant Use with Other Biologic Therapies was added with the following: “SAPHNELO has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Therefore, use of SAPHNELO is not recommended for use in combination with biologic therapies.” The review team concluded that healthcare providers should be aware of a potential safety risk of concomitant use of SAPHNELO with other biologic therapies; the risk is unknown as the safety of co-administering SAPHNELO with other biologics has not been studied.

- 9) Section 5 Warnings and Precautions—order of adverse reactions changed to the following:

- 5.1 Serious Infections
- 5.2 Hypersensitivity Reactions Including Anaphylaxis
- 5.3 Malignancies
- 5.4 Immunization
- 5.5 Not Recommended for Concomitant Use with Other Biologic Therapies

The review team concluded that the Warnings and Precautions section should reflect the relative clinical significance of the adverse reactions observed with anifrolumab and that conforming changes should also be made to the Highlights section.

- 10) Section 6 Adverse Reactions—subsection 6.1 Clinical Trials Experience included the following language to describe the sources of data informing safety:

“The safety of SAPHNELO was assessed through 52 weeks in patients with moderate to severe SLE who received anifrolumab-fnia 300 mg by IV infusion every 4 weeks (N=459), compared to placebo (N=466) in controlled clinical trials (Trials 1, 2 and 3) [see Clinical Studies (14)]. The population studied had a mean age of (b) (4) years (range: 18 to 69), of which 93% were female, 66% White, 13% Black/African American, and 11% Asian.

The review team concluded that the safety database for labeling would be the 52-week dataset from studies 1013, 05, and 04 (referred to, respectively, as Trials 1, 2, and 3 in the label). A number of specific adverse drug reactions—infections, serious infections (including infections resulting in death), herpes zoster, hypersensitivity reactions including anaphylaxis, infusion-related reactions, and malignancies—were observed during the 52-week studies, and the review team concluded that healthcare providers should be aware of potential safety risks of exposure to anifrolumab.

- 11) Section 8 Use in Specific Populations—subsection 8.2 Lactation included the following language: “No data are available regarding the presence of SAPHNELO in human milk, the effects on the breastfed child, or the effects on milk production. Anifrolumab-fnia was detected in the milk of female cynomolgus monkeys (b) (4) administered anifrolumab-fnia. Due to species-species differences in lactation physiology, animal data may not reliably predict drug levels in humans. Maternal IgG is known to be present in human milk. If anifrolumab-fnia is transferred into human milk, the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to anifrolumab-fnia are unknown.” This section was revised according to current labeling practices.

- 12) Section 11 Description included the following language:

“Anifrolumab-fnia is a type I interferon (IFN) receptor antagonist immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that is produced in mouse myeloma cells (NS0) by recombinant DNA technology. The molecular weight is XXX kDa.

SAPHNELO (anifrolumab-fnia) injection is a sterile, preservative free, clear to opalescent, colorless to slightly yellow, solution for intravenous use. SAPHNELO contains anifrolumab-fnia at a concentration of 150 mg/mL in a single-dose vial. Each vial contains 300 mg (150 mg/mL) of anifrolumab-fnia, L-histidine (3 mg), L-histidine hydrochloride monohydrate (6 mg), L-lysine hydrochloride (18 mg), polysorbate 80 (1 mg), trehalose dihydrate (98 mg), and Water for Injection, USP, the pH is 5.9.”

The review team concluded that the mechanism of action should be in alignment with the EPC description in the Highlights of Prescribing Information; that molecular weight should be included; that the appropriate package type term should be included; and that the order of inactive ingredients should appear in alphabetical order per USP guidelines.

13) Section 14 Clinical Studies included the following recommendations:

- a. The review team recommended moving the complete SRI-4 and BICLA definitions to the introductory section as both composite endpoints were studied in all three Trials (1, 2, and 3 corresponding to studies 1013, 05, and 04) contributing data on efficacy of SAPHNELO.
- b. The review team recommended that study design of all three Trials should be included, together with patient demographics and disease characteristics.
- c. The review team concluded that a qualitative statement could be included to indicated that the reduction in disease activity seen in the SRI-4 and BICLA was related to improvement in mucocutaneous and musculoskeletal organ systems, (b) (4)
- d. The review team recommended that 52-week SRI-4 and BICLA data be provided in two separate Tables including data from all three Trials.
- e. The review team recommended that (b) (4)
both be removed (b) (4)
- f. The statement (b) (4) was removed. Based on feedback from the consulting review teams from Division of Dermatology and Dentistry, the review team concluded (b) (4)
These concerns were previously conveyed in End-of-Phase 2 communication on November 24, 2014. (b) (4)
Respectively, a qualitative statement would be more appropriate to describe the effects seen in this component.
- g. The statement (b) (4) was removed. The review team concluded (b) (4)

- (b) (4) Respectively, a qualitative statement would be more appropriate to describe the effects seen in this component.
- h. The statement (b) (4) was removed. Based on feedback from the consulting review team from the Division of Clinical Outcome s Assessment, the review team concluded (b) (4)

- 14) Section 17 Patient Counseling Information including the following language to reflect current labeling practices:

“Hypersensitivity Reactions/Anaphylaxis

Inform patients that serious hypersensitivity reactions, including anaphylaxis, have been reported in patients who received SAPHNELO. Instruct patients to immediately tell their healthcare provider or go to the emergency department of their nearest hospital, if they experience symptoms of an allergic reaction (e.g., anaphylaxis) during or after the administration of SAPHNELO [see Warnings and Precautions (5.1)]. Symptoms may include swelling of the face, tongue, or mouth, breathing difficulties, and/or fainting, dizziness, feeling lightheaded (due to a drop in blood pressure).

Serious Infections

Inform patients that SAPHNELO may decrease their ability to fight infections, and that serious infections, including fatal ones, occurred in patients receiving SAPHNELO in clinical trials. Also inform that they are at increased risk of respiratory infections and herpes zoster during treatment with SAPHNELO [see Warnings and Precautions (5.2)]. Advise patients to contact their healthcare provider if they develop any symptoms of an infection, including fever or flu-like symptoms; muscle aches; cough; shortness of breath; burning when they urinate or urinating more often than usual; diarrhea or stomach pain; shingles (a red skin rash that can cause pain and burning).

Immunizations

Inform patients that they should not receive live or live-attenuated vaccines while receiving SAPHNELO. Advise patients to discuss with their healthcare provider before seeking immunizations on their own [see Warnings and Precautions (5.3)].

12. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the labeling mentioned. Therefore, the subsequent subsections are

not applicable for this review and have been omitted.

13. Postmarketing Requirements and Commitment

The review team considered the following issues to determine which post-marketing requirements should be addressed by the Applicant:

1. Significant proportion of patients who may receive anifrolumab are women of childbearing potential and it is expected that pregnancies may occur in women who use Saphnelo. The pre-approval safety database for Saphnelo was too limited to draw any conclusions about the effect of Saphnelo on obstetrical, maternal and fetal/neonatal outcomes. FDA requests an observational prospective pregnancy registry to examine the pregnancy and birth outcomes with Saphnelo use. The goal of this PMR registry study is to evaluate the effects of Saphnelo on obstetrical, maternal and fetal/neonatal outcomes. This is a registry-based, prospective observational exposure cohort study and will compare Saphnelo-exposed pregnancy to a disease-matched Saphnelo unexposed pregnancy cohort. Pregnant women 18 years of age at the time of enrollment, with or without Saphnelo exposure will be enrolled. The registry will identify and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. We request a prospective patient registry, complimentary to an electronic claims-based retrospective cohort study. The pregnancy registry ensures that exposed pregnant women are identified with data collection on baseline risk factors and safety outcomes prospectively identified with medical chart adjudication.
2. It is expected that pregnancies in women who use Saphnelo, target premenopausal women. The pre-approval safety database for Saphnelo was too limited to draw any conclusions about the effect of Saphnelo on pregnancies, maternal and fetal/neonatal outcomes. The goal of this observational study is to evaluate the effects of Saphnelo on obstetrical, maternal and fetal/neonatal outcomes. This study will use claims or electronic medical record data to assess major congenital malformations, early pregnancy loss, placenta previa, preeclampsia, premature delivery, and small for gestational age in women exposed to Saphnelo during pregnancy compared to an unexposed pregnancy control population. The observational study will assess the obstetrical, maternal, fetal and neonatal outcomes in Saphnelo-exposed pregnancies compared to an unexposed pregnant control population. This study will complement the prospective pregnancy registry study.
3. There are no data on the presence of anifrolumab in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of anifrolumab to an infant during lactation. The Division of Pediatric and Maternal Health determined that a PMR for a milk only lactation study is in order because the drug is an NME and use of Saphnelo (anifrolumab) is anticipated in females of reproductive potential; therefore, additional data are required to evaluate the quantity of drug, if any, that is transferred into human breastmilk.
4. See section 10 for explanation of PREA PMR pediatric trial.

Thus, the post-marketing requirements agreed on with the Applicant include:

1. Conduct a prospective pregnancy registry to evaluate the effects of Saphnelo (anifrolumab-fnia) on pregnancy and maternal and fetal/neonatal outcomes. This pregnancy registry study may be conducted as part of a multiple-product or disease-based pregnancy registry.
2. Conduct a retrospective cohort study in a claims-based database to evaluate the effects of Saphnelo (anifrolumab-fnia) on pregnancy-related outcomes.
3. Perform a lactation study, milk only, in lactating women who have received Saphnelo (anifrolumab-fnia) to assess concentrations of anifrolumab-fnia in breast milk using a validated assay. A mother-infant pair study may be required in the future depending on the results of this milk-only study.
4. Conduct a study to evaluate the safety, efficacy, and pharmacokinetics of anifrolumab-fnia plus background standard therapy in pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE).

There is a postmarketing commitment not subject to the reporting requirements under section 506B: Implement (b) (4) of anifrolumab drug product and update module 3.2.P.3.4 of the BLA with (b) (4) as a Critical Process Parameter.

14. Division Director (Clinical) Comments

The Applicant, Astra Zeneca, has submitted adequate data to support approval of anifrolumab, a type I interferon (IFN) receptor antagonist monoclonal antibody, 300 mg/2 mL (150 mg/mL) in a single-dose vial for intravenous infusion over a 30 minute period every 4 weeks, for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy. SLE is a serious and potentially life-threatening systemic autoimmune disease with significant morbidity and mortality as well as impact patients' function and quality of life. The toxicities associated with both the approved and the off-label SLE treatments contribute to the long-term morbidity and mortality observed in patients with SLE, highlighting the high unmet medical need in this disease.

The application raised important regulatory and scientific questions that were adequately addressed by the review team, as detailed in this document, which I will only summarize in my comments. Specifically, after the successful proof of concept, dose ranging phase 2 study (1013), the first of the phase 3 studies (05) did not meet its primary endpoint, SRI-4 at week 52. However, based on analyses of data from these two studies, the Applicant proposed a revised primary endpoint from SRI-4 to BICLA at week 52, of the second still blinded phase 3 study (04). Study 04 met its primary endpoint of BICLA at week 52, along with statistically positive results on the SRI-4 endpoint, ranked now a key secondary endpoint. Of note, both SRI and BICLA are complex composite instruments that capture similar relevant clinical concepts and domains of the disease and are both considered clinically meaningful endpoints for evaluating a treatment effect on clinical response/reduction in disease activity in SLE.^{47,48} Given the complex clinical development and changes to the primary endpoint for one of the phase 3 studies, the review team carefully considered the data supporting substantial evidence of effectiveness. I agree with the team's assessment and conclusions that the substantial evidence of effectiveness is provided by study 04 with confirmatory evidence from the other two studies (1013 and 05) and supportive mechanistic rationale. Study 04 which represents an adequate and well-controlled trial showing favorable and statistically significant changes on the pre-specified, clinically meaningful primary and secondary endpoints when comparing anifrolumab 300 mg IV versus placebo. Because the phase 2 trial (1013) was designed only as a proof of concept and dose-ranging study with inadequate multiplicity control and study 05, the first phase 3 trial, failed on its primary endpoint, these cannot be considered additional successful adequate and well-controlled trials. However, the review team concluded, and I agree, that when these trials are considered in combination, the consistent results observed in studies 1013 and 05 do provide confirmatory evidence that support the effectiveness of anifrolumab 300 mg IV in adults with moderate to severe SLE, a disease with high unmet need.

⁴⁷ Guidance for Industry: Systemic Lupus Erythematosus—Developing Medical Products for Treatment (June 2010); <https://www.fda.gov/media/71150/download>

⁴⁸ Salmon J, Niewold T, A Successful Trial for Lupus - How Good Is Good Enough?, N Engl J Med. 2020 Jan 16;382(3):287-288

Across the three studies, there are three randomized comparisons, each with adequate duration (52 weeks), that support the claim that anifrolumab 300 mg IV yields higher BICLA response rates compared to placebo. Further, two of the three studies provide support that anifrolumab 300 mg IV yields higher SRI-4 response rates compared to placebo at week 52. The review team also provided a plausible explanation of the discordant SRI-4 and BICLA results in study 05, as detailed in the document. In all three studies, additional confirmatory evidence was noted in the analyses of the secondary endpoints, including a greater proportion of subjects on anifrolumab than placebo able to reduce oral corticosteroid use and a lower proportion of subjects on anifrolumab experiencing a flare of SLE disease activity, further supporting the effectiveness of anifrolumab. For transparency, these results, including the results from the failed study 05 should be described and appropriately annotated in the product labeling.

The primary safety assessment of anifrolumab was informed by a blinded controlled safety comparison from the three studies (1013, 05, and 04) in 459 subjects treated with anifrolumab 300 IV dosing regimen compared with 466 on placebo for 52 weeks. Controlled long-term safety assessments beyond 52 weeks were also submitted for patients who rolled over from the phase 3 studies 04 and 05, even though this assessment is still ongoing. Overall, the safety profile of anifrolumab 300 mg IV every 4 weeks appeared similar to placebo, with the exception of certain infections (including herpes zoster) and infusion related reactions (including two cases of angioedema). In that long-term safety comparisons dataset, herpes zoster and other viral infections continued to occur at a higher rate in patients treated with anifrolumab 300 mg, and fatal respiratory infections occurred only in the anifrolumab 300 mg arm, including pneumonia and COVID-19. Malignancy was an adverse event of special interest because of the potential in rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. In the anifrolumab controlled safety database malignancies, excluding non-melanoma skin cancer, were balanced. Safety information was also assessed for 150 mg and 1000 mg dosing regimens used in studies 05 and 1013, respectively. One case of anaphylaxis was reported in a subject receiving the 150 mg dose, warranting a contraindication in patients with a history of anaphylaxis with anifrolumab. The potential safety risks can be adequately managed via appropriate product labeling.

In summary, the overall benefit risk profile is favorable, and the Division recommended action for this application is Approval, with appropriate labeling. This recommendation also considers the discussion and input from the FDA Medical Policy and Program Review Council on January 22, 2021.

Post-marketing required studies will include a pregnancy registry, additional pregnancy study, a lactation study, and a PREA study in pediatric patients with SLE 5 years of age and older. The OPQ review team also recommended a post-marketing commitment for the implementation of (b) (4) anifrolumab drug product.

If approved, anifrolumab, a first-in-class biologic with a unique mechanism of action, will provide a new treatment option for patients with SLE.

15. Office Director (Signatory authority) Comments

I concur with the recommendation of the Division of Rheumatology and Transplant Medicine to approve anifrolumab-fnia for the treatment of adults with moderate to severe systemic lupus erythematosus (SLE) who are receiving standard therapy. Anifrolumab is a first-in-class type I interferon (IFN) receptor antagonist and has been shown to neutralize the type I IFN gene signature in patients with a high baseline gene signature. Approval of anifrolumab will provide another therapeutic option for patients with this serious and life-threatening disease. The recommended dose is 300 mg, administered IV every 4 weeks.

The efficacy of anifrolumab was evaluated in three 52-week treatment period, multicenter, randomized placebo-controlled trials. Taken together, these studies demonstrate that anifrolumab confers clinically meaningful benefit relative to placebo as assessed by the composite endpoints of SRI-4 and BICLA. Efficacy was maintained throughout the 52 week treatment period. Additionally, evidence for reduction in the use of oral corticosteroids in all three trials, and in the reduction of SLE flares in one trial was also provided. The efficacy of anifrolumab has not been evaluated in patients with severe active lupus nephritis or in severe active central nervous system lupus.

The safety of anifrolumab was assessed in the three trials over the 52-week treatment period and compared to placebo. Overall, the safety profile of anifrolumab was similar to that of placebo, with the exception of certain infections, notably herpes zoster, and infusion-related reactions. Product labeling will adequately convey the drug's risks.

Postmarketing studies will be required to assess the safety and pharmacokinetics of anifrolumab when used with standard therapy in pediatric SLE patients ages 5 to 17 years, to assess adverse pregnancy outcomes and adverse effects on exposed infants, and to measure the presence of the drug in human breast milk.

16. Appendices

16.1. References

[Insert text here]

16.2. Financial Disclosure

Study CDIA-MEDI-546-1013:

Covered Clinical Study (Name and/or Number): 1013

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>373</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>4</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>6</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Study D3461C00004:

Covered Clinical Study (Name and/or Number): 04

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>537</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>6</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Study D3461C00005:

Covered Clinical Study (Name and/or Number): 05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>539</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>3</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>14</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

16.3.1. Excipients

The anifrolumab drug product is provided as a sterile liquid formulation (300 mg anifrolumab per vial, nominal, in 2.0 mL) intended for IV administration. The dosing regimen consists of one 300 mg anifrolumab IV infusion Q4W. The composition of the anifrolumab drug product includes 150 mg/ml anifrolumab, (b) (4) mM L-histidine, (b) (4) mM L-histidine hydrochloride monohydrate, (b) (4) mM L-lysine (b) (4) hydrochloride, (b) (4) mM trehalose dihydrate, and (b) (4) % polysorbate 80, and approximately (b) (4) M water for injection. All excipients meet the quality standards from JP (Japanese Pharmacopeia), NF (National Formulary), Ph. Eur. (European Pharmacopoeia) and/or USP (United States Pharmacopeia). There are no novel excipients for the IV route of administration and there are no nonclinical safety concerns with the levels of these excipients.

16.3.2. Impurities

Among product-related impurities, the levels (b) (4) for clinical and commercial batches were detected up to (b) (4) % and (b) (4) %, respectively. Since drug product batches used in nonclinical IV toxicity studies contained up to (b) (4) % (b) (4) s and (b) (4) % (b) (4) and a minimal 28-fold AUC-based safety margin for anifrolumab for the proposed MRHD of 300 mg Q4W was estimated, the (b) (4) are considered qualified from the nonclinical perspective and of minimal safety risk.

Among process-related impurities, (b) (4) was detected in drug substance as < (b) (4) µIU/mg (b) (4)

Other potential impurities (b) (4) were identified (b) (4)

The calculated maximum (max.) human exposures of these impurities and estimated acceptable daily intake (ADI) are shown below.

Table 71. Calculated maximum human exposure of process-related impurities in drug substance for the MRHD of 300 mg anifrolumab/50 kg/28 days

Impurities	Level in conditioned medium before clearance (µg/mL)	LOD or estimated conc. after clearance (µg/mL)	Max. human exposure (µg/dose)	Max. human exposure (µg/day) ^e	Estimated ADI (µg/day) ^h	Fold ⁱ
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The extractables and leachables studies were submitted and reviewed under the BLA application. These studies aimed to identify potential leachables of safety concern. Based on the review conducted by Dr. Xiaochun Chen dated 03/31/2021, critical components (b) (4)

(b) (4) were subjected to extractables and leachables studies. No leachables were identified above the threshold of toxicological concern (TTC). (b) (4)

(b) (4) no leachables were identified above the TTC. Also, based on the ongoing stability study for three lots of process validation products, no elemental impurities have been identified with a safety concern. Overall, no nonclinical safety concerns for leachables from the drug product were noted.

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

16.4.1. Summary of Bioanalytical Assays

Anifrolumab concentrations in human serum samples have been measured using a validated electrochemiluminescent (ECL)-based immunoassay. The assay was initially developed and validated by MedImmune and then transferred to (b) (4) and re-validated (Table 72, Table 73, Table 74). All clinical samples were analyzed within the established stability period.

Table 72. Bioanalytical methods for determination of anifrolumab concentrations in human serum

Method	Site	Report No. ^a	LLOQ ng/mL	Validated range ng/mL	Study numbers
ECL immunoassay with MSD					
CT-050158	MedImmune	CTVR-0059	20	20 to 1280	MI-CP180, CD-IA-MEDI-546-1013, CD-IA-MEDI-546-1145, D3461C00002, D3461C00006
ICD 622	(b) (4)	REWL2 and REWL5	20	20 to 1280	D3461C00004, D3461C00005, D3461C00008 D3461C00009

(Source: Table 2 of Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Table 73. Summary of the bioanalytical validation report CTVR-0059

Items	Results
Methodology	ECL assay
Biological matrix	Human serum
Calibration curve range	20 to 1280 ng/mL
Analyte of interest	MEDI-546 (anifrolumab)
Inter-run accuracy (mean)	20 mg/mL (LLOQ): -12.7% 50 mg/mL (LQC): -0.8% 200 mg/mL (MQC): -0.1% 1000 mg/mL (HQC): 1.0% 1280 ng/mL (ULOQ): 0.7%
Inter-run precision	20 mg/mL (LLOQ): 11.9% 50 mg/mL (LQC): 6.3% 200 mg/mL (MQC): 5.1% 1000 mg/mL (HQC): 5.9% 1280 ng/mL (ULOQ): 8.1%
Dilution integrity	Dilution QC: 200 ng/mL (dilution factor: 10, 100, 1000) Accuracy: $\leq 9.2\%$ Precision: $\leq 2.2\%$
Selectivity	10 individual normal human serum Mean bias: $\leq 5.2\%$ Precision $\leq 11.7\%$ 10 SLE patients' serum Mean bias: $\leq 15.8\%$ Precision $\leq 8.3\%$
Short-term or bench-top temperature stability	Demonstrated for up to 20 hours at room temperature
Long-term stability	Demonstrated for 825 days at -80°C
Freeze-thaw stability	Demonstrated for 5 cycles at -80°C
Stock solution stability	Demonstrated for up to 14 days at $5 \pm 3^{\circ}\text{C}$, and 30 days at $-80 \pm 10^{\circ}\text{C}$ or $-20 \pm 5^{\circ}\text{C}$
Processed sample stability	The ECL counts showed a $>50\%$ decrease within the first 10 minutes after addition of MSD read buffer solution. Therefore, the plates should be read within 5 minutes of adding the read buffer.
ISR	$> 67\%$ of samples acceptable

LLOQ: lower limit of quantification; QC: quality control; ULOQ: upper limit of quantification

Table 74. Summary of the bioanalytical validation reports REWL2 and REWL5

Items	Results
Methodology	ECL assay
Biological matrix	Human serum
Calibration curve range	20 to 1280 ng/mL
Analyte of interest	MEDI-546 (anifrolumab)
Inter-run accuracy (mean)	REWL2 20 mg/mL (LLOQ): 2.5% 50 mg/mL (LQC): 3.3% 200 mg/mL (MQC): 2.3% 1000 mg/mL (HQC): 0.4% 1280 ng/mL (ULOQ): -2.3% REWL5 20 mg/mL (LLOQ): 6.3% 50 mg/mL (LQC): 3.3% 200 mg/mL (MQC): -1.9% 1000 mg/mL (HQC): 10.2% 1280 ng/mL (ULOQ): 5.5%
Inter-run precision	REWL2 20 mg/mL (LLOQ): 11.7% 50 mg/mL (LQC): 10.0% 200 mg/mL (MQC): 7.7% 1000 mg/mL (HQC): 13.7% 1280 ng/mL (ULOQ): 15.1% REWL5 20 mg/mL (LLOQ): 1.4% 50 mg/mL (LQC): 2.4% 200 mg/mL (MQC): 4.8% 1000 mg/mL (HQC): 18.5% 1280 ng/mL (ULOQ): 13.4%
Dilution integrity	REWL2 Dilution QC: 2, 20, 200, 505 µg/mL (dilution factor: 10, 100, 400, 1000, 4000) Accuracy: ≤12.4% Precision: ≤4.9% REWL5 Dilution QC: 200 µg/mL (dilution factor: 4000) Accuracy: ≤-1.5% Precision: ≤2.1%
Selectivity	10 SLE patients' serum Mean bias: ≤10.9% Precision ≤1.0%

Short-term or bench-top temperature stability	Referred to Report CTVR-0059
Long-term stability	
Freeze-thaw stability	
Stock solution stability	
Processed sample stability	

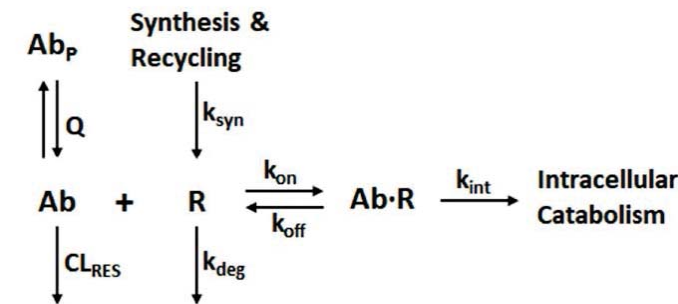
16.4.2. Population Pharmacokinetics

The population PK model was supported by 6049 anifrolumab concentrations from 670 subjects (664 SLE patients and 6 healthy volunteers) from studies 1013, 02, 04, 05 and the IV arm of 06.

16.4.2.1. Structural Model

The pharmacokinetics (PK) of anifrolumab was described by a 2-compartment model with parallel first-order elimination and target mediated drug disposition with Quasi-steady-state (QSS) approximation (Dua et al 2015), where the binding rate of anifrolumab to IFN-αR1 is balanced by the sum of the dissociation and internalization of anifrolumab-IFN-αR1 complex. In QSS approximation, $k_{on} \cdot Ab \cdot R - (k_{int} + k_{off}) \cdot [Ab \cdot C] = 0$; and $k_{ss} = (k_{int} + k_{off}) / k_{on}$.

Figure 20. Anifrolumab PK Model



Ab, anifrolumab concentration in the central compartment; Ab_p, anifrolumab concentration in the peripheral tissue compartment; Ab·R, anifrolumab–IFN-αR1 complex concentration; CL_{RES}, clearance by the reticuloendothelial system but is simplified as CL hereafter; IFN-αR1, type I IFN receptor subunit 1; k_{int}, internalization rate constant; k_{off}, dissociation rate constant; k_{on}, association rate constant; k_{syn}, k_{deg}, endogenous production and degradation rate constant of IFN-αR1; PK, pharmacokinetic; Q, intercompartmental clearance; R, free receptor concentration; R₀, free receptor concentration at baseline. (source: Figure 1 in Population PK Report)

16.4.2.2. Covariate Effect

Demographics, laboratory test results, disease characteristics, SLE-related treatment at baseline were evaluated for their effect on anifrolumab PK, these baseline patients characteristics are summarized in Table 75 to Table 78. Due to the very low prevalence of ADA (6.9% [46/670]), the effect of ADA on anifrolumab CL was not evaluated. A post-hoc analysis was performed; there was no evidence that ADA positive or persistent ADA positive impacted PK.

Table 75. Summary statistics of baseline patient characteristics by study and for the pooled dataset

Parameter	Study					Pooled dataset (N=670)
	06 (N=6)	1013 (N=200)	02 (N=17)	05 (N=267)	04 (N=180)	
Weight (kg)						
n	6	200	17	267	180	670
Median (min, max)	79.20 (64.2, 91.1)	67.69 (43.2, 132.9)	52.60 (45.9, 73.9)	71.00 (42.0, 144.8)	67.85 (43.9, 130.8)	68.6 (42.0, 144.8)
Missing % (n/total)	--	--	--	--	--	--
Body mass index (kg/m ²)						
n	6	200	17	267	180	670
Median (min, max)	26.70 (23.30, 29.70)	25.61 (16.06, 45.73)	21.50 (18.80, 33.70)	26.48 (16.0, 56.56)	25.78 (16.71, 49.84)	25.76 (16.0, 56.56)
Missing % (n/total)	--	--	--	--	--	--
Age (years)						
n	6	200	17	267	180	670
Median (min, max)	29 (21, 43)	39 (19, 65)	36 (20, 61)	40 (18, 69)	44 (18, 69)	41 (18, 69)
Missing % (n/total)	--	--	--	--	--	--
Gender, % (n/total)						
Male	83.3% (5/6)	5.5% (11/200)	5.9% (1/17)	7.9% (21/267)	6.7% (12/180)	7.5% (50/670)
Female	16.7% (1/6)	94.5% (189/200)	94.1% (16/17)	92.1% (246/267)	93.3% (168/180)	92.5% (620/670)
Race, % (n/total)						
White	33.3% (2/6)	42.5% (85/200)	--	69.7% (186/267)	61.1% (110/180)	57.2% (383/670)
Asian	--	4.5% (9/200)	100% (17/17)	6.7% (18/267)	16.7% (30/180)	11.0% (74/670)
Black or African American	50% (3/6)	14.5% (29/200)	--	15.7% (42/267)	9.4% (17/180)	13.6% (91/670)
Other	16.7% (1/6)	38.5% (77/200)	--	7.9% (21/267)	8.3% (15/180)	17.0% (114/670)
Missing	--	--	--	--	4.4% (8/180)	1.2% (8/670)
Ethnicity, % (n/total)						
Hispanic or Latino	16.7% (1/6)	42.5% (85/200)	--	18.35% (49/267)	30% (54/180)	28.2% (189/670)
Not Hispanic or Latino	83.3% (5/6)	57.5% (115/200)	100% (17/17)	81.65% (218/267)	65.55% (118/180)	70.6% (473/670)
Missing	--	--	--	--	4.44% (8/180)	1.2% (8/670)
Parameter	Study					Pooled dataset (N=670)
	06 (N=6)	1013 (N=200)	02 (N=17)	05 (N=267)	04 (N=180)	
Region, % (n/total)						
Asia Pacific	--	4.5% (9/200)	100% (17/17)	6.4% (17/267)	15% (27/180)	10.45% (70/670)
Europe	--	26.5% (53/200)	--	35.95% (96/267)	28.3% (51/180)	29.85% (200/670)
Latin America	--	37.0% (74/200)	--	13.11% (35/267)	19.4% (35/180)	21.49% (144/670)
North America	100% (6/6)	32.0% (64/200)	--	41.95% (112/267)	35.5% (64/180)	36.72% (246/670)
Rest of World	--	--	--	2.62% (7/267)	1.7% (3/180)	1.49% (10/670)
Asia Pacific Region, % (n/total)						
Japan	--	--	100% (17/17)	--	13.3% (24/180)	6.1% (41/670)
South Korea	--	1.5% (3/200)	--	2.25% (6/267)	1.7% (3/180)	1.8% (12/670)

max, maximum; min, minimum; N, number of subjects in the study; n, number of subjects in the analysis.

(source: Table 5 in Population PK Report)

Table 76. Summary statistics of baseline laboratory values by study and for the pooled dataset

Parameter	Study					Pooled dataset (N=670)
	06 (N=6)	1013 (N=200)	02 (N=17)	05 (N=267)	04 (N=180)	
ALT (μkat/L)						
n	6	200	17	267	180	670
Median (min, max)	0.467 (0.40, 0.683)	0.300 (0.0833, 2.117)	0.267 (0.10, 1.717)	0.284 (0.10, 1.252)	0.259 (0.10, 1.169)	0.284 (0.0833, 2.117)
Missing % (n/total)	--	--	--	--	--	--
AST (μkat/L)						
n	6	200	17	267	180	670
Median (min, max)	0.325 (0.283, 0.450)	0.350 (0.150, 1.567)	0.367 (0.167, 1.40)	0.334 (0.0835, 1.186)	0.334 (0.150, 1.236)	0.334 (0.0835, 1.567)
Missing % (n/total)	--	--	--	--	--	--
Total bilirubin (μmol/L)						
n	6	200	17	267	180	670
Median (min, max)	13.68 (5.13, 17.10)	5.13 (1.71, 27.36)	10.26 (5.13, 17.10)	5.00 (3.00, 29.0)	5.00 (3.00, 21.0)	5.13 (1.71, 29.0)
Missing % (n/total)	--	--	--	--	--	--
Albumin (g/L)						
n	6	200	17	267	180	670
Median (min, max)	41.5 (39.0, 49.0)	39.0 (25.0, 51.0)	41.0 (29.0, 45.0)	42.0 (29.0, 53.0)	42.0 (33.0, 54.0)	41.0 (25.0, 54.0)
Missing % (n/total)	--	--	--	--	--	--
Creatinine (μmol/L)						
n	6	200	17	265	180	670
Median (min, max)	87.52 (60.11, 114.04)	61.88 (35.36, 123.76)	49.50 (38.90, 82.21)	62.0 (27.0, 145.0)	62.0 (35.0, 124.0)	62 (27.0, 145)
Missing % (n/total)	--	--	--	--	--	--
GFR (mL/min/1.73 m²)						
n	6	200	17	265	180	670
Median (min, max)	91.78 (80.97, 110.95)	96.78 (43.86, 203.50)	122.88 (61.29, 177.20)	92.47 (33.01, 228.83)	90.77 (39.40, 191.65)	94.08 (33.01, 228.83)
Missing % (n/total)	--	--	--	--	--	--
Parameter	Study					Pooled dataset (N=670)
	06 (N=6)	1013 (N=200)	02 (N=17)	05 (N=267)	04 (N=180)	
Renal function based on estimated GFR, % (n/total)						
Normal	50% (3/6)	60% (120/200)	88.2% (15/17)	55.4% (148/267)	50.6% (91/180)	56.3% (377/670)
Mild decrease in GFR	50% (3/6)	35.5% (71/200)	11.8% (2/17)	38.2% (102/267)	42.2% (76/180)	37.9% (254/670)
Moderate decrease in GFR	--	4.5% (9/200)	--	6.4% (17/267)	7.2% (13/180)	5.8% (39/670)
Severe decrease in GFR	--	--	--	--	--	--
End stage renal disease	--	--	--	--	--	--
Urine protein/creatinine ratio (mg/mmol)						
n	6	200	17	267	180	664
Median (min, max)	--	5.99 (1.58, 238.6)	7.903 (2.258, 47.98)	6.79 (1.47, 380.98)	7.62 (2.03, 322.79)	6.56 (1.47, 380.98)
Missing % (n/total)	100% (6/6)	--	--	--	--	--

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; max, maximum; min, minimum; N, number of subjects in study; n, number of subjects in the analysis.

(source: Table 6 in Population PK Report)

Table 77. Baseline SLE disease characteristics by study and for the pooled dataset

Parameter	Study ^a				Pooled dataset ^b (N=664)
	1013 (N=200)	02 (N=17)	05 (N=267)	04 (N=180)	
SLEDAI-2K					
n	200	17	267	180	664
Median (min, max)	10 (4, 24)	10 (6, 21)	10 (4, 32)	11 (6, 25)	10 (4, 32)
Missing % (n/total)	--	--	--	--	--
Anti-dsDNA, % (n/total)					
Normal	19.0% (38/200) ^b	41.2% (7/17)	53.9% (144/267)	52.2% (94/180)	-- ^c
High	59.0% (118/200) ^b	58.8% (10/17)	46.1% (123/267)	47.8% (86/180)	-- ^c
Missing	22.0% (44/200) ^b	--	--	--	--
C3, % (n/total)					
Normal	62.5% (125/200)	58.8% (10/17)	65.9% (176/267)	60% (108/180)	63.1% (419/664)
Abnormal	37.5% (75/200)	41.2% (7/17)	34.1% (91/267)	40% (72/180)	36.9% (245/664)
C4, % (n/total)					
Normal	75.5% (151/200)	35.3% (6/17)	79% (211/267)	72.8% (131/180)	75.2% (499/664)
Abnormal	24.5% (49/200)	64.7% (11/17)	21% (56/267)	27.2% (49/180)	24.8% (165/664)

^a Only studies conducted in the SLE patient population are included in the pooled analysis set; ie, study 06, conducted in healthy volunteers, is not included.

^b The FARR assay, the most specific method for detecting dsDNA auto antibodies, was used in study 1013.

^c Due to the use of different assays across studies, the statistics were not computed for the pooled dataset.

Anti-dsDNA, anti- double-stranded deoxyribonucleic acid; C3, complement 3; C4, complement 4; max, maximum; min, minimum; N, number of patients in study or population; n, number of patient in analysis; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

(source: Table 7 in Population PK Report)

Table 78. SLE-related treatment at baseline by study and dose group

SLE-related treatment	Study							
	1013 (N=200)		02 (N=17)			05 (N=267)		04 (N=180)
	300 mg	1000 mg	100 mg	300 mg	1000 mg	150 mg	300 mg	300 mg
OCS, % (n/total)								
Yes	79.8%	88.1%	100%	100%	100%	83.7%	82.95%	79.4%
OCS dose (mg)								
Median (min, max)	10 (0, 30)	10 (0, 40)	11.5 (9, 18)	10 (5, 12.5)	16.25 (4, 30)	10 (0, 40)	10 (0, 99)	7.75 (0, 40)
Antimalarials, % (n/total)								
Yes	76.8%	66.3%	--	--	--	81.3%	68.7%	66.1%
Azathioprine, % (n/total)								
Yes	23.2%	20.8%	33.3%	20.0%	16.7%	17.6%	17.6%	16.7%
Methotrexate, % (n/total)								
Yes	19.2%	24.8%	16.7%	40.0%	33.3%	14.3%	11.9%	18.9%
Mycophenolate mofetil mycophenolic acid, % (n/total)								
Yes	11.1%	10.9%	16.7%	20.0%	--	9.9%	17.6%	12.8%
Mizoribine, % (n/total)								
Yes	--	--	--	--	--	--	--	2.2%
NSAIDs, % (n/total)								
Yes	52.5%	51.5%	NC	NC	NC	41.8%	40.9%	38.3%
Angiotensin-converting enzyme (ACE) inhibitors, % (n/total)								
Yes	16.2%	16.8%	NC	NC	NC	16.5%	18.2%	20.6%
HMG-CoA reductase inhibitor, % (n/total)								
Yes	13.1%	9.9%	NC	NC	NC	12.1%	10.8%	7.2%

HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients; NC, not computed; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; SLE, systemic lupus erythematosus.

(source: Table 8 in Population PK Report)

Body weight was identified to be the most statistically significant covariate on anifrolumab clearance (CL), followed by type I IFN gene signature test status on CL; IFN gene signature status was found to have a larger drop in objective functional value on linear CL than R0. In addition to IFN gene signature status on CL, baseline body weight on CL was also found to be a statistically significant covariate. Body weight was also found to be a statistically significant covariate on central volume of distribution (Vc).

To account for the increasing trend in concentrations over time, an empirical sigmoidal time dependent function was added to the linear CL of the final model:

$$CL = \theta_{CL} (\times \theta_{CL,IFN \text{ status } if \text{ type I IFN test low}}) \exp\left(\frac{TMAX \cdot time}{TC50 + time}\right) \left(\frac{Body \text{ weight}}{69.1}\right)^{\theta_{CL,wt}} \eta_{CL},$$

The final PopPK model parameter estimates are given in Table 79.

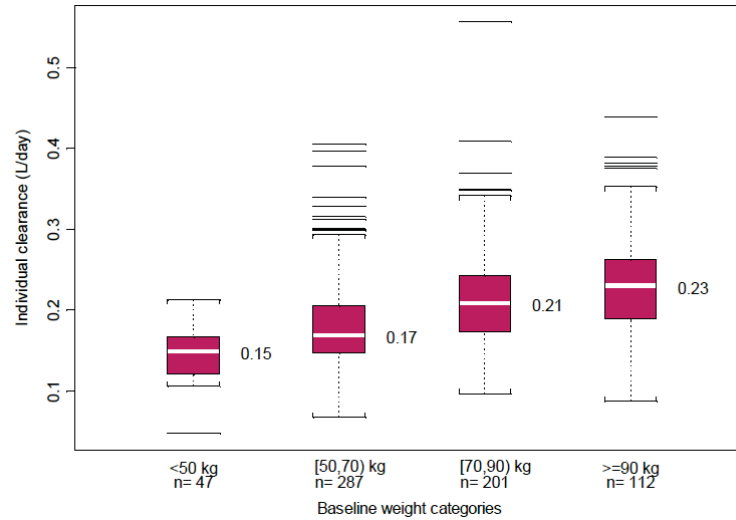
Table 79. Summary of parameters from the final PK model with time-varying linear clearance

Parameters	Point Estimate	Standard Error	%RSE
Systemic clearance (CL) (L/day)	0.189	0.0158	8.36%
Volume of distribution, central (Vc) (L)	3.27	0.0403	1.23%
Intercompartmental clearance (Q) (L/day)	0.924	0.0716	7.75%
Volume of distribution, peripheral (Vp) (L)	3.77	0.104	2.76%
Steady-state constant (Kss) (nmol/L)	0.731	0.0474	6.48%
Baseline IFN-αR1 level (R0) (nmol/L)	0.103	0.00271	2.63%
Internalization rate constant (kint) (day ⁻¹)	77.4 (Fixed)	--	--
Baseline 4-gene signature status on CL	0.739	0.0695	9.40%
Body weight on CL	0.583	0.127	21.78%
Body weight on Vc	0.457	0.0257	5.62%
Maximal possible change in the log of clearance (Tmax)	-0.187	0.00443	2.37%
Time to reach half the maximal change in log clearance (TC50)	216	53.4	24.7%
Variance (CL)	0.278 (CV = 52.72%)	0.0304	5.47%
Variance (Vc)	0.0397 (CV = 19.92%)	0.00191	2.40%
Variance (R0)	0.0681 (CV = 26.09%)	0.00656	4.82%
Variance (Tmax)	0.146 (CV = 38.21%)	0.0168	5.75%
Additive error	18.4	0.121	0.66%
Proportional error	0.319	0.00183	0.57%

CV, coefficient of variation; EST, estimate; %RSE, percent relative standard error (100% × SE/EST); PK, pharmacokinetic.
(source: Table 15 in Population PK Report)

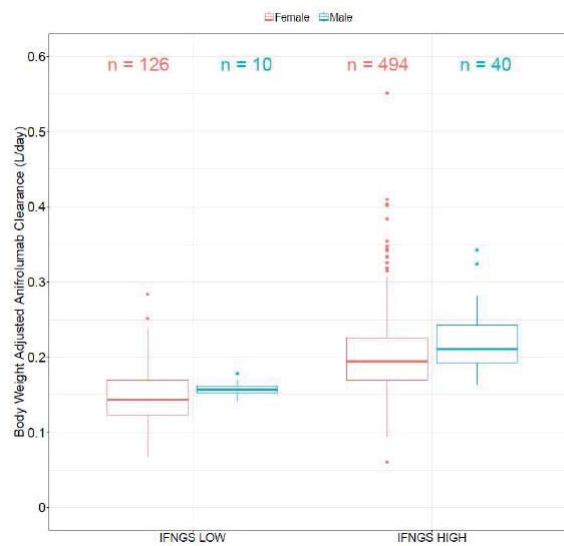
Age, sex, region, ethnicity, race, eGFR, CLcr, AST, ALT, total bilirubin, albumin, ADA status, and background medications (including antimalarials, azathioprine, methotrexate, mycophenolate mofetil, steroids, Mizorbine, NSAIDs, ACE inhibitors, HMG-CoA reductase inhibitors) were not found to be significant on CL. Patients with high UPCR appeared to have higher CL, but the impact was not significant. The exclusion criteria for UPCR was 2 mg/mg in the SLE clinical trials. The covariate effect on clearance are depicted in Figure 21 to Figure 30.

Figure 21. Individual clearance by weight categories



(source: Figure 34 in Population PK Report)

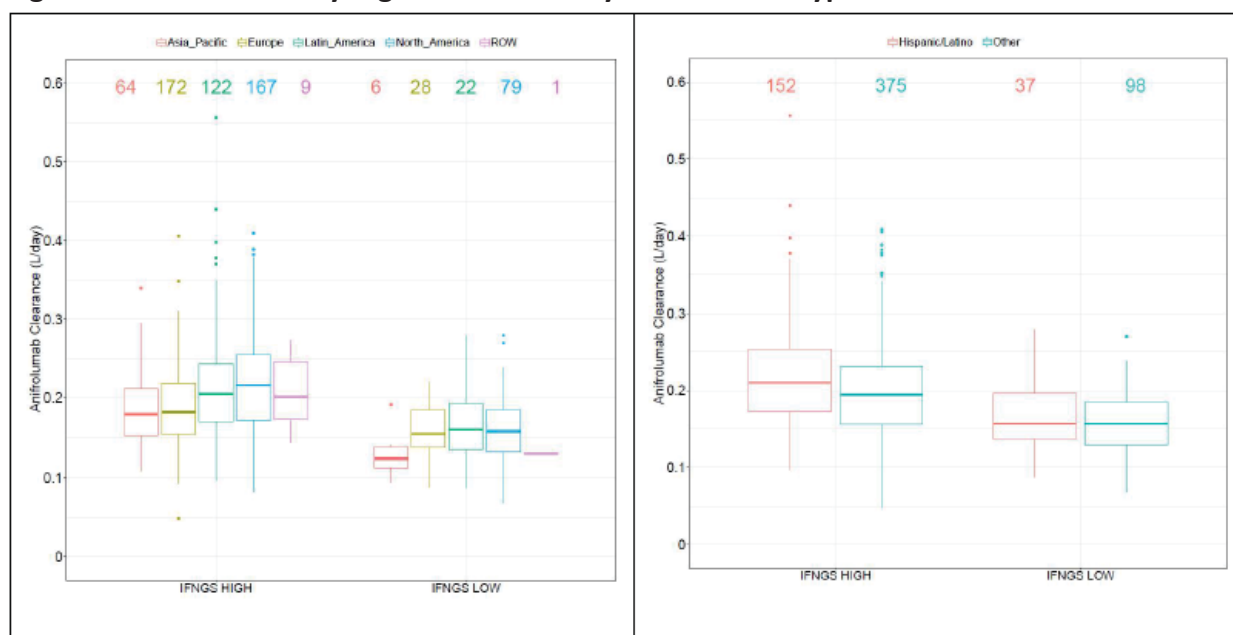
Figure 22. Body weight-adjusted CL stratified by sex and baseline type I IFN status



CL, systemic clearance; IFN, interferon; IFNGS, baseline type I IFN gene signature.

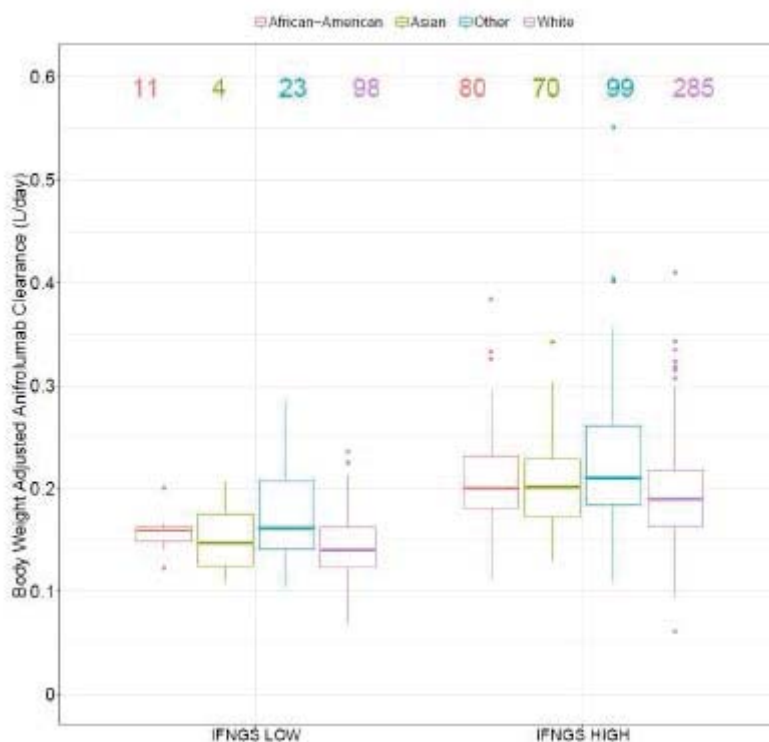
(source: Figure 35 in Population PK Report)

Figure 23. CL stratified by region and ethnicity and baseline type I IFN status



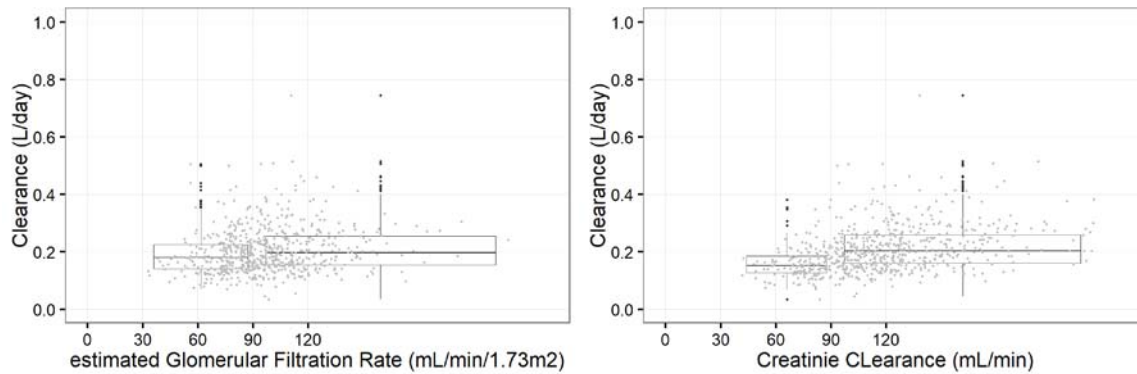
CL, systemic clearance; IFN, interferon; IFNGS, baseline type I IFN gene signature: ROW, Rest of World.
(source: Figure 36 in Population PK Report)

Figure 24. Body weight-adjusted CL stratified by race, by Japanese and South Korean patient populations, and baseline type I IFN status



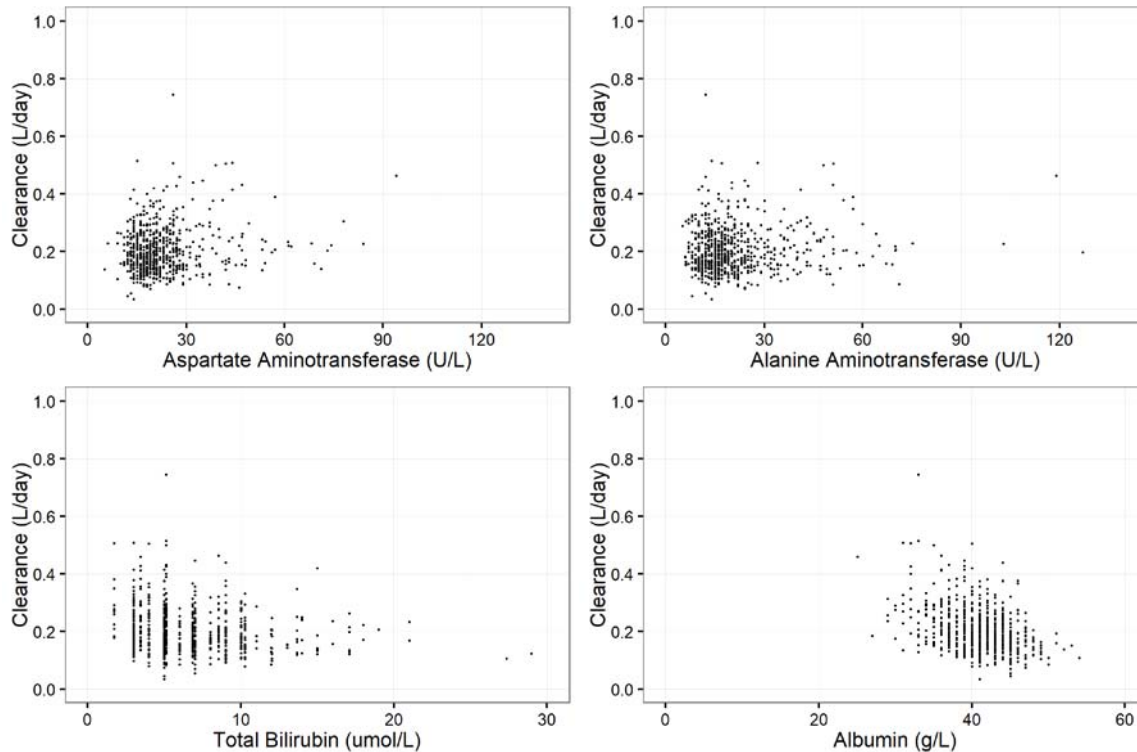
(source: Figure 37 in Population PK Report)

Figure 25. Effect of renal function (eGFR and CLcr) on clearance



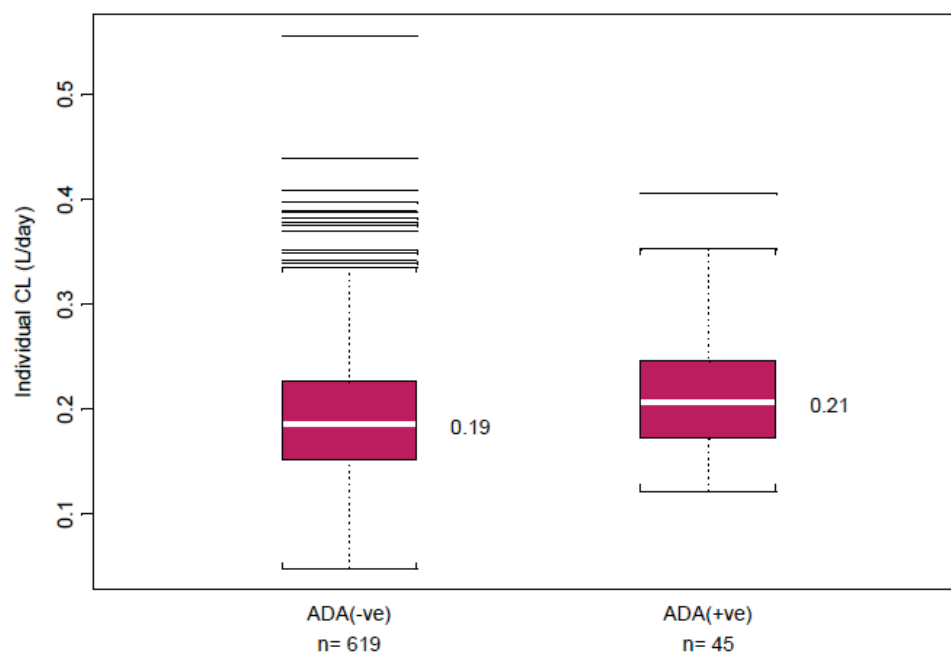
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Figure 26. Effect of hepatic function (AST, ALT, total bilirubin, albumin) on clearance



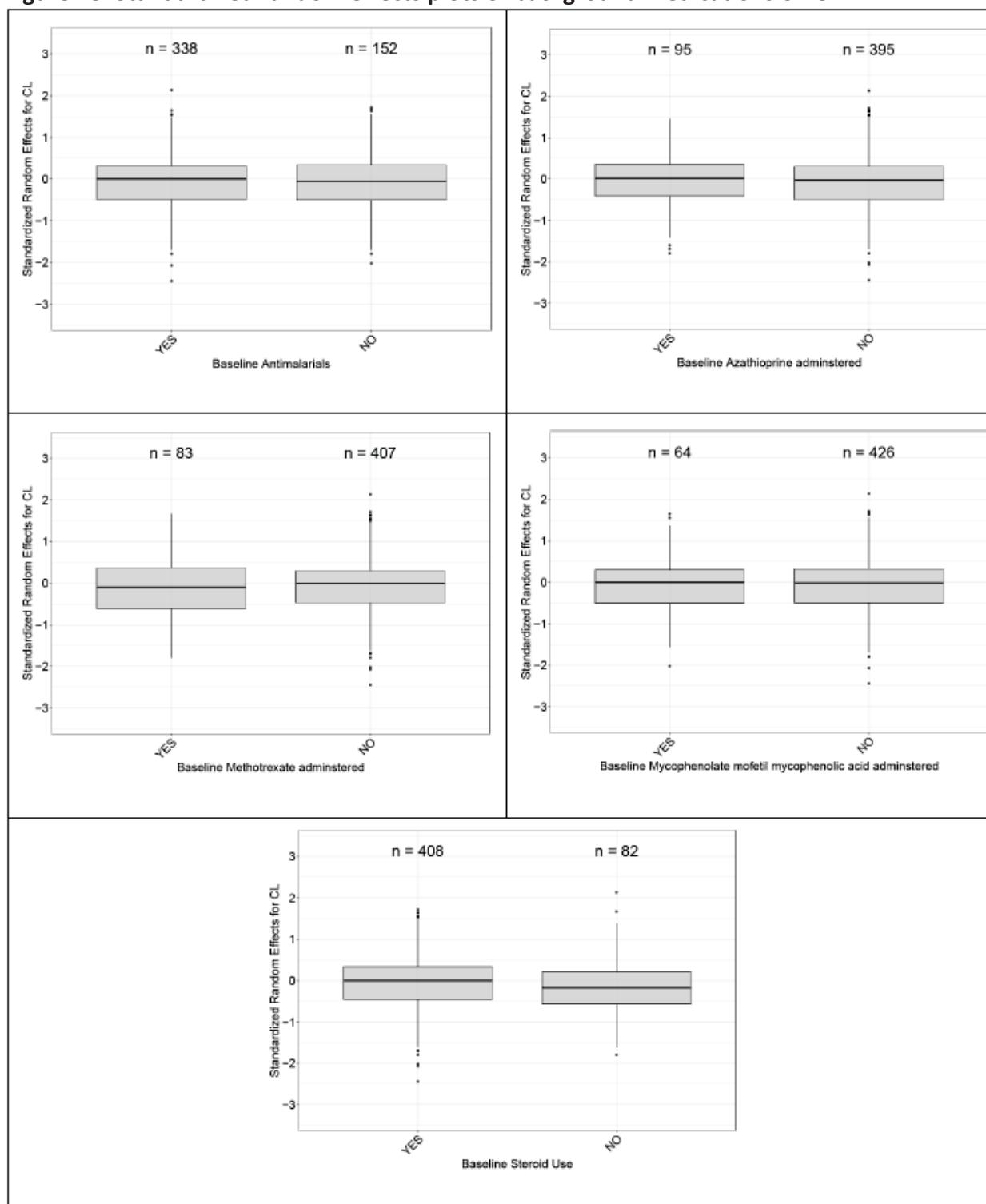
(source: reproduced by the reviewer based on the Applicant's analysis)

Figure 27. Individual CL versus ADA status in SLE patients from studies 1013, 02, 04, and 05
All treatment arms from studies 1013, 02, 04 and 05



ADA, anti-drug antibody; ADA(+ve), ADA positive; ADA(-ve), ADA negative; CL, clearance; SLE, systemic lupus erythematosus.
(source: Figure 38 in Population PK Report)

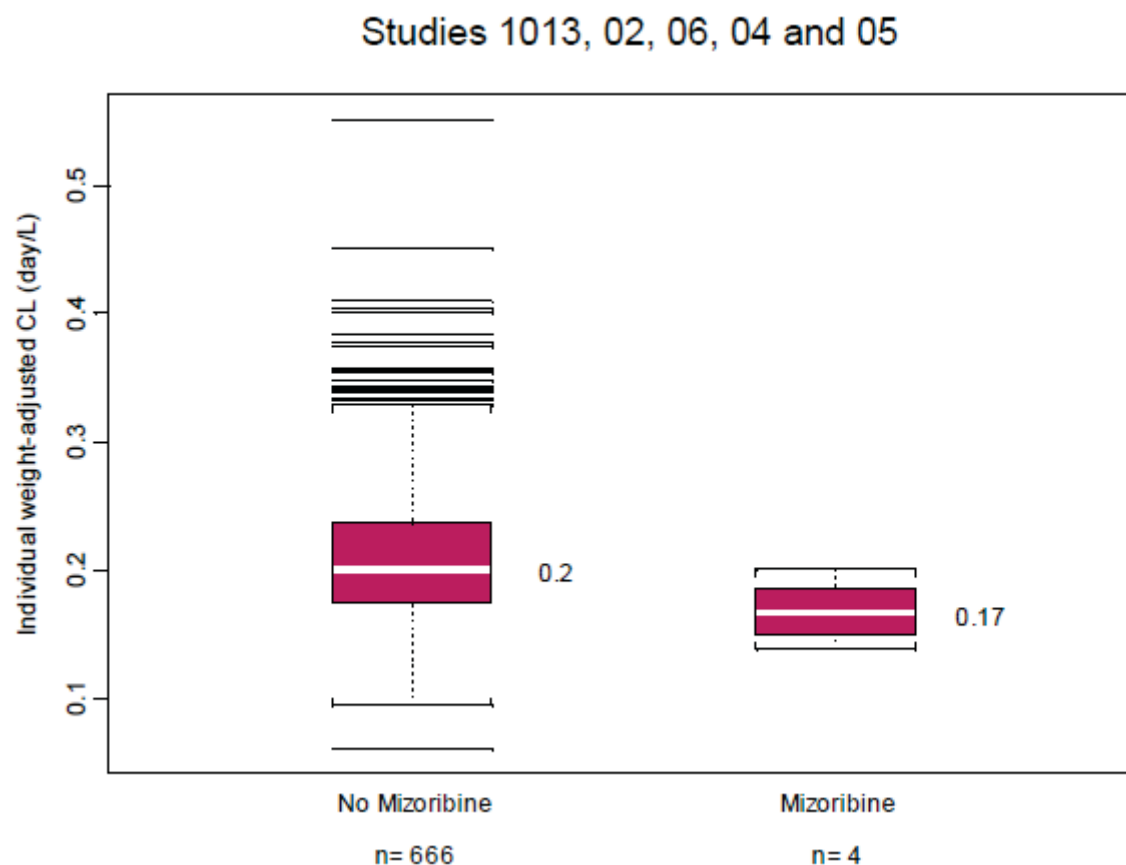
Figure 28. Standardized random effects plots of background medications on CL



CL, clearance.

(source: Figure D1 in Population PK Report)

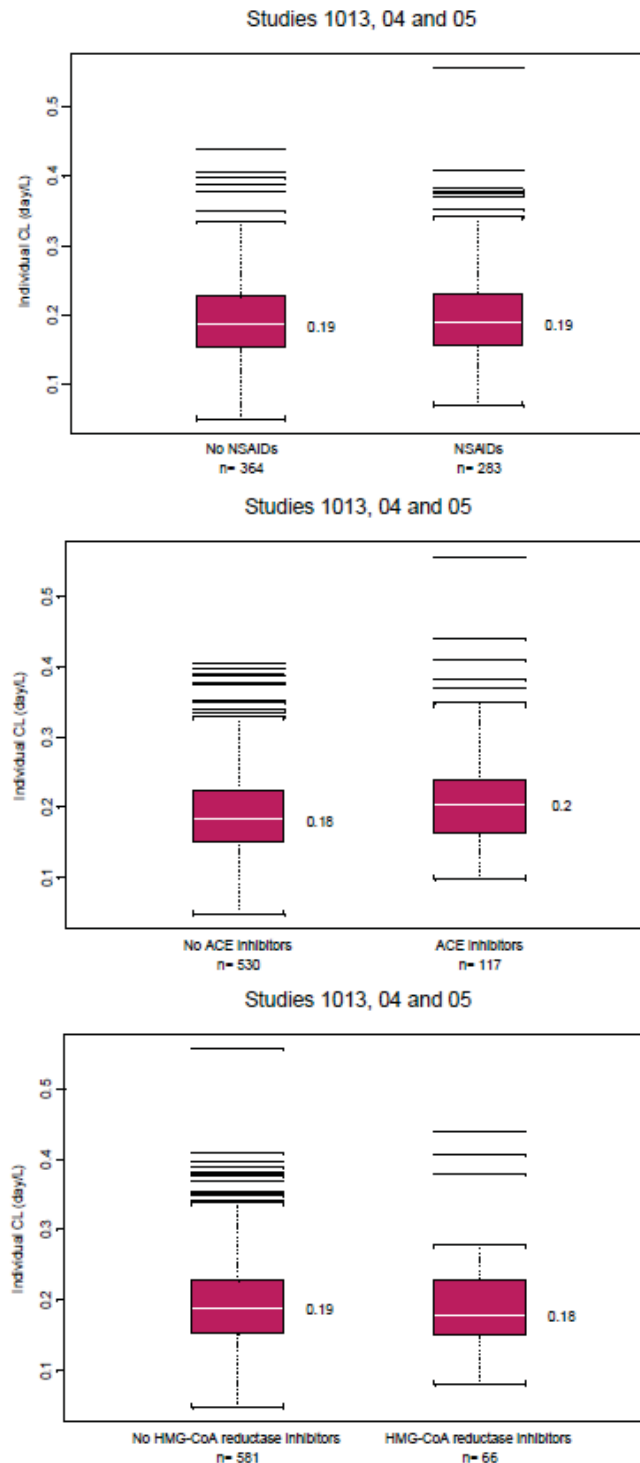
Figure 29. Individual weight-adjusted CL to 69.1 kg versus mizoribine in studies 1013, 02, 04, 05, and 06 (post-hoc analysis)



All 4 patients that received mizoribine in study 04 were from Asia (3 from Japan and 1 from South Korea) where body weights were lower. CL, clearance.

(source: Figure D2 in Population PK Report)

Figure 30. Individual CL versus NSAIDs, ACE inhibitors, and HMG-CoA reductase inhibitors in studies 1013, 04, and 05 (post-hoc analysis)



ACE, angiotensin-converting enzyme; CL, clearance; HMG-CoA, hydroxymethylglutaryl-CoA; NSAIDs, nonsteroidal anti-inflammatory drugs.

(Source: Figure D3 in Population PK Report)

16.4.2.3. Conclusion

The Applicant's population pharmacokinetic analysis is replicable and acceptable. No covariate had clinically meaningful impact on the PK characteristics of anifrolumab based on population PK analysis.

16.4.3. Exposure Response Relationship

The exposure response (ER) analysis for BICLA, SRI(4), annualized flare rate, and herpes zoster incidence rate in the two Phase 3 studies (04 and 05) using ITT population, completers, and completers with high baseline type 1 IFN gene signature were used to support the dose selection along with the Phase 2 dose ranging study 1013.

To evaluate the exposure-response relationship of anifrolumab for efficacy, the pooled phase 3 (studies 04 and 05) population was analyzed using the full exposure-response analysis set. All patients in the full exposure-response analysis set are also referred to as 'all-comers' (or intent-to-treat, ITT) in subsequent sections. Patients who discontinued from treatment were considered non-responders for BICLA, SRI(4), OCS reduction, and CLASI. Thus, in order to examine the exposure-response relationship in the absence of confounding effect with discontinuation, additional analyses of BICLA and SRI(4) were performed in the subgroup of patients who completed treatment for 1) all-comers, and 2) patients who were type I IFN gene signature test high.

Based on the treatment received and anifrolumab exposure quartiles (Q1 to Q4), patients were divided into 6 groups: placebo, 150 mg, 300 mg Q1, 300 mg Q2, 300 mg Q3, and 300 mg Q4. The reviewer's assessment of exposure response relationship of different efficacy endpoints (BICLA, SRI(4), OCS reduction, annualized flare rate) and safety events (herpes zoster) were based on the divides mentioned above in different patient subgroups (all-comer/ITT, completers, completers who were type I IFN gen signature test high).

16.4.3.1. Baseline demographics and disease characteristics

Baseline demographics and disease characteristics for each patient population mentioned above are summarized in Table 80 to Table 82 below with the corresponding anifrolumab exposure (average concentration, C_{ave}).

Table 80. Baseline demographics and disease characteristics in ITT

Group	N	Age (year)	BMI	Weight (kg)
Placebo	366	41 ± 11.9	27.5 ± 6.8	72.8 ± 18.4
150 mg	93	41 ± 12.0	27.3 ± 6.8	73.6 ± 19.5
300 mg	360	43 ± 12.0	27.8 ± 6.9	73.5 ± 19.6
300 mg Q1	100	40 ± 10.8	31.0 ± 7.2	85.3 ± 20.1
300 mg Q2	98	44 ± 12.4	29.5 ± 6.8	77.8 ± 18.0

300 mg Q3	81	43 ± 12.7	26.7 ± 6.0	68.7 ± 16.3
300 mg Q4	77	43 ± 11.8	23.2 ± 4.2	58.8 ± 10.6

Group	N	OCS (mg)	IFN High	SLEDAI	PGA	Cave (ug/mL)
Placebo	366	9.4 ± 8.2	83%	11.5 ± 3.7	1.8 ± 0.4	
150 mg	93	10.3 ± 9.1	82%	11.1 ± 3.5	1.8 ± 0.4	11.8 ± 4.3
300 mg	360	9.5 ± 9.9	83%	11.4 ± 3.8	1.8 ± 0.4	38.7 ± 15.1
300 mg Q1	100	11.4 ± 12.4	93%	12.3 ± 4.3	1.8 ± 0.4	22.6 ± 3.5
300 mg Q2	98	9.2 ± 7.3	80%	11.1 ± 3.9	1.8 ± 0.4	33.9 ± 3.3
300 mg Q3	81	9.3 ± 11.7	77%	11.5 ± 3.7	1.8 ± 0.4	43.6 ± 2.8
300 mg Q4	77	7.9 ± 6.2	79%	10.8 ± 3.0	1.7 ± 0.4	60.7 ± 12.1

BMI, body mass index; OCS, oral corticosteroid; IFN High, IFN gene; SLEDAI, systemic lupus erythematosus disease activity index; PGA, patient global assessment

Four patients without predicted Cave in 300 mg were excluded from all the 300 mg quartiles but included in 300 mg group. All these 4 patients did not complete the clinical trials.

(Source: Reviewer's Analysis)

Table 81. Baseline demographics and disease characteristics in patients who completed treatment

Group	N	Age (year)	BMI	Weight (kg)
Placebo	284	42 ± 12.0	27.5 ± 6.9	72.5 ± 18.7
150 mg	76	42 ± 11.6	27.7 ± 7.0	74.4 ± 20.1
300 mg	302	43 ± 11.7	27.8 ± 6.9	73.3 ± 19.4
300 mg Q1	78	41 ± 10.5	31.0 ± 7.3	85.7 ± 20.2
300 mg Q2	77	45 ± 12.2	30.0 ± 6.8	79.3 ± 17.7
300 mg Q3	73	42 ± 12.6	26.6 ± 6.0	68.2 ± 16.0
300 mg Q4	74	43 ± 11.5	23.2 ± 4.2	59.0 ± 10.7

Group	N	OCS (mg)	INF High	SLEDAI	PGA	Cave (ug/mL)
Placebo	284	9.3 ± 8.3	82%	11.3 ± 3.4	1.8 ± 0.4	
150 mg	76	9.9 ± 8.8	83%	10.9 ± 3.5	1.9 ± 0.4	11.8 ± 4.4
300 mg	302	9.5 ± 10.1	82%	11.3 ± 3.8	1.8 ± 0.4	40.1 ± 15.5
300 mg Q1	78	11.5 ± 12.9	91%	12.1 ± 4.4	1.8 ± 0.4	22.8 ± 3.4
300 mg Q2	77	9.3 ± 7.3	81%	10.8 ± 4.0	1.8 ± 0.4	34.2 ± 3.2
300 mg Q3	73	9.3 ± 11.9	77%	11.4 ± 3.6	1.8 ± 0.4	43.6 ± 2.7
300 mg Q4	74	7.8 ± 6.3	78%	10.7 ± 2.8	1.7 ± 0.4	61 ± 12.2

BMI, body mass index; OCS, oral corticosteroid; INF High, IFN gene; SLEDAI, systemic lupus erythematosus disease activity index; PGA, patient global assessment

(Source: Reviewer's Analysis)

Table 82. Baseline demographics and disease characteristics in Completer with type I IFN gene signature high

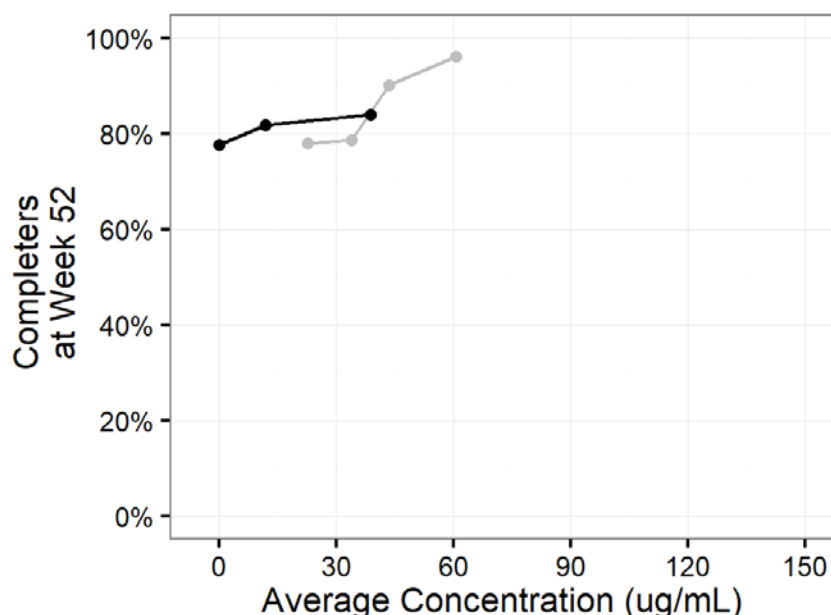
Group	N	Age (year)	BMI	Weight (kg)
Placebo	234	41 ± 11.7	26.9 ± 6.3	71.1 ± 17.6
150 mg	63	41 ± 10.9	26.9 ± 6.0	71.9 ± 17.2
300 mg	247	42 ± 11.6	27.3 ± 6.8	71.8 ± 19.2
300 mg Q1	71	40 ± 10.0	31.2 ± 7.5	85.5 ± 20.4
300 mg Q2	62	44 ± 12.0	28.9 ± 6.1	76.2 ± 16.3
300 mg Q3	56	41 ± 12.6	25.4 ± 5.2	64.7 ± 13.9
300 mg Q4	58	42 ± 11.8	22.8 ± 3.9	57.1 ± 9.5

Group	N	OCSN	SLEDAI	PGA	Cave (ug/mL)
Placebo	234	9.7 ± 8.5	11.5 ± 3.5	1.8 ± 0.4	
150 mg	63	11.1 ± 9.1	11.2 ± 3.6	1.8 ± 0.4	11.2 ± 3.9
300 mg	247	10.3 ± 10.5	11.5 ± 3.9	1.8 ± 0.4	38.9 ± 14.8
300 mg Q1	71	11.7 ± 13.3	12.3 ± 4.4	1.8 ± 0.5	22.7 ± 3.4
300 mg Q2	62	10.0 ± 6.8	11.1 ± 4.2	1.8 ± 0.4	34.0 ± 3.1
300 mg Q3	56	10.6 ± 13.2	11.5 ± 3.6	1.8 ± 0.4	43.2 ± 2.5
300 mg Q4	58	8.4 ± 6.3	10.9 ± 2.9	1.7 ± 0.4	59.8 ± 10.2

BMI, body mass index; OCS, oral corticosteroid; IFN High, IFN gene ;SLEDAI, systemic lupus erythematosus disease activity index; PGA, patient global assessment
(Source: Reviewer's Analysis)

A summary of patients who completed the 52 weeks treatment in study 04 and 05 is depicted in Figure 31.

Figure 31. Percent of patients completed the study by treatment and exposure quartiles



Completer rate by treatment (placebo, 150 mg, 300 mg)

Completer rate by exposure based quartiles of 300 mg

(Source: Reviewer's Analysis)

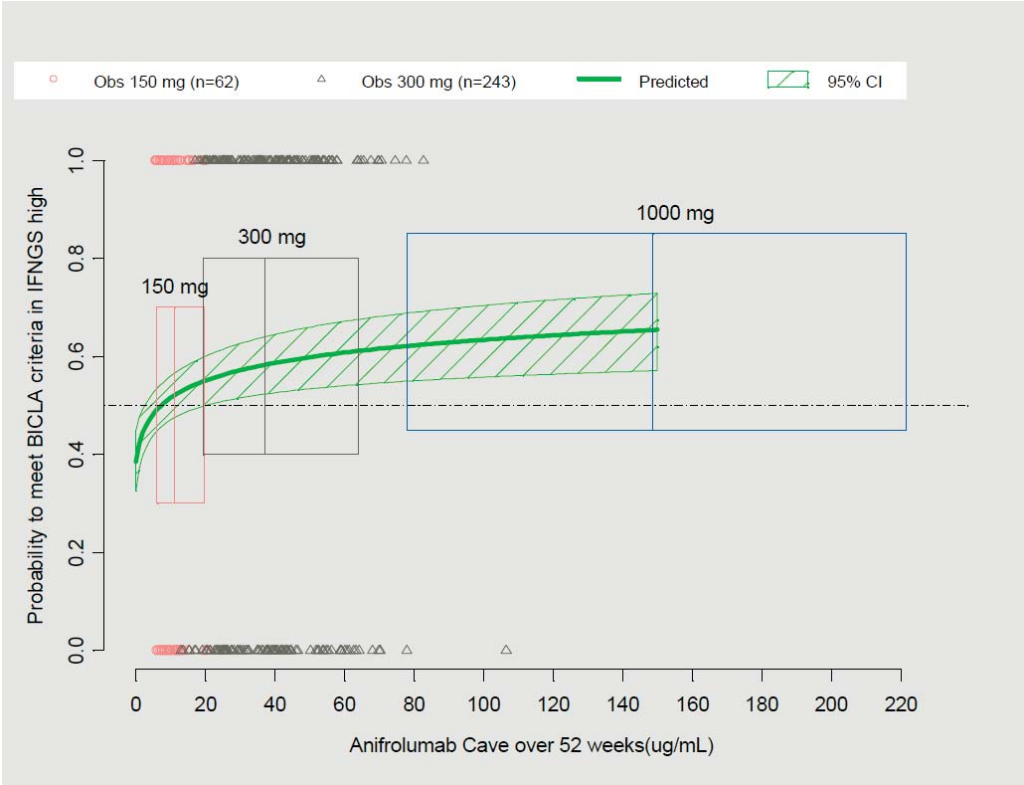
The demographics and baseline disease characteristics were similar across different patient population subgroups in the corresponding treatment group and exposure quartiles, indicating the dropouts were not demographics and baseline disease characteristics dependent. However, patients with lower exposure in 300 mg treatment group tend to have a higher bodyweight at baseline, as bodyweight is positively correlated with anifrolumab clearance. Also, patients with lower exposure in 300 mg treatment group tend to have a higher type I IFN gene signature, SLEDAI, and oral corticosteroids dose at baseline. Due to these unbalanced disease characteristics at baseline, the positive exposure response relationship with in 300 mg treatment group (as shown in grey color in all the following analysis) unnecessarily indicated a positive exposure response relationship below or beyond the observed exposure range in 300 mg Q4W dosing regimen.

16.4.3.2. BICLA

BICLA in High IFN Completer

The Applicant conducted a logistic regression analysis of the BICLA response rate by evaluating the significance of a continuous Cave in type I IFN test high patients who completed treatment (150 mg and 300 mg). The analysis results are depicted in Figure 32, and the parameter estimates are listed in Table 83.

Figure 32. Predicted BICLA response rate at week 52 in patients with type I IFN gene signature test high who completed treatment (full exposure response analysis set)



227 type I IFN test high placebo patients from pooled studies 04 and 05 who completed the treatment were included in the analysis; Cave was set to 0 µg/mL.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; Cave, average serum concentration; CI, confidence interval; IFN, interferon; IFNGS, interferon gene signature; Obs, observed.

(Source: Figure 15 in Clinical Exposure-Response Modeling Report)

Table 83. Logistics regression of BICLA response at week 52 parameter estimates in type I IFN gene signature test high patients who completed treatment (full exposure-response analysis set)

Parameter	Parameter estimates	Standard error	t-value
Intercept, α	-0.47	0.13	-3.49
$\text{Log}(1+C_{\text{ave}})$	0.22	0.05	4.31

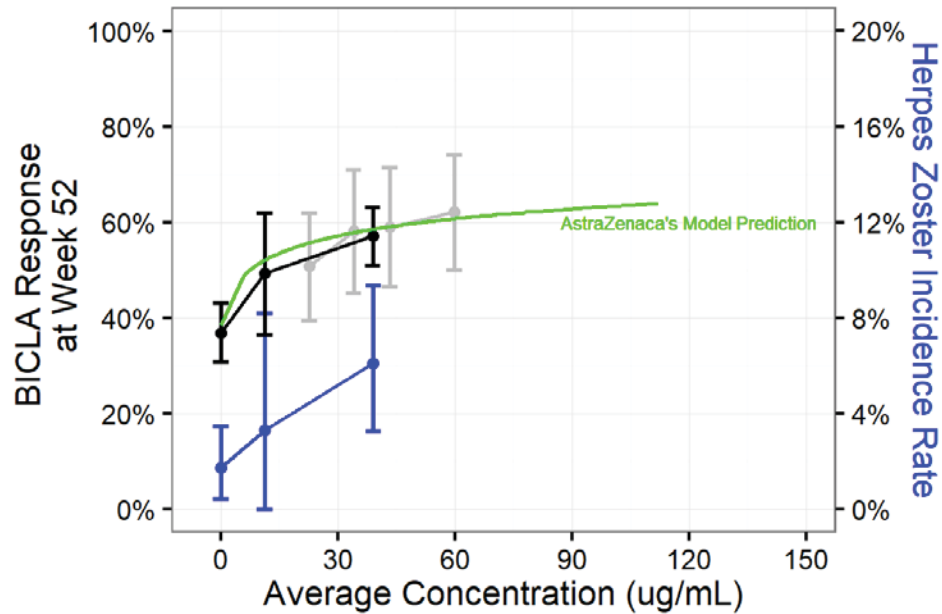
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; C_{ave} , average serum concentration; IFN, interferon.

(source: Table B1 in Clinical Exposure-Response Modeling Report)

Reviewer's analysis

The reviewer reproduced the Applicant's modeling results and compared with the corresponding observations in Phase 3 studies 04 and 05. The comparison is depicted in Figure 33 with exposure response relationship for the herpes zoster incidence rate in patients with type I IFN gene signature test high who completed treatment.

Figure 33. Reviewer's assessment of exposure response (BICLA) in patients with type I IFN gene signature test high who completed treatment



Exposure response for BICLA by treatment (placebo, 150 mg, 300 mg)

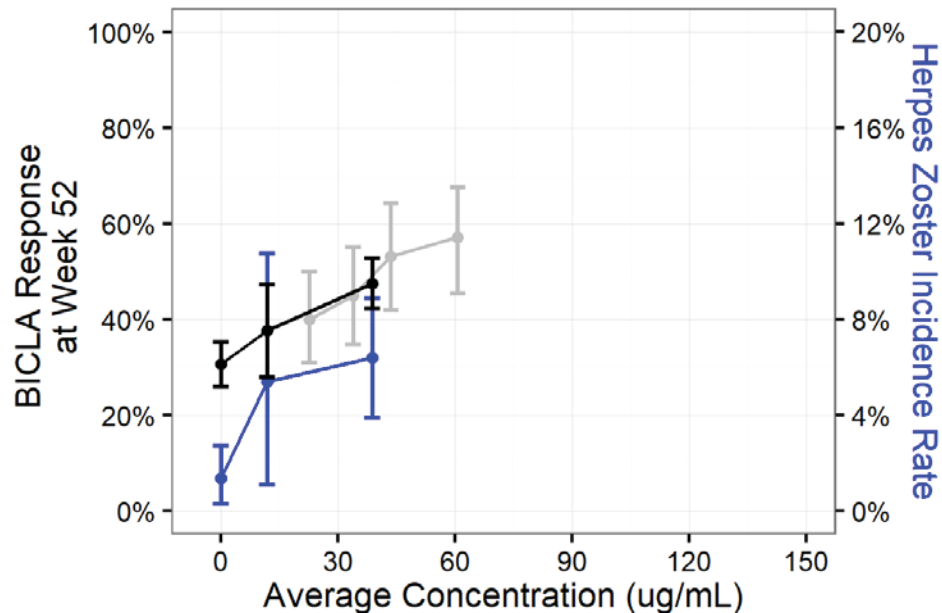
Exposure response for BICLA by exposure based quartiles of 300 mg

Exposure response for herpes zoster

(source: reviewer's analysis)

The Applicant did not perform an ER analysis for BICLA in ITT or completers, the following figure represent the analysis depicted in Figure 34 and Figure 35.

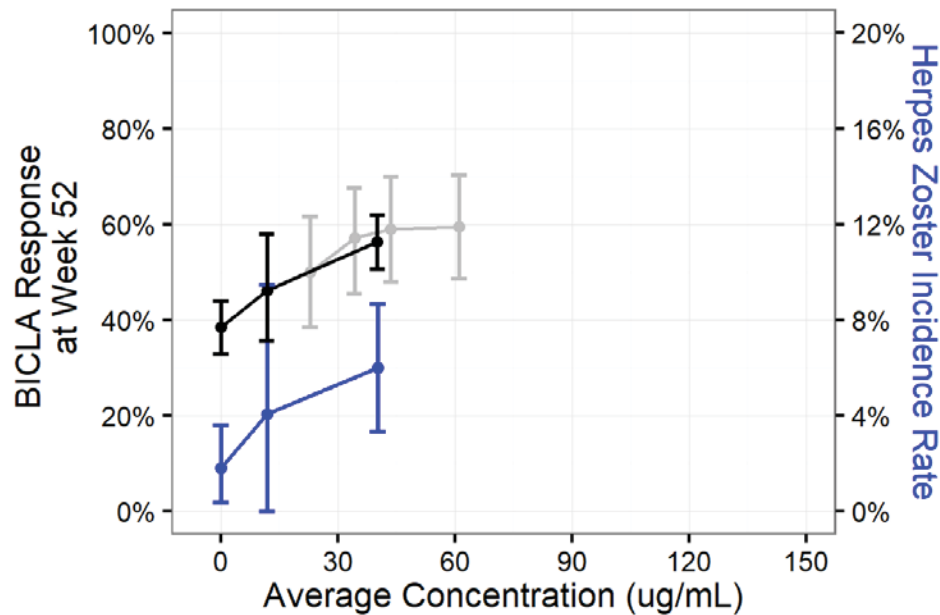
Figure 34. Reviewer's assessment of exposure response (BICLA) in all the patients



Exposure response for BICLA by treatment (placebo, 150 mg, 300 mg)

Exposure response for BICLA by exposure-based quartiles of 300 mg
Exposure response for herpes zoster
(source: reviewer's analysis)

Figure 35. Reviewer's assessment of exposure response (BICLA) in all the patients who completed treatment



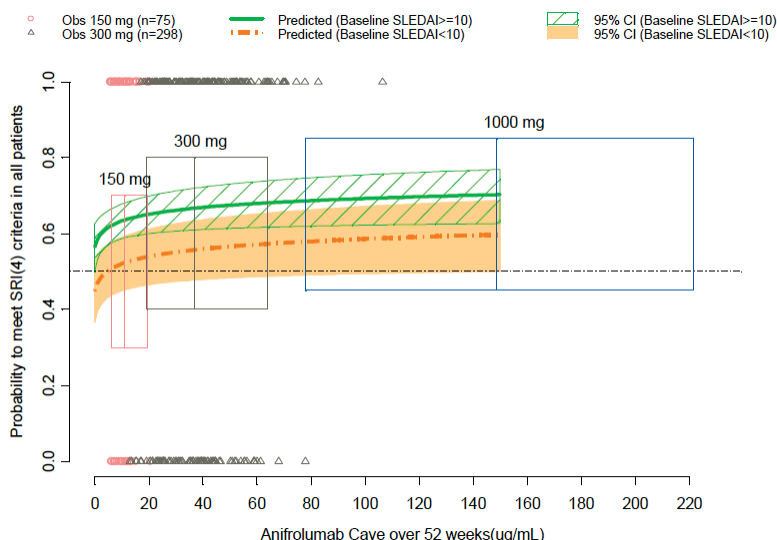
Exposure response for BICLA by treatment (placebo, 150 mg, 300 mg)
Exposure response for BICLA by exposure based quartiles of 300 mg
Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)
(source: reviewer's analysis)

16.4.3.3. SLE Responder Index

SRI(4) Completer

Similarly, the ER relationship was evaluated for the other efficacy endpoint SRI(4) using logistic regression. The analysis results are depicted in Figure 36, and the parameter estimates are listed in Table 84.

Figure 36. Predicted SRI(4) response rate at week 52 in patients who completed treatment (full exposure-response analysis set)



276 placebo patients from pooled studies 04 and 05 that completed the treatment were included in the analysis; C_{ave} was set to 0 $\mu\text{g/mL}$.

C_{ave} , average serum concentration; CI, confidence interval; IFN, interferon; IFNGS, interferon gene signature; Obs, observed; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index ≥ 4 .

(source: Figure 22 in Clinical Exposure-Response Modeling Report)

Table 84. Logistics regression of SRI(4) response at week 52 parameter estimates in all patients who completed treatment (full exposure-response analysis set)

Parameter	Parameter estimates	Standard error	t-value
Intercept, α	-0.21	0.17	-1.22
$\text{Log}(1+C_{ave})$	0.12	0.05	2.61
Baseline SLEDAI-2K (≥ 10 points)	-0.47	0.17	2.69

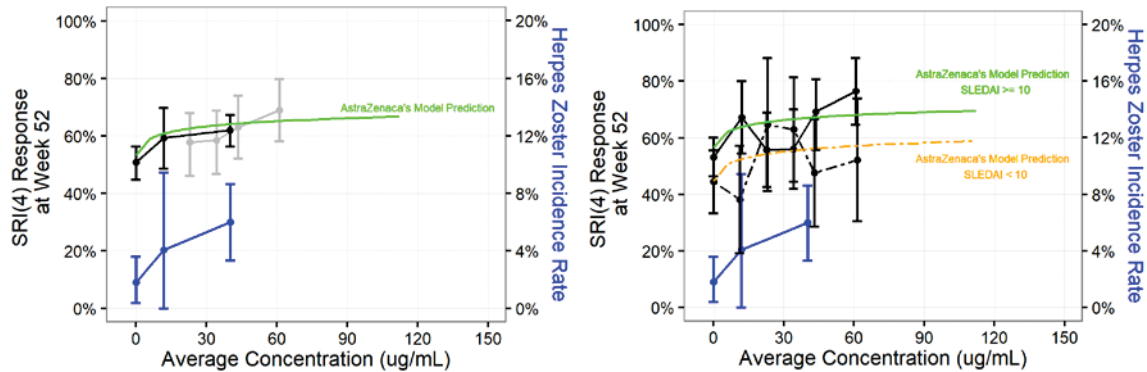
C_{ave} , average serum concentration; IFN, interferon; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index ≥ 4 .

(source: Table B2 in Clinical Exposure-Response Modeling Report)

Reviewer's analysis

The reviewer reproduced the Applicant's modeling results and compared with the corresponding observations in Phase 3 studies 04 and 05. The comparison is depicted in Figure 37 with exposure response relationship for the herpes zoster incidence rate in patients who completed treatment.

Figure 37. Reviewer's assessment of exposure response (SRI(4)) relationship in patients who completed treatment



Exposure response for SRI(4) by treatment (placebo, 150 mg, 300 mg)

Exposure response for SRI(4) by exposure based quartiles of 300 mg

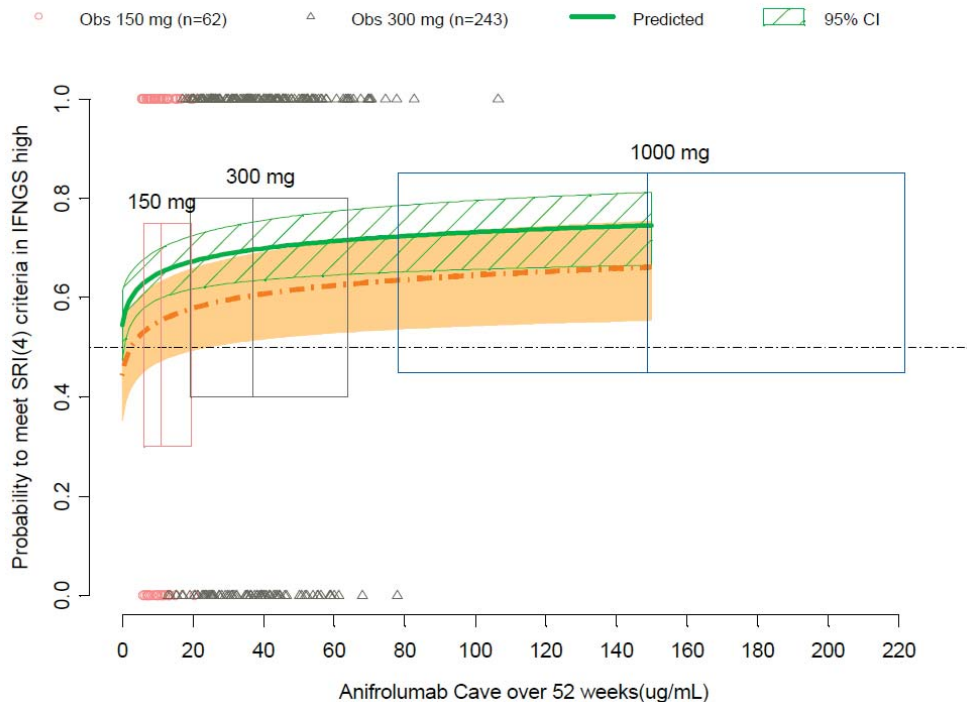
Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

(source: reviewer's analysis)

SRI(4) Completer IFN High

A similar exposure response analysis was conducted by the Applicant for SRI(4). The analysis results are depicted in Figure 38, and the parameter estimates are listed in Table 85.

Figure 38. Predicted SRI(4) response rate at week 52 in patients with type I IFN gene signature test high who completed treatment (full exposure response analysis set)



227 type I IFN test high placebo patients from pooled studies 04 and 05 that completed the treatment were included in the analysis; Cave was set to 0 $\mu\text{g/mL}$.

BLA 761123 Multi-disciplinary Review and Evaluation

Saphnelo (anifrolumab-fnia) for adults with SLE

Cave, average serum concentration; CI, confidence interval; IFN, interferon; IFNGS, interferon gene signature; Obs, observed; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index ≥ 4 .

(Source: Figure 23 in Clinical Exposure-Response Modeling Report)

Table 85. Logistics regression of SRI(4) response at week 52 parameter estimates type I IFN test high patients who completed treatment (full exposure response analysis set)

Parameter	Parameter estimates	Standard error	t-value
Intercept, α	-0.23	0.19	-1.20
Log (1+C _{ave})	0.18	0.05	3.45
Baseline SLEDAI-2K (≥ 10 points)	0.41	0.20	2.09

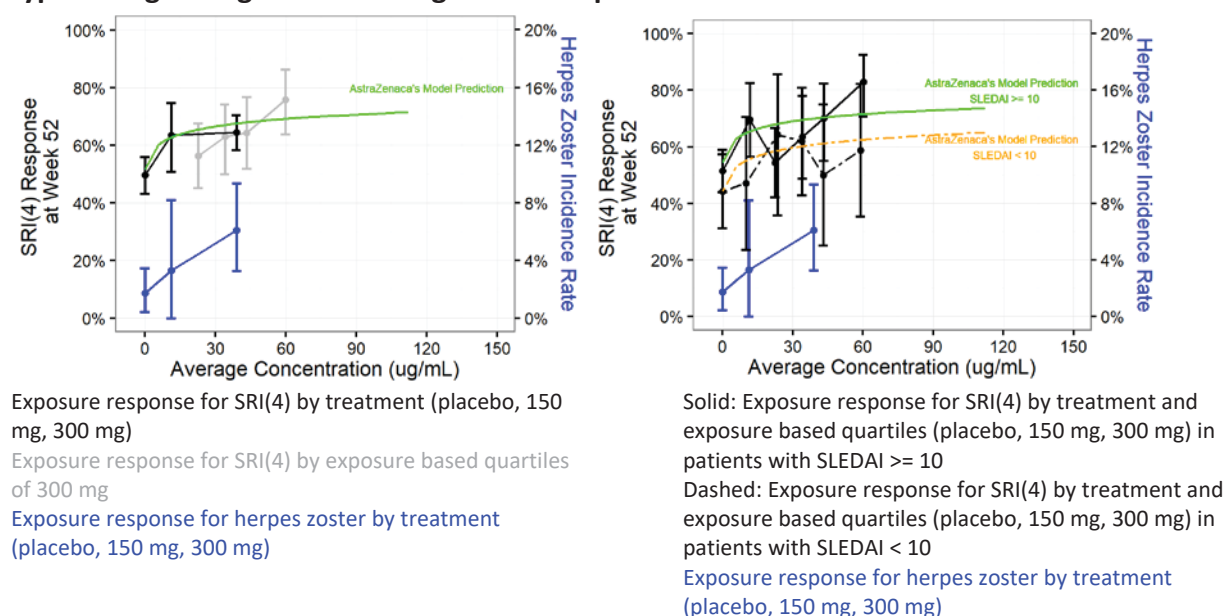
C_{ave}, average serum concentration; IFN, interferon; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index ≥ 4 .

(source: Table B3 in Clinical Exposure-Response Modeling Report)

Reviewer's analysis

The reviewer reproduced the Applicant's modeling results and compared with the corresponding observations in Phase 3 studies 04 and 05. The comparison is depicted in Figure 39 with exposure response relationship for the herpes zoster incidence rate in patients with type I IFN gene signature test high who completed treatment.

Figure 39. Reviewer's assessment of exposure response (SRI(4)) relationship in patients with type I IFN gene signature test high who completed treatment



(source: reviewer's analysis)

In summary, the Applicant's ER analyses are replicable. The findings in SRI(4) and BICLA across different populations support the proposed dosing regimen of 300 mg Q4W as the optimal dosing regimen in patients with SLE.

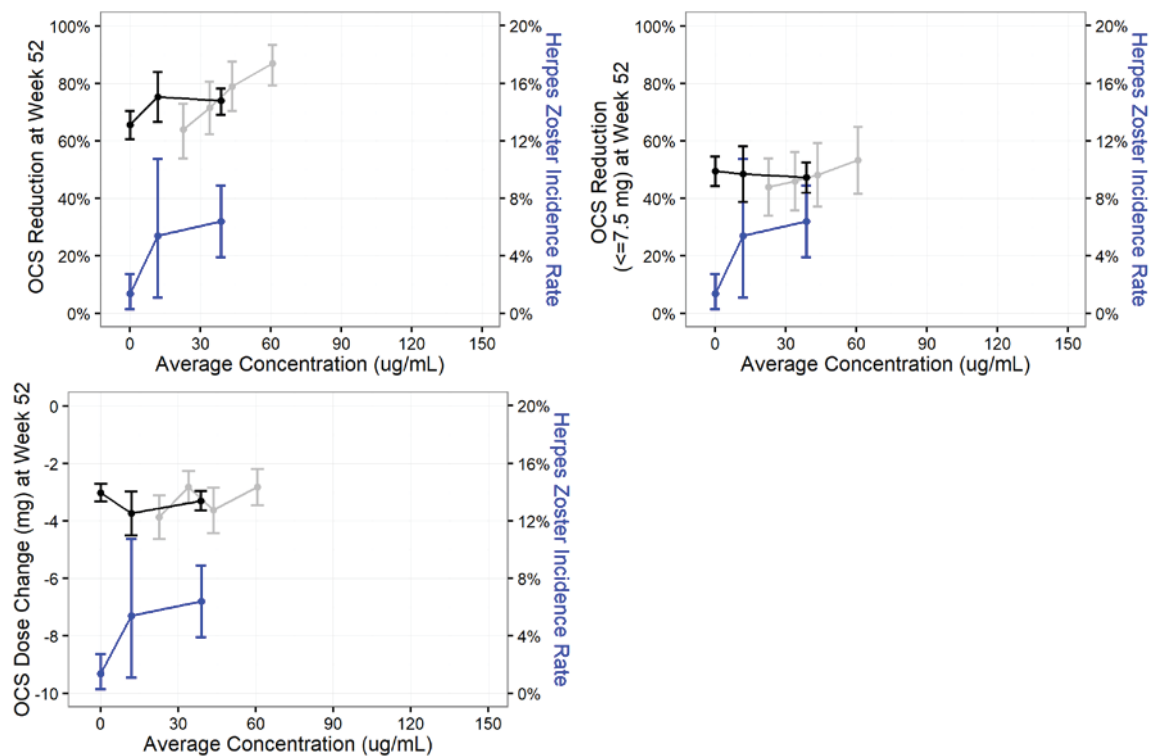
16.4.3.4. OCS Reduction and annualized flare rate

In addition to the efficacy endpoints of SRI(4) and BICLA mentioned above, two additional efficacy endpoints were also evaluated by the reviewer: oral corticosteroids (OCS) dose reduction and annualized flare rate.

Oral corticosteroid

The proportion of patients had OCS dose reduction, OCS dose reduction to ≤ 7.5 mg prednisone equivalent dose, the amount of OCS dose reduction (prednisone equivalent) are depicted in Figure 40 below.

Figure 40. Oral corticosteroid (OCS) reduction



Exposure response for OCS reduction by treatment (placebo, 150 mg, 300 mg)

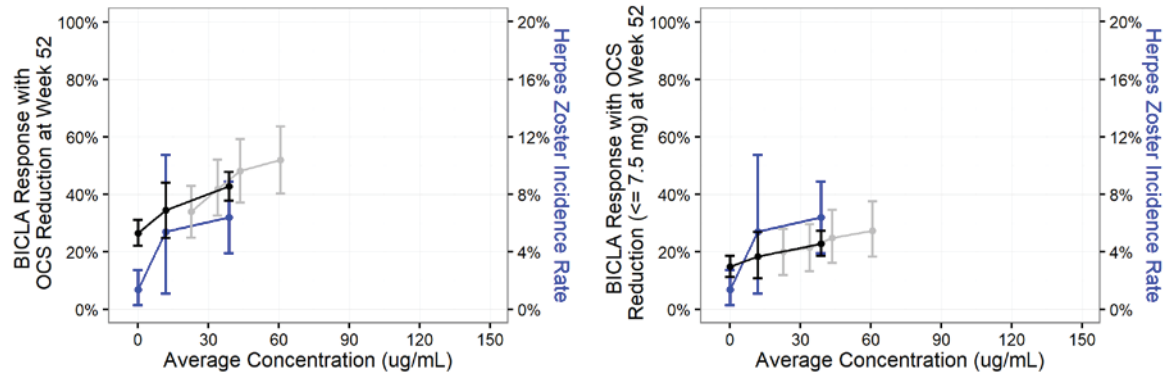
Exposure response for OCS reduction by exposure based quartiles of 300 mg

Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

(source: reviewer's analysis)

The BICLA response and SRI(4) response with OCS reduction or OCS reduction to ≤ 7.5 mg prednisone equivalent dose are depicted in Figure 41 and Figure 42, respectively.

Figure 41. BICLA response with oral corticosteroid reduction



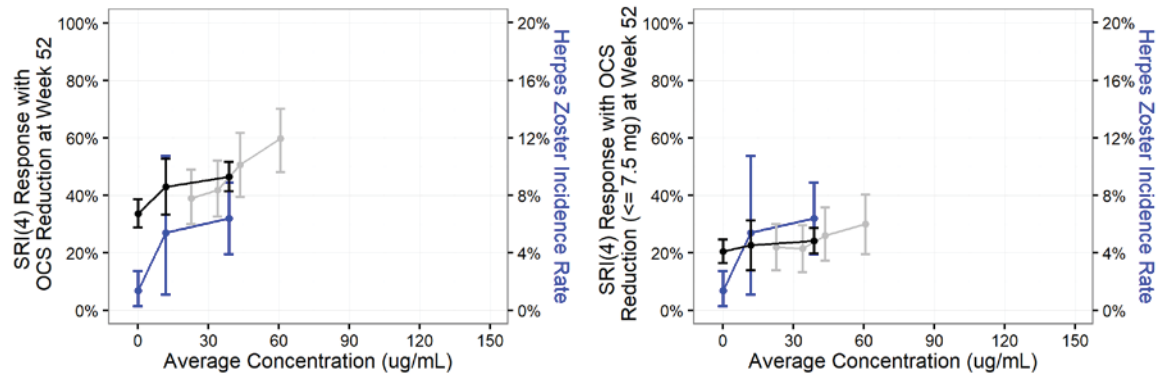
Exposure response for BICLA with OCS reduction at week 52 by treatment (placebo, 150 mg, 300 mg)

Exposure response for BICLA with OCS reduction at week 52 by exposure based quartiles of 300 mg

Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

(source: reviewer's analysis)

Figure 42. SRI(4) response with oral corticosteroid reduction



Exposure response for SRI(4) with OCS reduction by treatment (placebo, 150 mg, 300 mg)

Exposure response for SRI(4) with OCS reduction by exposure based quartiles of 300 mg

Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

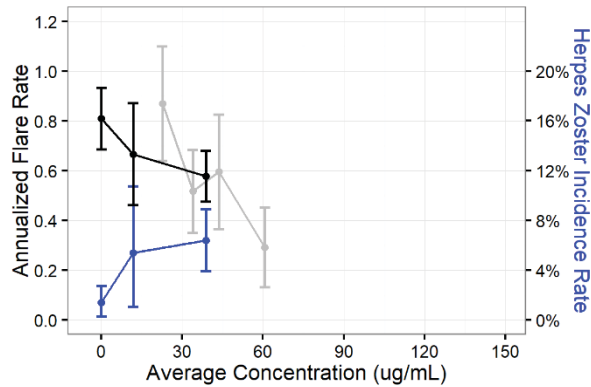
(source: reviewer's analysis)

Annualized flare rate

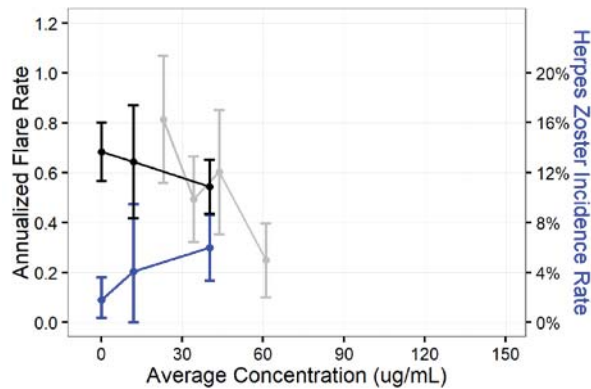
The annualized flare rate in patients are depicted in Figure 43.

Figure 43. Annualized flare rate

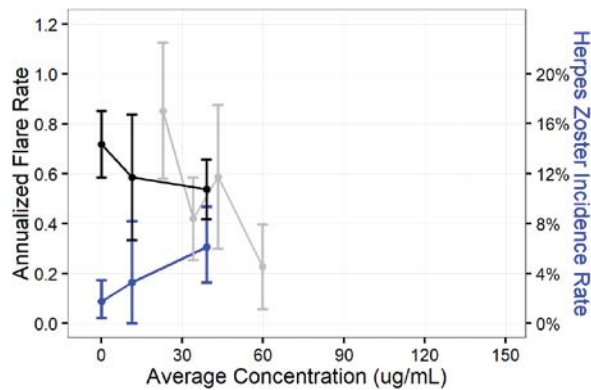
ITT



Completer



IFN High who completed treatment



Exposure response for annual flare rate by treatment (placebo, 150 mg, 300 mg)

Exposure response for annual flare by exposure based quartiles of 300 mg

Exposure response for herpes zoster by treatment (placebo, 150 mg, 300 mg)

(source: reviewer's analysis)

16.5. Additional Clinical Outcome Assessment Analyses

Refer to subsection “Considerations on the Clinical Endpoints” and Figure 13. Pooled Studies 04 and 05: Cumulative distribution function of FACIT-F score change from baseline at Week 52, by treatment arm in Section 8.1.1

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RAJ NAIR
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07/30/2021 01:52:17 PM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA LABELING REVIEW AND EVALUATION

Application Number*: 761123

Supporting Document Number/s: 1, 32, 45, 47

CDER Receipt Date: 7/31/2020, 5/14/2021, 7/14/2021, 7/26/2021

Applicant: AstraZeneca AB, c/o AstraZeneca
Pharmaceuticals, L.P.

Product: Saphnelo (anifrolumab, MEDI-546)

Pharmacologic Class: Type I interferon receptor antagonist

Indication: Systemic lupus erythematosus (SLE)

Therapeutic area: Rheumatology

Clinical Review Division: Division of Rheumatology and Transplant
Medicine (DRTM)

Pharm/Tox Division: Division of Pharm/Tox for Immunology and
Inflammation (DPT-II)

Reviewer: Xiaochun Chen, PhD

Acting Team Leader: Eleni Salicru, PhD

Project Manager: Christine Ford, MS, RPh

Purpose of Review: Other

If "Other": Labeling review

Alternative Assays: None

Reviewer Completion Date: July 28, 2021

Template Version: Sep 11, 2020

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY.....	3
1.1	INTRODUCTION	3
1.3	RECOMMENDATIONS	3
1.3.3	<i>Labeling</i>	3
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	6

1 Executive Summary

1.1 Introduction

AstraZeneca submitted a 351(a) Biologics License Application (BLA) on July 22, 2020, for Saphnelo™ (anifrolumab-fnia, MEDI-546) a proposed type I interferon receptor subunit 1 (IFNAR1) antagonist for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4). This is a review of the nonclinical sections of the Applicant's proposed labeling received on July 31, 2020 (Supporting Document Number [SDN] 1). This review evaluated the Applicant's proposed Indications and Usage section under Highlights of Prescribing Information and the following sections under Full Prescribing Information: Section 8.1 (Pregnancy), Section 8.2 (Lactation), Section 11 (Description; first paragraph only), Section 12.1 (Mechanism of Action), and Section 13 (Nonclinical Toxicology). An integrated review and evaluation of the nonclinical pharmacology and toxicology studies to support the safety of anifrolumab-fnia for approval was completed on March 31, 2021 and is included in the BLA multidisciplinary review and evaluation document (i.e., the unireview).

1.3 Recommendations

1.3.3 Labeling

Provided below are the recommended nonclinical changes to the sections of the Applicant's proposed prescribing information mentioned in the **Introduction**.

The underlined text is recommended for insertion and the ~~strikethrough~~ text is recommended for deletion.

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

(b) (4) SAPHNELO is a type I interferon (IFN) receptor (b) (4) antagonist indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4) (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

Risk Summary

(b) (4) limited (b) (4) human data (b) (4) with SAPHNELO use in pregnant women (b) (4) are insufficient to inform on drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcome. Monoclonal IgG antibodies are (b) (4) known to be actively transported across the placenta as pregnancy progresses; therefore,

anifrolumab-fnia exposure to the fetus may be greater during the third trimester of pregnancy.

In an enhanced pre- and post-natal (b) (4) development study (b) (4) with pregnant cynomolgus monkeys that received intravenous administration of anifrolumab-fnia, there was no evidence of (b) (4) embryotoxicity or fetal malformations with exposures up to approximately (b) (4) 28 times the exposure at the maximum recommended human dose (MRHD) (b) (4) on an Area Under Curve (AUC) basis [(see Data)].

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: In an enhanced pre- and post-natal (b) (4) development study, pregnant cynomolgus monkeys received anifrolumab-fnia (b) (4) at (b) (4) intravenous doses of 30 or 60 mg/kg once every 2 weeks from confirmation of pregnancy at Gestation Day 20, throughout the gestation period, and continuing until 1-month post-partum (approximately Lactation Day 28). There was no evidence of anifrolumab-fnia related maternal toxicity, embryo-fetal toxicity, or post-natal developmental effects. No anifrolumab-fnia related effect on T-cell-dependent antibody response in the infants was noted up to Day 180 after birth. The no observed adverse effect level (NOAEL) for maternal and developmental toxicity was identified as 60 mg/kg (b) (4) approximately (b) (4) 28 times the MRHD (b) (4) on an AUC basis). In the infants, mean serum concentrations of anifrolumab-fnia on Day 30 after birth increased with dose and were approximately 4.2% to 9.7% of the respective maternal concentrations. The anifrolumab-fnia concentrations in the infant serum were up to approximately 22 times the concentrations in the maternal milk, suggesting that anifrolumab-fnia had transferred via the placenta.

8.2 Lactation

Risk Summary

No data are available regarding the presence of (b) (4) SAPHNELO in human milk, the effects on the breastfed child, or the effects on milk production.

Anifrolumab-fnia (b) (4) was detected in the milk of female cynomolgus monkeys administered anifrolumab-fnia (b) (4)

Due to species-species differences in lactation physiology, animal data may not reliably predict drug levels in humans. Maternal IgG is known to be present in human milk. If anifrolumab-fnia is transferred into human milk, the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to anifrolumab-fnia are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for anifrolumab-fnia- (b) (4) and any potential adverse effects on the breast-fed child from anifrolumab-fnia- (b) (4) or from the underlying maternal condition.

11 DESCRIPTION

Anifrolumab-fnia- (b) (4) is a type I interferon (IFN) receptor antagonist (b) (4), immunoglobulin G1 kappa (IgG1k) monoclonal antibody that (b) (4)

(b) (4) is produced in mouse myeloma cells (NS0) by recombinant DNA technology. The molecular weight is approximately 148 kDa.

SAPHNELO (b) (4) (anifrolumab-fnia- (b) (4)) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow, solution for intravenous use. SAPHNELO contains anifrolumab-fnia at a concentration of 150 mg/mL in a single-dose vial.

(b) (4) Each vial contains 300 mg (150 mg/mL) of anifrolumab-fnia (b) (4), L-histidine (3 mg), L-histidine hydrochloride monohydrate (6 mg), L-lysine hydrochloride (18 mg), polysorbate 80 (1 mg), trehalose dihydrate (98 mg), polysorbate 80 (1 mg) and wWater for injection, USP. The pH is 5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Anifrolumab-fnia- (b) (4) is a human IgG1k monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR) (b) (4) with high specificity and affinity. This binding inhibits type I IFN signaling, thereby blocking the biologic activity of type I IFNs. Anifrolumab-fnia- (b) (4) also induces the internalization of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signaling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalized peripheral T-cell subsets, (b) (4)

Type I IFNs play an important role in the pathogenesis of SLE. (b) (4)
(b) (4) Approximately 60-80% adult patients with active SLE express elevated levels of type I IFN inducible genes, (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic and genotoxic potential of anifrolumab-fnia-^{(b) (4)} have not been evaluated. In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown.

Effects on male and female fertility have not been directly evaluated in animal studies. No anifrolumab-fnia-related adverse effects on indirect measures of male or female fertility, based on semen analysis, spermatogenesis staging, menses cycle, organ weights and histopathological findings in the reproductive organs were observed in 9-month repeat-dose toxicity studies in cynomolgus monkeys at doses up to 50 mg/kg intravenous ^{(b) (4)} once weekly (approximately ^{(b) (4)} 58 times the MRHD on an AUC basis).

11 Integrated Summary and Safety Evaluation

Presented above is the Applicant's proposed draft labeling text for the SAPHNELO (anifrolumab-fnia) prescribing information dated July 31, 2020 (SDN 1) and the nonclinical revisions to the Applicant's proposed labeling. The underlined text is recommended for insertion and the ~~strikethrough~~ text is recommended for deletion from the Applicant's proposed text. Below are rationales for the proposed changes for each section.

INDICATIONS AND USAGE

SAPHNELO is a human IgG1κ that binds to IFNAR1. Since this is a first-in-class product targeting IFNAR, the Applicant proposed "type I interferon (IFN) receptor-^{(b) (4)}" as the established pharmacological class (EPC) for anifrolumab. The relevant pharmacology data as listed below were reviewed by Dr. Luqi Pei on 01/18/2011 under IND 101849.

- Anifrolumab has high affinity for IFNAR1 expressed on human and cynomolgus monkey peripheral blood mononuclear cells (PBMCs) with KD of 0.29 and 0.65 nM, respectively (study# RIA546-0002).
- Anifrolumab bound to the sub-domain 3 of human IFNAR1 (265-307) with residues 276-279 identified as the critical epitope (study# RIA546-0004).
- Anifrolumab competitively inhibited the binding of IFN-α-2a to IFNAR in Daudi cells (study# RIA546-0003).
- Anifrolumab inhibited
 - IFN-stimulated response elements (ISRE) activation induced by all the recombinant human IFN-α subtypes (study# RIA546-0006) and SLE sera (study# RIA546-0008),
 - expression of Type-I IFN responsive genes (USP18, HERC5/6, IFIT1/3/5, G1P2/3, MX1/2, OAS1/2, IFI44, IFI44L, Ly6E) from PBMCs by sera of SLE patients (study# RIA546-0005),
 - expression of differentiation markers (CD123 and CD38) and cytokines/chemokines (IL-6, IL-10, MCP-1, MCP-2) from monocytes by leukocyte-IFNs (study# RIA546-0005).

These data suggest that anifrolumab is specifically targeting IFNAR1 and inhibiting type I IFN signaling, thereby blocking the biologic activity of type I IFNs. Our internal EPC

assessment, which included a request by email on 01/12/2021 to Dr. Paul Brown of the Office of New Drug Immediate Office for an evaluation of the EPC text phrase, also determined that,

- It may be best to not include (b) (4) in the EPC so the term focuses on the pharmacology rather than (b) (4).
- (b) (4)
(b) (4)
Since anifrolumab is binding to the IFNAR1 receptor and preventing activity there, it is more appropriate to be classified as an antagonist.

Therefore, “type I IFN receptor antagonist” is recommended as the EPC for SAPHNELO.

8.1 Pregnancy and 8.2 Lactation

General edits were made to Sections 8.1 and 8.2 to remove unnecessary text. The post marketing requirement (PMR) for pregnancy and lactation, including Pregnancy Registry was recommended by the Division of Pediatrics and Maternal Health (DPMH) on 5/24/2021. The Applicant agreed with the recommendations on 07/26/2021 (SDN 47). The language for Pregnancy Exposure Registry was added to Section 8.1 (not shown in this review because it is not relevant to nonclinical labeling text).

For Risk Summary in Section 8.1, the Applicant estimated that the exposures in pregnant monkeys without maternal and developmental toxicity was up to approximately (b) (4) times the exposure at the MRHD on an AUC basis. Since the AUC_{0-14d} for the NOAEL of 60 mg/kg once every 2 weeks was 20900 $\mu\text{g.d/mL}$, and the highest mean AUC_{0-28d} in patients with SLE receiving repeat IV dosing of 300 mg anifrolumab-fnia (once every 4 weeks for 52 weeks) was 1472 $\mu\text{g.d/mL}$ between Weeks 48 to 52 for low Type 1 IFN gene signature subjects, the safety margin was calculated to be 28 ($= 20900 \times 2/1472$). A factor of 2 is applied to match the duration of AUC values before the comparison, i.e., 14 days vs. 28 days.

For Animal Data in Section 8.1, language was added to indicate that there is no anifrolumab-fnia related effect on T-cell-dependent antibody response in the infants up to Day 180 after birth. Additional language was added to indicate the potential of placenta transfer of anifrolumab-fnia based on the detection of anifrolumab-fnia in the serum of neonates up to one month after birth.

For Risk Summary in Section 8.2, additional standard language was added. Although anifrolumab-fnia was detected in the milk of female cynomolgus monkeys, we added that “due to species-species differences in lactation physiology, animal data may not reliably predict drug levels in humans”.

11 DESCRIPTION

Revisions to the first paragraph of Section 11 were made by nonclinical. The term “type I IFN receptor antagonist” was used to be consistent with the recommend EPC text

phrase in the Indications and Usage section under Highlights of Prescribing Information. The description (b) (4) was deleted (b) (4) Molecular weight was added.

Edits in the remaining paragraphs of Section 11 were made by the Office of Biotechnology Products (OBP).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Revisions to Section 12.1 were made to remove any potential promotional language.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Blocking the IFNAR1 pathway is expected to have increased carcinogenic potential. In 2014, the Applicant proposed to address the carcinogenic potential by product labeling and clinical risk management practices without performing additional in vivo animal studies. The agency agreed with their plan on 10/15/2014 under IND 101849 (End of Phase 2 meeting minutes). The Applicant also reiterated the same conclusion regarding carcinogenicity risk assessment in Modules 2.4 and 2.6.6 of the BLA submission.

The Applicant proposed the following language for this section on 7/31/2020 (SDN 1):

“The carcinogenic and genotoxic potential of anifrolumab-xxxx have not been evaluated”.

In a nonclinical information request (IR) dated 05/07/2021 the Applicant was asked to provide appropriate labeling to address the potential carcinogenic risk, as discussed above. The Applicant provided updated language for this section on 5/14/2021 (SDN 32). They proposed to add the following language:

“In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown”.

A request for an evaluation of the proposed labeling for Section 13.1 was made by email on 06/08/2021 to the Executive Carcinogenicity Assessment Committee (Exec CAC). The Exec CAC considered the above language sufficient to reveal carcinogenic potential.

In addition, the Applicant estimated that the exposures in cynomolgus monkeys receiving 9-month repeat dosing without drug-related adverse effects on male or female fertility was up to approximately (b) (4) times the exposure at the MRHD on an AUC basis. Since the AUC_{0-7d} for the NOAEL of 50 mg/kg/week was 21600 µg.d/mL, and the highest mean AUC_{0-28d} in patients with SLE receiving repeat IV dosing of 300 mg anifrolumab-fnia (once every 4 weeks for 52 weeks) was 1472 µg.d/mL between Weeks 48 to 52 for low Type 1 IFN gene signature subjects, the safety margin was calculated

to be around 58 ($= 21600 \times 4 / 1472$). A factor of 4 is applied to match the duration of AUC values before the comparison, i.e., 7 days vs 28 days.

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/s/

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

Application Number*: 761123

Supporting Document Number/s: 1, 13, 21

CDER Receipt Date: 7/31/2020, 1/8/2021, 3/19/2021

Applicant: AstraZeneca AB, c/o AstraZeneca
Pharmaceuticals, L.P.

Product: Saphnelo (anifrolumab, MEDI-546, 01P006)

Pharmacologic Class: Type I interferon receptor antagonist

Indication: Systemic lupus erythematosus (SLE)

Therapeutic area: Rheumatology

Clinical Review Division: Division of Rheumatology and Transplant
Medicine (DRTM)

Pharm/Tox Division: Division of Pharm/Tox for Immunology and
Inflammation (DPT-II)

Reviewer: Xiaochun Chen, PhD

Acting Team Leader: Eleni Salicru, PhD

Project Manager: Christine Ford, MS, RPh

Purpose of Review: Other

If "Other": Safety Assessment of Extractables and
Leachables Studies

Alternative Assays: None

Reviewer Completion Date: March 31, 2021

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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY.....	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
2	DRUG INFORMATION.....	5
2.1	DRUG	5
	Code Name(s): <i>MEDI-546, 01P006</i>	5
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs	5
2.3	DRUG FORMULATION	6
2.4	COMMENTS ON NOVEL EXCIPIENTS	6
2.5	COMMENTS ON EXTRACTABLES AND LEACHABLES STUDIES	6
3	STUDIES SUBMITTED	15
3.1	STUDIES REVIEWED	15
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	15

1 Executive Summary

1.1 Introduction

AstraZeneca submitted a 351(a) Biologics License Application (BLA) on July 22, 2020, for Saphnelo™ (anifrolumab, MEDI-546) a proposed type I interferon receptor subunit 1 (IFNAR1) antagonist for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4) The extractables and leachables study reports were submitted on January 8, 2021 and March 19, 2021.

The anifrolumab Drug Substance (DS) is stored (b) (4)



his review is a nonclinical safety evaluation of potential extractables and leachables for the primary CCSs and in-process materials used in the DS and DP manufacture processes. Elemental analysis for the DP during stability study is also reviewed.

1.2 Brief Discussion of Nonclinical Findings

For the safety evaluation (b) (4)



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(b) (4)

3 Studies Submitted

3.1 Studies Reviewed

1. EHIVE03-1918845568-553 ED 001: MEDI-546 (Anifrolumab) DS Extractables and Leachables—(b) (4) Results Summary
2. EHIVE03-294243812-477 ED 001: Anifrolumab (MEDI-546) DP Extractables and Leachables - (b) (4) Results Summary
3. EHIVE03-294243812-476 ED 001: Anifrolumab (MEDI-546) DP Fill/Finish: In-process Leachable Risk Assessment Report
4. AZDoc0103863: VX-710108-TER: In-Process Extractables and Leachables Risk Assessment for Anifrolumab (MEDI-546)
5. AZDoc0162213: VG-502228: Final Report for the Membrane Extractables and Leachables Report: MEDI-546 (Anifrolumab) (b) (4)
6. EHIVE03-294243812-2118 ED 001: Anifrolumab (MEDI-546) DP - (b) (4) Elemental Impurities and Leachables Testing and Results Summary

11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of potential leachables (b) (4) for DS storage, and the glass vial for the DP, based on data submitted by the sponsor and other available information. The sponsor is seeking approval for the DP at

a dose of 300 mg of anifrolumab Q4W via IV infusion. The sponsor established the TTC of (b) (4) µg/day for nonmetals with genotoxic potential based on ICH M7 (2018). This correlated to an AET of (b) (4) µg/mL for the dose volume of 2 mL/day. For metals, the ICH Q3D (2014) was followed for safety assessment.

Critical components from these CCSs, identified as the (b) (4) and the glass vial and stopper, were subjected to extractables and leachables studies. No leachables were identified above the TTC. For in-process materials used during the manufacture processes, no leachables were identified above the TTC. Also, based on the ongoing stability study for 3 lots of process validation products, no elemental impurities have been identified with safety concern.

Overall, there appear to be no nonclinical safety concerns for leachables from the DP.

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