Protocol ITN092AI

Combining a CD40L-Binding Protein (VIB4920) with a TNF-α Inhibitor for the Treatment of Inadequately Controlled Rheumatoid Arthritis

CD40L antagonism in RA

Version 7.0 (June 20, 2025)

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INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR SIGNATURE PAGE	
Protocol Number: ITN092AI	**Version/Date: 7.0 / June 20, 2025**
Title: Combining a CD40L-Binding Protein (VIB4920) with a TNF-α Inhibitor for the Treatment of Inadequately Controlled Rheumatoid Arthritis	
IND Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
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I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference for Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID. *[*The site Principal Investigator should print, sign, and date at the indicated location below. A written signature/date is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).]* _____ **Site Principal Investigator (Print)** _____ _____ **Site Principal Investigator (Signature)** **Date**	

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TABLE OF CONTENTS

INVESTIGATOR SIGNATURE PAGE **3**

TABLE OF CONTENTS **4**

PROTOCOL SYNOPSIS **10**

GLOSSARY OF TERMS AND ABBREVIATIONS **20**

1. BACKGROUND AND RATIONALE **23**

1.1 BACKGROUND AND SCIENTIFIC RATIONALE 23

1.2 RATIONALE FOR SELECTION OF THE INVESTIGATIONAL PRODUCT AND USE WITH A TNF INHIBITOR 24

1.2.1 Rationale for the Dose of the Investigational Product 26

1.3 NON-CLINICAL EXPERIENCE 26

1.3.1 Non-clinical Studies 26

1.4 CLINICAL STUDIES 28

1.4.1 Safety Data for VIB4920 28

1.4.2 Clinical Efficacy Data for VIB4920 31

2. STUDY HYPOTHESES AND OBJECTIVES **32**

2.1 HYPOTHESES 32

2.2 PRIMARY OBJECTIVE 32

2.3 SECONDARY OBJECTIVES 33

2.4 EXPLORATORY OBJECTIVES 33

3. STUDY DESIGN **34**

3.1 DESCRIPTION OF THE STUDY DESIGN 34

3.2 DEFINITION OF DISEASE ACTIVITY MEASURES 36

3.2.1 Simplified Disease Activity Index (SDAI) 36

3.2.2 Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP) 37

3.2.3 ACR20, ACR50, and ACR70 response 37

3.2.4 Routine Assessment of Patient Index Data 3 (RAPID3) 38

3.3 PRIMARY ENDPOINT 38

3.4 SECONDARY ENDPOINTS 39

3.5 EXPLORATORY ENDPOINTS 40

3.6 RANDOMIZATION, STRATIFICATION, AND BLINDING/MASKING 41

3.6.1 Randomization and Stratification 41
3.6.2 Blinding 41
3.6.3 Procedure for Unblinding / Unmasking 41

4. SELECTION OF PARTICIPANTS 42
4.1 RATIONALE FOR STUDY POPULATION 42
4.2 INCLUSION CRITERIA 43
4.3 EXCLUSION CRITERIA 43
4.4 IDENTIFICATION OF PARTICIPANTS FOR "DENSE SAMPLING" 46

5. KNOWN AND POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS 46
5.1 RISKS OF INVESTIGATIONAL PRODUCT AS CITED IN THE INVESTIGATOR'S BROCHURE 46
5.1.1 Other potential risks: 47
5.2 RISKS OF INVESTIGATIONAL PRODUCT CITED IN MEDICAL LITERATURE 47
5.3 RISKS OF OTHER PROTOCOL SPECIFIED MEDICATIONS 47
5.4 RISKS OF STUDY PROCEDURES 51
5.5 POTENTIAL BENEFITS 52

6. INVESTIGATIONAL AGENT 52
6.1 INVESTIGATIONAL AGENTS: VIB4920 AND VIB4920 PLACEBO 52
6.1.1 VIB4920 52
6.1.2 VIB4920 Placebo 54
6.2 DRUG ACCOUNTABILITY 54
6.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH INVESTIGATIONAL AGENT 55
6.4 TOXICITY MANAGEMENT 55
6.4.1 Infusion or hypersensitivity reactions 55
6.4.2 Infection 56
6.4.3 Liver Chemistry Abnormalities 56
6.5 DISCONTINUATION OF STUDY DRUG ADMINISTRATION 56
6.6 ALTERNATE MONITORING SCHEDULE 57
6.6.1 Participants with persistent disease activity that may require a change in disease-modifying therapy 57
6.6.2 Participants who escalate disease-modifying therapy or receive treatment with a prohibited medication 58

7. OTHER MEDICATIONS 59
7.1 CONCOMITANT MEDICATIONS 59

7.1.1 Protocol Mandated....59
7.1.2 Other Permitted Concomitant Medications....60
7.2 PROPHYLACTIC MEDICATIONS....61
7.3 PROHIBITED MEDICATIONS AND PROCEDURES....61
7.4 RESCUE MEDICATIONS....62
7.5 CONTRACEPTION AND AVOIDING PREGNANCY....62
8. STUDY PROCEDURES / ASSESSMENTS....62
8.1 ENROLLMENT....62
8.2 SCREENING/BASELINE VISIT....63
8.2.1 Screening Visit....63
8.2.2 Baseline Visit....63
8.3 STUDY ASSESSMENTS....63
8.3.1 General Assessments....63
8.3.2 Clinical Assessments....64
8.3.3 Disease Specific Assessments....64
8.3.4 Mechanistic Assessments....65
8.3.5 Study Drug Administration....65
8.4 TREATMENT MODIFICATION VISIT....65
8.5 STUDY DISCONTINUATION VISIT....66
8.6 UNSCHEDULED VISITS....66
8.7 VISIT WINDOWS....66
9. MECHANISTIC ASSAYS....67
9.1 MECHANISTIC HYPOTHESES....67
9.2 PROPOSED MECHANISTIC ASSAYS....67
9.2.1 Peripheral Blood Cells....67
9.2.2 Serum and Plasma Assays....68
9.2.3 Whole Blood Assays....69
9.3 FUTURE / UNPLANNED STUDIES....70
10. BIOSPECIMEN STORAGE....70
11. CRITERIA FOR PARTICIPANT AND STUDY COMPLETION AND PREMATURE STUDY TERMINATION....71
11.1 PARTICIPANT COMPLETION....71
11.2 PREMATURE TERMINATION OF STUDY PARTICPATION....71
11.3 PARTICIPANT REPLACEMENT....71

11.4 FOLLOW-UP AFTER PREMATURE TERMINATION OF STUDY PARTICIPATION 71
11.5 STUDY STOPPING RULES 71

12. SAFETY MONITORING AND REPORTING 72
12.1 OVERVIEW 72
12.2 DEFINITIONS 72
12.2.1 Adverse Event (AE) 72
12.2.2 Unexpected Adverse Event 72
12.2.3 Serious Adverse Event (SAE) 73
12.2.4 Adverse Event of Special Interest 73
12.3 GRADING AND ATTRIBUTION OF ADVERSE EVENTS 74
12.3.1 Grading of Liver Chemistry Abnormalities 74
12.3.2 Grading of Other Adverse Events 74
12.3.3 Attribution Definitions 75
12.4 COLLECTION AND RECORDING OF ADVERSE EVENTS 76
12.4.1 Collection Period 76
12.4.2 Collecting Adverse Events 76
12.4.3 Recording Adverse Events 76
12.5 REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST 76
12.5.1 Reporting of Adverse Events 76
12.5.2 Reporting of Serious Adverse Events and Adverse Events of Special Interest to Sponsor 77
12.5.3 Reporting to Health Authority 77
12.5.4 Reporting of Adverse Events to IRB/IECs 78
12.6 PREGNANCY REPORTING 79
12.7 REPORTING OF OTHER SAFETY INFORMATION 79
12.8 REVIEW OF SAFETY INFORMATION 79
12.8.1 Medical Monitor Review 79
12.8.2 DSMB Review 80

13. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN 81
13.1 OVERVIEW 81
13.2 ENDPOINTS 82
13.3 MEASURES TO MINIMIZE BIAS 82
13.4 ANALYSIS PLAN 82
13.4.1 Analysis Populations 82

13.4.2 Primary Analysis of Primary Endpoint 82
13.4.3 Supportive Analyses of the Primary Endpoint 83
13.4.4 Analyses of Secondary Endpoints 84
13.4.5 Exploratory Analysis 85
13.4.6 Descriptive Analyses 86
13.5 INTERIM ANALYSES 86
13.5.1 Futility 86
13.5.2 Safety and Data Quality 86
13.6 STATISTICAL HYPOTHESES 87
13.7 SAMPLE SIZE CONSIDERATIONS 87

14. IDENTIFICATION AND ACCESS TO SOURCE DATA 88
14.1 SOURCE DATA 88
14.2 ACCESS TO SOURCE DATA 88

15. QUALITY ASSURANCE AND QUALITY CONTROL 88

16. PROTOCOL DEVIATIONS 89
16.1 PROTOCOL DEVIATION DEFINITIONS 89
16.2 REPORTING AND MANAGING PROTOCOL DEVIATIONS 89

17. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE 90
17.1 STATEMENT OF COMPLIANCE 90
17.2 INFORMED CONSENT PROCESS 90
17.3 PRIVACY AND CONFIDENTIALITY 90

18. PUBLICATION POLICY 90

19. REFERENCES 91

LIST OF APPENDICES

Appendix 1. Schedule of Events: Screening and Study Drug Administration 94
Appendix 2. Schedule of Events: Post-Drug Administration with Dense Sampling Collection 97
Appendix 3. Schedule of Events: Post-Drug Administration without Dense Sampling Collection 99
Appendix 4. Schedule of Events: Alternate Monitoring 101
Appendix 5. 28 and 44 Joint Count 102
Appendix 6. Patient Global, Provider Global, and Pain Assessment 103
Appendix 7. Health Assessment Questionnaire Disability Index (HAQ-DI)[1] 104
Appendix 8. RAPID3 Assessment 106
Appendix 9. 2010 ACR-EULAR Classification Criteria For Rheumatoid Arthritis 107
Appendix 10. PROMIS-29 Profile 108
Appendix 11. Clinical Criteria for Diagnosing Anaphylaxis 110

LIST OF TABLES

Table 1. Categories of disease activity defined by the SDAI 37
Table 2. Categories of disease activity defined by the DAS28-CRP.....37
Table 3. Definitions of ACR20, ACR50, and ACR70 Responses.....38
Table 4. Categories of disease severity defined by the RAPID3 38
Table 5. Dose Modification for Liver Chemistry Abnormalities 56
Table 6. Participant's follow-up based on the status of their RA treatment regimen during the study....59
Table 7. Visit Windows 66
Table 8. Attribution of Adverse Events 75
Table 9. Infection rule for triggering an ad hoc DSMB review. 80
Table 10. 95% Confidence Limits for events occurring in <20% of participants 88

LIST OF FIGURES

Figure 1. Study Schematic 35
Figure 2. Percent of participants with serious infections in RA trials using two biologic agents. 50
Figure 3. Joints assessed in a 44 and 28 joint count. 102

PROTOCOL SYNOPSIS

Title	Combining a CD40L-Binding Protein (VIB4920) with a TNF-α Inhibitor for the Treatment of Inadequately Controlled Rheumatoid Arthritis
Short Title	CD40L antagonism in RA
Clinical Phase	Phase II
Number of Sites	Approximately 12 - 15 US sites
IND Sponsor/Number	DAIT NIAID/152787
Study Objectives	Primary Objective To determine if the addition of a 12-week course of treatment with VIB4920 (also known as dazodalibep and HZN-4920) to background disease-modifying RA therapy with a TNF-α inhibitor (TNFi) in patients with moderately-to-highly active rheumatoid arthritis (RA) improves clinical disease control compared to background disease-modifying RA therapy with TNFi and without the addition of VIB4920. Secondary Objectives 1. To determine if the addition of a 12-week course of treatment with VIB4920 to background disease-modifying rheumatoid arthritis (RA) therapy with a TNFi in participants with moderately-to highly active RA sustains clinical disease control compared to background disease-modifying RA therapy with a TNFi without the addition of VIB4920. 2. To compare the safety and tolerability of adding a 12-week course of VIB4920 in participants with moderately-to highly active RA receiving background disease-modifying RA therapy with a TNFi to continuing background disease-modifying RA therapy with a TNFi but without the addition of VIB4920 and to switching from a TNFi to a 12-week course of VIB4920 while maintaining other background therapy. 3. To assess the quality of life during and after treatment in participants with moderately-to-highly active RA who receive a 12-week course of treatment with VIB4920 added to background disease-modifying rheumatoid arthritis (RA) therapy with a TNFi, continue background disease-modifying rheumatoid arthritis (RA) therapy with a TNFi but without the addition of VIB4920, or switch from a TNFi to VIB4920 while continuing other background disease-modifying RA therapy.

	Exploratory Objectives 1. To explore in patients with moderately-to-highly active RA receiving background disease-modifying therapy with a TNFi, if switching a TNFi to a 12-week course of treatment with VIB4920 improves clinical disease control compared to continuing background disease-modifying RA therapy with a TNFi without adding VIB4920 or adding a 12 week course of VIB4920 to background disease-modifying RA therapy with a TNFi. 2. To determine how the addition of a 12-week course of VIB4920 to a TNFi affects blood B cell and T cell activation and cytokine production in participants with moderately-to highly active RA compared to those who continue background disease-modifying RA therapy with a TNFi without the addition of VIB4920, or switch from a TNFi to VIB4920 and continue other background disease-modifying RA therapy. 3. To determine how the addition of VIB4920 to a TNFi affects the development of anti-drug antibodies to VIB4920 and TNFi compared to use of VIB4920 without TNFi and use of TNFi without VIB4920. 4. To compare the drug levels of VIB4920 in the VIB4920 with TNFi and VIB4920 without TNFi study arms. 5. To compare the drug levels of TNFi in the VIB4920 with TNFi and VIB4920 placebo with TNFi arms. 6. To explore in participants who meet the primary endpoint at week 16 if circulating fibroblast and activated B cell gene signatures from whole blood obtained weekly at home predict RA flare.
Study Design	This study is a phase 2, multi-site, prospective, randomized, placebo-controlled, three-arm [two arms double-blinded, one arm evaluator-blinded (participant is aware of his/her treatment status, but evaluator is not)] trial of VIB4920 in 104 adults with seropositive RA in the United States. Individuals will be eligible if they have moderate or high disease activity (Simplified Disease Activity Index [SDAI] ≥ 17, Section 3.2.1) despite treatment with a TNFi for at least 12 weeks. All FDA-approved TNFi (including biosimilars) administered subcutaneously and utilizing FDA-approved dosing regimens are permitted. Participants will be randomized in a 2:1:1 fashion into one of the following three study arms:

	1. VIB4920 with TNFi (n≈52): Participants will receive VIB4920 in a blinded fashion intravenously at a dose of 1500 mg at weeks 0, 2, 4, 8, and 12 and continue all background disease-modifying RA therapy (e.g., methotrexate, hydroxychloroquine, etc.), including the TNFi, through the study period. 2. VIB4920 placebo with TNFi (n≈26): Participants will receive VIB4920 placebo in a blinded fashion intravenously at weeks 0, 2, 4, 8, and 12 and continue all background disease-modifying RA therapy, including the TNFi, through the study period. 3. VIB4920 without TNFi (n≈26): Participants will stop TNFi after randomization to this arm, and receive VIB4920 in an evaluator-blinded fashion intravenously at a dose of 1500 mg at weeks 0, 2, 4, 8, and 12 while maintaining all other background disease-modifying RA therapy through the study period. This arm is evaluator-blinded (evaluator not aware of treatment status), with the participant aware of treatment status due to not using a TNFi placebo in this study. After week 12, all participants randomized to VIB4920 or VIB4920 placebo will continue treatment with their background disease-modifying drugs, including their TNFi, and will be followed through week 40. Participants randomized to receive VIB4920 after stopping their TNFi will not restart their TNFi and will be followed through week 40. In addition, participants who achieve the primary endpoint at week 16 will be followed through week 40 and be eligible to undergo weekly home fingerstick blood sampling ("dense sampling") and RAPID3 assessment to explore transcriptional signatures that may be associated with increases in disease activity after achieving a pre-defined treatment response (SDAI ≤ 11 at week 16).
Primary Endpoint	The primary endpoint is the proportion of participants achieving low disease activity as defined by a SDAI ≤ 11 at week 16. Participants who escalate their disease-modifying therapy or take any prohibited medications for treatment of RA prior to week 16 are considered to have failed the primary endpoint. The primary analysis will compare the primary endpoint between the two blinded study arms: VIB4920 with TNFi and VIB4920 placebo with TNFi.
Secondary Endpoints	All secondary endpoints will be assessed across all three study treatment arms. For efficacy endpoints listed under A-D below, participants who escalate their disease-modifying therapy or take prohibited medications for treatment of their

	RA prior to the specified timepoint(s) are considered to have failed that secondary endpoint. <u>Secondary efficacy endpoints:</u> A. Sustained remission (key secondary endpoint). 1. Proportion of participants who achieve sustained remission defined by SDAI ≤ 3.3 at all available disease activity assessments between week 16 and week 40. B. Low disease activity by DAS28-CRP. 2. Proportion of participants achieving low disease activity defined by DAS28-CRP ≤ 3.2 at week 16. C. Remission. 3. Proportion of participants achieving remission defined by SDAI ≤ 3.3 at week 16. 4. Proportion of participants achieving remission defined by DAS28-CRP < 2.6 at week 16. D. ACR20/50/70 endpoints. 5. The proportion of participants achieving an ACR20 response at week 16. 6. The proportion of participants achieving an ACR50 response at week 16. 7. The proportion of participants achieving an ACR70 response at week 16. 8. The proportion of participants achieving an ACR20 response at week 40. 9. The proportion of participants achieving an ACR50 response at week 40. 10. The proportion of participants achieving an ACR70 response at week 40. E. Time to low disease activity or remission. For participants who fail to achieve low disease activity or remission prior to escalating their disease-modifying therapy or taking a prohibited medication for treatment of RA, we will assume low disease activity and remission is not achievable within 40 weeks. 11. Time to first occurrence of low disease activity as defined by SDAI ≤ 11. 12. Time to first occurrence of low disease activity as defined by DAS28-CRP ≤ 3.2.

	13. Time to first occurrence of remission as defined by SDAI ≤ 3.3. 14. Time to first occurrence of remission as defined by DAS28-CRP < 2.6. F. Time to loss of low disease activity or remission. Participants who escalate their disease-modifying therapy or take prohibited medications for treatment of their RA will be considered to have lost the low disease activity or remission response. 15. Time to loss of low disease activity defined by SDAI > 11 for the subset of individuals achieving low disease activity by the SDAI criteria at week 16. 16. Time to loss of low disease activity defined by DAS28-CRP > 3.2 for the subset of individuals achieving low disease activity by the DAS28-CRP criteria at week 16. 17. Time to loss of remission defined by SDAI > 3.3 for the subset of individuals achieving remission by the SDAI criteria at week 16. 18. Time to loss of remission defined by DAS28-CRP ≥ 2.6 for the subset of individuals achieving remission by the DAS28-CRP criteria at week 16. G. Longitudinal trends. 19. Longitudinal trends in SDAI from week 0 to week 40. 20. Longitudinal trends in DAS28-CRP from week 0 to week 40. H. HAQ-DI and PROMIS-29. 21. Change in HAQ-DI from week 0 to week 16. 22. Change in HAQ-DI from week 0 to week 40. 23. Change in PROMIS-29 from week 0 to week 16. 24. Change in PROMIS-29 from week 0 to week 40. <u>Secondary safety endpoints</u>: 1. Incidence of grade 2 or higher adverse events. 2. Incidence of serious adverse events. 3. Incidence of adverse events of special interest (AESI, Section 12.2.4).
Accrual Objective	104 participants

Study Duration	Accrual is expected to take approximately two years. Individuals will remain in the trial for up to 40 weeks. Total study duration can be expected to last approximately 2.75 years.
Treatment Description	Participants will receive VIB4920 or VIB4920 placebo given intravenously at a dose of 1500 mg at weeks 0, 2, 4, 8, and 12. Participants randomized to VIB4920 with TNFi or VIB4920 placebo with TNFi will continue their background disease-modifying therapy, including their TNFi. Participants randomized to VIB4920 without TNFi will discontinue TNFi therapy while maintaining all other background disease-modifying RA therapy.
Inclusion Criteria	Individuals who meet all of the following criteria at screening are eligible for enrollment: 1. Participant or legally authorized representative must be able to understand and provide informed consent 2. Adults ≥ 18 years of age 3. Diagnosed with RA by fulfilling the ACR/EULAR 2010 Classification Criteria for RA ≥ 6 months prior to screening (Appendix 9) 4. Documented positive test for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (ACPA) 5. SDAI ≥ 17 6. At least 4 tender and 4 swollen joints by a 44 joint count (Appendix 5) 7. Receiving treatment with an FDA-approved TNFi (including biosimilars) that is dosed subcutaneously at an FDA-approved dosing regimen for at least 12 weeks 8. Willing to continue or discontinue treatment with their current TNFi at the same dose depending upon study arm assignment 9. If treated with leflunomide, sulfasalazine, or hydroxychloroquine, must be taking a stable dose for at least 12 weeks 10. If treated with methotrexate, must be taking a stable dose for at least 12 weeks. The following exceptions are permitted within the 12 weeks prior to screening: a. Holding methotrexate after COVID-19 vaccination as per American College of Rheumatology guidance (https://rheumatology.org/) b. Holding methotrexate for 1 or 2 weeks after influenza vaccination 11. All participants who engage in sexual activity that could lead to pregnancy must agree to use abstinence or an FDA-approved contraception for the duration of the study to prevent pregnancy (Section 7.5)
Exclusion Criteria	Individuals who meet any of these criteria at screening are not eligible for enrollment as study participants:

	1. Inability or unwillingness to give written informed consent or comply with the study protocol 2. Prior or ongoing systemic inflammatory or autoimmune disease (other than RA and secondary Sjögren's syndrome) requiring or potentially requiring other systemic immunomodulatory therapy during the 40-week study period 3. Use of glucocorticoid and/or disease-modifying therapies as specified below: a. Prior treatment with any B cell depleting therapy (e.g., rituximab) b. Treatment with other biologic therapy (i.e., not targeting TNF-α), including abatacept, tocilizumab, or sarilumab within the previous 12 weeks c. Treatment with a JAK inhibitor within the previous 12 weeks d. Concurrent use of methotrexate and leflunomide in combination e. Prednisone > 10 mg a day or equivalent glucocorticoid use within the previous 4 weeks f. Intramuscular, intra-articular, or intravenous glucocorticoids within the previous 4 weeks g. Other immunomodulatory medications within the previous 12 weeks except for methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine 4. Lack of any subjective or objective clinical response (i.e., complete non-responder) to treatment with the current TNFi, in the opinion of the study investigator based on available documentation in the medical record and/or history provided by the patient and referring rheumatologist 5. Use of an investigational agent including VIB4920 in the past 30 days or 5 half-lives, whichever is longer 6. History of a severe allergy, hypersensitivity reaction, or infusion reaction to any component of the VIB4920 formulation 7. History of Felty's syndrome 8. History of interstitial lung disease with FVC < 70% predicted, DLCO < 70% predicted, or requiring supplemental oxygen 9. Arterial or deep venous thromboembolism including pulmonary embolism in the prior two years 10. Infection: a. Evidence of current or prior infection with hepatitis B, as indicated by a positive test for the hepatitis B surface antigen (HBsAg) or a positive test for the hepatitis B core antibody (HBcAb)

	b. Positive HCV serology unless treated with an anti-viral regimen resulting in a sustained virologic response (undetectable viral load 24 weeks after cessation of therapy) c. Evidence of HIV infection d. Evidence of active tuberculosis, untreated or incompletely treated latent tuberculosis, or recent close contact with a person who has active tuberculosis e. Positive QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test without history of completing treatment for active or latent TB f. Indeterminate QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test which remains indeterminate on repeat testing, and any of the following additional required screening which indicates an increased risk of TB infection: i. History of tuberculosis exposure ii. History of travel to an area where tuberculosis is endemic iii. Findings on chest radiograph suggestive of prior exposure to tuberculosis (e.g., granulomas or apical scarring) obtained at screening or within the past 3 months iv. Positive purified protein derivative (PPD) skin test for tuberculosis, either obtained at screening or within in the past 3 months v. Prior history of a positive QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, T-SPOT.TB, or purified protein derivative (PPD) test without history of previous treatment for latent TB g. Symptoms of presumed or documented SARS-CoV-2 infection in the past 30 days h. More than one episode of herpes zoster in the past 12 months i. An opportunistic infection in the past 12 months j. Acute or chronic infection, including current use of suppressive systemic anti-microbial therapy for chronic or recurrent bacterial or fungal infection, hospitalization for treatment of infection in the past 60 days, or parenteral anti-microbial (including anti-bacterial, anti-viral, or anti-fungal agents) use in the past 60 days for infection k. History of bronchiectasis with recurrent pulmonary infections 11. History of a primary immunodeficiency disorder 12. Vaccination with a live vaccine within the past 30 days 13. Women who are pregnant or breast-feeding

	14. White blood cell count < 3.0 x 10^3/µl 15. Absolute neutrophil count < 1.5 x 10^3/µl 16. Hemoglobin < 9 g/dL 17. Platelet count < 100 x 10^3/µl 18. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2x the upper limit of normal (ULN) 19. History of malignant neoplasm within the last 5 years, except for basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma *in situ* of the uterine cervix treated locally 20. Current, diagnosed, mental illness or current, diagnosed or self-reported drug or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements 21. Any new or uncontrolled condition occurring within the past 12 weeks which, in the judgment of the investigator, could interfere with participation in the trial (e.g., diabetes mellitus with HbA1c ≥ 9.0%, myocardial infarction, or stroke) 22. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study 23. Inability to comply with study and follow-up procedures
Study Stopping Rules	The following events will trigger an *ad hoc* comprehensive DSMB Safety Review: ∞ Any death which is possibly related or related to study treatment. ∞ A grade 3 or higher SAE of the same preferred term that is possibly related or related to study treatment in two or more of the participants who have received a study treatment. ∞ The observed rate of grade 3 or higher infections is higher than anticipated in the VIB4920 with TNFi arm, the VIB4920 without TNFi arm, or in the two VIB4920 arms pooled together, as indicated in Table 9. This rule will be monitored for each treatment arm separately and for both VIB4920 treatment arms pooled together by an unblinded statistician. ∞ A grade 2 or higher thromboembolic event in 2 or more participants who have received any assigned study treatment. ∞ Two grade 4 (life-threatening) infusion reactions, including anaphylaxis, that occur during administration of study treatment, or in the first 24 hours after each study treatment.

	∞ Any event which in the opinion of the Protocol Chair or Medical Monitor merits DSMB review.

GLOSSARY OF TERMS AND ABBREVIATIONS

ADA	Anti-drug antibodies
AE	adverse event
AESI	Adverse events of special interest
ACPA	Anti-cyclic citrullinated peptide antibody
ALT	Alanine aminotransferase
APCs	Antigen presenting cells
AST	Aspartate aminotransferase
Baseline	Visit 0 (Week 0)
CBC	complete blood count
CD40L	CD40 ligand
CDSMC	Clinical Data and Safety Management Center
CFR	Code of Federal Regulations
CRF	case report form
DMARD	Disease modifying anti-rheumatic drug
DSMB	Data and Safety Monitoring Board
DV	Study discontinuation visit: For participants who withdraw from the study
eCRF	Electronic case report form
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
Evaluator blinded	The clinical evaluator is blinded to the participant's treatment assignment, but the participant and other study personnel are not
FDA	US Food and Drug Administration
GCP	good clinical practice
JAK	Janus kinase
KLH	Keyhole limpet hemocyanin
IB	Investigator brochure

ICH	International Conference on Harmonisation
IRB	institutional review board
ITN	Immune Tolerance Network
LDA	Low disease activity
MedDRA	Medical Dictionary for Regulatory Activities
HAQ-DI	Health Assessment Questionnaire – Disability Index
mITT	Modified intent to treat
MOP	Manual of Procedures
NCI-CTCAE	National Cancer Institute *Common Terminology Criteria for Adverse Events* (version 5.0, November 27, 2017)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
PD	Pharmacodynamics
PK	Pharmacokinetics
PoR	Pharmacist of record
PP	Per protocol
PPD	Purified protein derivative
QC	Quality control
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SCCC	Statistical and Clinical Coordinating Center
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TNFi	Tumor necrosis factor α inhibitor

TM	Treatment modification visit: For participants who escalate their immunosuppression or use a prohibited medication to treat their rheumatoid arthritis
Treg	T regulatory
ULN	Upper limit of normal

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic joint inflammation and destruction of articular cartilage and bone. RA is the most common inflammatory arthritis and affects approximately 0.5- 1% of the United States population. [1] Inadequately controlled disease can lead to progressive joint deformity due to tendon and ligamentous laxity and erosion of articular cartilage and underlying bone. Persistent joint inflammation and destruction can result in loss of physical function, thereby negatively impacting activities of daily living, caring for the family and household, and maintaining employment. [2] Up to 40% of patients experience extra-articular disease, which include subcutaneous nodules, pleurisy, pericarditis, interstitial lung disease, peripheral neuropathy, and inflammatory eye disease, as well as Felty's syndrome. [3] RA is also associated with an increased risk of lymphoma. [4] Serum from approximately 70 – 75% of patients contain rheumatoid factor (RF) or antibodies to citrullinated proteins (ACPA), or both, and patients with "seropositivity" have a higher risk for severe joint damage and extra-articular manifestations compared with those who have seronegative disease.

Current treatment paradigms recommend early treatment with disease modifying anti-rheumatic drugs (DMARDs), since achieving disease control as soon as possible limits joint damage and disability. Initial therapy is usually comprised of conventional synthetic DMARDs (csDMARDs) such as methotrexate. Patients whose RA responds inadequately to methotrexate have several treatment options, including the addition of hydroxychloroquine and sulfasalazine (e.g., "oral triple therapy"); the addition of a biologic agent, such as a tumor necrosis factor alpha (TNF-α) inhibitor (TNFi) [etanercept, adalimumab, infliximab, certolizumab pegol, golimumab], abatacept, or an IL-6 receptor inhibitor (tocilizumab or sarilumab); or the addition of a targeted synthetic DMARD, such as a Janus kinase (JAK) inhibitor (tofacitinib, baricitinib, upadacitinib). Rituximab may be considered for the treatment of patients whose RA is not adequately controlled by a TNF-α inhibitor (TNFi). Glucocorticoids are sometimes prescribed in low doses (e.g., prednisone 5-10 mg/day) for patients whose disease remains active despite optimal DMARD therapy.

Only 50-75% of patients achieve clinical remission or low disease activity (LDA) with currently approved therapies when assessed at a single point in time. Sustained remission or remission/LDA is far less common and only occurs in 5-9% and 9-16% of patients, respectively. [5] Thus, a substantial proportion of patients do not maintain low disease activity or remission and therefore are at risk for disease progression. Moreover, it is not yet possible to predict which DMARD will be most effective in which patient, often resulting in sequential trials of different agents to find the optimal treatment. New treatment strategies are needed to improve disease control and avoid the frequent need for changing therapy.

1.2 RATIONALE FOR SELECTION OF THE INVESTIGATIONAL PRODUCT AND USE WITH A TNF INHIBITOR

The complex disease mechanisms underlying RA reflect a dysregulated innate and adaptive immune system in which antigen presentation and subsequent T and B cell activation likely drive an aberrant inflammatory response. This chronic inflammatory response involves many cell types, including T cells, B cells, macrophages, fibroblasts, chondrocytes, neutrophils, mast cells, and dendritic cells.

The CD40 ligand (CD40L)-CD40 pathway has emerged as a promising therapeutic target in RA because of its role in promoting T and B cell activation. Following the interaction between the T cell receptor and the MHC molecule on antigen presenting cells (APCs), T cells transiently upregulate the expression of CD40L, which engages CD40 on APCs, including dendritic cells, macrophages, and B cells. This binding induces APCs to upregulate the expression of CD80, CD86, MHC class I, and MHC class II, and secrete proinflammatory cytokines, such as TNF-α, IL-12, and IL-23. CD40-CD40L interactions also stimulate B cell differentiation, germinal center formation, and antibody isotype switching.

CD40L expression is increased on circulating CD4+ T cells from patients with RA, as well as in synovial tissue from patients with both early and established disease, and correlates positively with disease activity (DAS28-ESR). [6, 7] Moreover, certain *CD40* alleles are associated with increased RA risk; genetic associations near *TRAF1* and *TNFAIP3* (which codes for A20) further support the involvement of the CD40 signaling pathway in RA pathogenesis through downstream NF-kB activation. B cells homozygous for the *CD40* risk allele display increased surface expression of CD40 compared to their non-risk allele counterparts. [8]

Viela Bio developed VIB4920, a CD40L antagonist comprised of 2 identical Tn3 modules fused to human serum albumin. Each Tn3 is an engineered form of the third fibronectin type III (Fn3) protein domain of human tenascin C. Tn3 is a 90 amino acid long protein scaffold with immunoglobulin-like folds analogous to antibody complementarity-determining regions that can be randomized to select for specific binding properties. Candidate Tn3 clones were selected from a phage expression library that specifically bound to human CD40L and in turn optimized by affinity maturation for potent binding to human CD40. Based on their binding properties, VIB4920 was generated by fusing a bivalent CD40L-specific Tn3 to serum albumin for improved half-life.[9] Viela Bio was acquired by Horizon Therapeutics Ireland DAC, which was subsequently acquired by AMGEN Inc. VIB4920 is now also known as HZN-4920 and dazodalibep.

In a randomized, double-blind, placebo-controlled, phase 1b, multiple ascending dose study in RA (Study D5100C00002) [10], 57 individuals with adult-onset RA receiving a stable dose of methotrexate were randomized to VIB4920 (n=42) or placebo (n=15).

VIB4920 was administered as an intravenous infusion every 2 weeks at a dose of 75, 500, 1000, or 1500 mg for 7 doses. Disease activity as assessed by DAS28-CRP was significantly reduced at day 85 for the individuals receiving 1000 or 1500 mg every 2 weeks ($p<0.001$); no benefit was observed for patients who had received the 75 or 500 mg doses. Low disease activity or remission was achieved in 50% of subjects from the 1000 mg dose group and in 75% of subjects from the 1500 mg dose group compared to 13.4% in the placebo group at day 85. The effect of VIB4920 on DAS28-CRP was rapid, with reductions in disease activity evident as early as day 15 after a single dose of drug. In the groups receiving 1000 mg or 1500 mg, the benefit observed at day 85 was maintained until day 169. A sustained reduction in rheumatoid factor was also observed at day 85.

The goal of this study is to further investigate the efficacy of VIB4920 for the treatment of RA and assess its ability to induce long-term disease control in combination with a TNFi. Approximately 35-50 % of patients with RA that are treated with a TNFi do not achieve low disease activity, which in clinical practice calls for a change in disease-modifying therapy. The differential response to TNFi therapy may be explained at least in part by the pathologic heterogeneity of RA and the likelihood that the disease is driven by a balance of innate and adaptive immune mechanisms particular to a given patient. This view is supported by an analysis of synovial tissue samples from patients with established RA that delineates subgroups of myeloid, lymphoid, and mixed phenotypes, which in turn, correlate with serum levels of ICAM and CXCL13 [11]. The hypothesis that an individual patient's treatment response depends on the synovial tissue phenotype was indirectly explored in the ADACTA trial, which compared the clinical efficacy of adalimumab, an anti-TNF-α monoclonal antibody, to tocilizumab, an anti-IL-6 receptor antibody [12]. In this study, patients with high serum ICAM/CXCL13 ratios (myeloid phenotype) showed the best treatment response to adalimumab, while those with high CXCL13/serum ICAM ratios (lymphoid phenotype) benefited more from tocilizumab therapy. The results of another clinical trial validated these predictive biomarkers of treatment response [13].

TNF-α plays a crucial pro-inflammatory role in the pathogenesis of RA, with effects mainly on innate immunity. Among its many activities, it primes or directly mediates leukocyte activation, adhesion, and migration; endothelial activation and angiogenesis; chemokine expression; stromal cell activation; chondrocyte activation; and osteoclast differentiation in combination with receptor activator of NFκB ligand (RANKL) [14]. IL-6 also has prominent biological effects on both innate and adaptive immunity in RA. [15] IL-6 promotes the differentiation of CD4+ T cells into T helper 17 (Th17) cells in combination with transforming growth factor-β (TGF-β) and inhibits the differentiation of TGF-β-driven T regulatory (Treg) cell differentiation, resulting in up-regulation of the Th17/Treg balance and disruption of tolerance mechanisms. IL-6 also promotes T follicular helper cell differentiation and induces the differentiation of activated B cells into antibody-secreting cells. Thus, the differential treatment effects of TNF-α inhibitors and an IL-6 receptor blocking antibody exemplify the heterogeneity of disease

mechanisms across the RA population as a whole and the complex role of adaptive and innate immunity in driving the pathologic response.

VIB4920 inhibition of the CD40-CD40L pathway would be expected to specifically target the adaptive immune response. Combining VIB4920 with a TNFi provides an opportunity to directly test the hypothesis that established RA is driven by varied contributions of antigen-dependent (adaptive) and antigen-independent (innate) immune mechanisms. Thus, we will test whether combining TNF-α inhibition with blockade of the CD40-CD40L pathway by VIB4920 disrupts the pathologic innate and adaptive immune responses in a manner that restores normal tolerance mechanisms and promotes sustained disease control. We further hypothesize that treatment with a TNFi in combination with VIB4920 will be more effective in controlling disease activity than maintaining a TNFi alone or replacing a partially effective TNFi with VIB4920, an antagonist of adaptive immunity.

1.2.1 Rationale for the Dose of the Investigational Product

In this study, VIB4920 will be given intravenously at a dose of 1500 mg at weeks 0, 2, 4, 8, and 12. This dose was recommended by Horizon Therapeutics plc and is being investigated by the company in a dose ranging study of patients with RA, as well as in a phase 2 study of patients with Sjögren's syndrome.

For the current trial, the cumulative dose of VIB4920 (7500 mg) will be similar to that of the 1000 mg group (7000 mg; 1000 mg every 2 weeks x 7 doses) in the phase 1b, multiple ascending dose study in RA (Study D5100C00002). In addition, clinical trial simulations indicate that the average concentration of VIB4920 from week 0 to week 16 using the dosage schedule herein would be similar to that of the 1000 mg every 2-week dosage regimen used in the phase 1b trial dose (141 µg/mL vs. 134 µg/mL, respectively).

Our rationale for this approach is further supported by the robust clinical responses observed in the phase 1b trial for both the 1000 mg and 1500 mg every 2-week groups, while limited clinical efficacy was seen in the 500 mg every 2 week group (cumulative dose 3500 mg). In addition, no dose-dependent safety signals were observed across the different doses investigated in the phase 1b study. Thus, we have chosen for this trial a dosing regimen of 1500 mg at weeks 0, 2, 4, 8, and 12 to generate a drug exposure similar to that of a clinically effective dosage regimen (1000 mg every 2 weeks). This strategy avoids potential subtherapeutic dosing and reduces the burden to study participants by decreasing the total number of infusions.

1.3 NON-CLINICAL EXPERIENCE

1.3.1 Non-clinical Studies

1.3.1.1 *Non-clinical Safety Data*

Single-dose and repeat-dose toxicity studies of the VIB4920 IV and SC formulations of VIB4920 have been conducted in cynomolgus monkeys. Data from the non-clinical studies indicate no special hazards for humans based on conventional safety

pharmacology or repeat-dose toxicity studies in monkeys. [16] In two studies of VIB4920 administered as 5 weekly intravenous doses, the no observed adverse effect level (NOAEL) was calculated to be 150 mg/kg and 300 mg/kg for IV administration.

Weekly IV administration of 150 or 300 mg/kg VIB4920 to sexually mature cynomolgus monkeys for 6 months resulted in early euthanasia of 1 animal receiving 150 mg/kg on Day 92 due to declining clinical condition, adverse clinical pathology changes suggesting a potential systemic infection, and microscopic evidence of inflammatory cell infiltrates in multiple tissues. One animal receiving 300 mg/kg had an enlarged spleen with a nodular and abnormal appearance at scheduled necropsy on Day 192. Multiple organs and tissues showed increased amounts of inflammatory cell infiltrates, with evidence of a systemic opportunistic fungal infection (*Penicillium marneffei*); these toxicities were considered secondary to the pharmacology of VIB4920. Therefore, no NOAEL was established for IV dosing in the 6-month study.

Prior clinical studies of antibodies targeting CD40L have failed, in part due to thromboembolic complications resulting from cross-linking CD40L on the cell surface of platelets. VIB4920 has not induced platelet aggregation in assays using washed human platelets *in vitro*, or *in vivo* in mice when compared to CD40L-specific monoclonal antibody 5C8. [10] This agent was specifically designed to avoid the complication of platelet aggregation and subsequent thromboembolic events by using a non-antibody scaffold (lacking an Fc region) structure consisting of an engineered anti-CD40L Tn3 backbone fused to human serum albumin.

1.3.1.2 *Non-clinical Efficacy Data*

VIB4920 neutralizes the engagement of CD40L with its receptor, CD40, in PBMC stimulation assays, NFκB reporter assays, and primary B cell stimulation assays. VIB4920 blocks stimulation of an NFκB luciferase reporter cell line expressing human CD40 with recombinant human CD40L in a dose dependent fashion. VIB4920 also blocks CD40L mediated up-regulation of CD86 in primary human B cells and CD40L-dependent expansion of primary B cells. The inhibitory effect of VIB4920 on primary human B cell activation, proliferation, and plasma cell differentiation was similar to an antibody-based inhibitor. [10]

The effect of VIB4920 on T cell dependent antibody responses was studied in murine models with a murine analog to Tn3, M31. Mice inoculated with sheep red blood cells and then M31 exhibited decreased germinal center B cell frequency in a dose dependent fashion, compared to controls not receiving M31. Germinal center formation was completely suppressed at a dose of 30 mg/kg. Anti-sheep red blood cell IgG levels also decreased at higher doses of anti-CD40L Tn3.

1.4 CLINICAL STUDIES

1.4.1 Safety Data for VIB4920

In the investigator's brochure (version 6.0, including data as of September 8, 2022) [9], safety data are presented from phase 1 and phase 2 studies.

1.4.1.1 *DC5100C0001*

Study DC5100C0001 was a phase 1 randomized, blinded, placebo-controlled single ascending dose study in 56 healthy individuals, where VIB4920 (n=44) or placebo (n=12) was administered as a single IV infusion at doses of 3, 10, 30, 100, 300, 1000, or 3000 mg.

Treatment emergent adverse events (TEAEs) were reported in 68.2% of the VIB4920 group and 91.7% of the placebo group. The most frequent TEAEs by preferred term (incidence > 15%) were nasopharyngitis (VIB4920, 10 subjects [22.7%] vs placebo, 1 subject [8.3%]) and headache (VIB4920, 8 subjects [18.2%] vs placebo, 4 subjects [33.3%]). One serious adverse event (SAE), a tibia fracture occurring in the placebo group, was reported during the trial and deemed not related to study treatment. There were no deaths, thromboembolic events, severe or serious hypersensitivity reactions, infusion-related reactions, or serious or severe infection events.

1.4.1.2 *D5100C00002*

Study D5100C00002 was a phase 1b randomized, double-blind, placebo-controlled multiple ascending dose study in 57 individuals with adult-onset RA receiving a stable dose of methotrexate. VIB4920 (n=42) or placebo (n=15) was administered via IV infusion every 2 weeks at a dose of 75, 500, 1000, or 1500 mg for 7 doses.

At least 1 TEAE was reported for 61.9% of subjects who received VIB4920 and 86.7% of those who received placebo. The most common TEAEs were diarrhea, hyperhidrosis, upper respiratory tract infection, increased alanine aminotransferase, and urinary tract infection, each occurring in 3 patients (7.1%) who received VIB4920. Two subjects discontinued the investigational product due to adverse events (AEs). One subject discontinued treatment with VIB4920 75 mg after 2 doses due to diarrhea and vomiting. A second subject discontinued dosing of VIB4920 1500 mg after 6 doses due to a Grade 4 SAE of encephalitis. No etiologic agent was identified during the trial; however, the subject was subsequently diagnosed with metastatic melanoma of the brain. There were 4 events of herpes simplex reported, and none were serious: oral herpes (500 mg and 1000 mg), nasal herpes (1500 mg), and herpes simplex (1500 mg). There were no other serious events of infection. There were no thrombotic events, severe or serious hypersensitivity reactions, or infusion-related reactions. [9, 10]

1.4.1.3 *MIDORA (VIB4920.P2.S3)*

MIDORA (VIB4920.P2.S3) was a phase 2, randomized, double-blind, placebo-controlled, parallel-cohort study of 78 adults with active, moderate-to-severe seropositive adult-onset RA with an inadequate response to MTX, cDMARD, or a TNFi. VIB4920 was administered IV in the following fashion:

- Cohort 1: VIB4920 1500 mg on days 1, 15, 29, and 57
- Cohort 2: VIB4920 1500 mg on days 1 and 57, VIB4920 placebo on days 15 and 29
- Cohort 3: VIB4920 3000 mg on days 1 and 57, VIB4920 placebo on days 15 and 29
- Cohort 4: VIB4920 3000 mg on day 1 and VIB4920 placebo on days 15, 29, and 57
- Cohort 5: VIB4920 placebo on days 1, 15, 29, and 57

In this study, a broadly similar proportion of participants reported at least one TEAE related to the investigational product in the VIB4920 groups (14.3% to 23.5%) and the placebo group (25.0%). The most frequently reported TEAE system organ class in the VIB4920 total group and the placebo group was infections and infestations (32.3% and 31.3%, respectively). COVID-19 was the most commonly reported TEAE in this group, reported in 8 (12.9%) participants in the VIB4920 total group (with no dose relationship) and 1 (6.3%) in the placebo group.

Of the three participants who had a treatment emergent serious adverse event (TESAE), two participants (one in cohort 2 and one in cohort 4) experienced a grade 3 or greater TESAE related to COVID-19. For the participant in cohort 4, this TESAE led to the discontinuation of the investigational product. One participant in cohort 1 experienced a grade 2 TESAE of nephrolithiasis. None of the TESAEs were considered treatment related.

There was one death in the study. A participant in cohort 2 developed a grade 3 TESAE of COVID-19 pneumonia 223 days after the last dose of study drug and died of unknown causes after being hospitalized for COVID-19. The investigator did not consider the death to be related to VIB4920.

There were no reports of thrombotic and embolic events, related anaphylaxis and clinically significant (≥ grade 3) hypersensitivity reactions, severe infusion-related reactions (≥ grade 3), events of immune complex disease, or opportunistic infections. [9]

1.4.1.4 *ALISS (VIB4920.P2.S2)*

ALISS (VIB4920.P2.S2) is an ongoing phase 2, randomized, double-blind, placebo-controlled study of 2 groups of adults fulfilling ACR/EULAR classification for Sjögren's syndrome. Individuals in population 1 (n=74) have moderate-to-severe systemic disease activity (EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥ 5). Individuals in population 2 (n=104) have limited systemic disease activity (ESSDAI < 5) and high symptomatic burden (EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) ≥ 5). There were 2 stages of dosing: in stage 1, participants received VIB4920 1500 mg IV or placebo every 2 weeks for 3 doses, and then every 4 weeks for 4 doses. In stage 2, subjects initially randomized to placebo were scheduled to receive VIB4920 and subjects initially randomized to VIB4920 were allocated to placebo every 4 weeks for 5 doses.

As reported in the investigator's brochure, population 1 has completed the study. In stage 1 of population 1, one participant who had received VIB4920 had two TESAEs: COVID-19 and death. Adverse events that occurred while on placebo included drug-induced liver injury and deep vein thrombosis in one participant, multiple injuries, and cervical dysplasia. Adverse events while on VIB4920 included COVID-19 and death in one participant and One participant in the placebo-to-VIB4920 group developed a TESAE of chronic cholecystitis.

Three treatment-emergent AESI have been reported for population 1. In stage I, a AESI events of grade 3 COVID-19 (1 participant) and grade 2 herpes zoster (1 participant) were each reported in the VIB4920 1500 mg group. The COVID-19 treatment-emergent AESI was a TESAE, was not considered by the investigator to be related to the investigational product, and did not lead to discontinuation of the investigational product. The herpes zoster AESI occurred 10 days after the first dose of VIB4920, and one dose of the investigational product was held. The participant was treated and recovered without sequelae. This event was considered by the investigator to be related to the investigational product and was not a TESAE. In Stage II, there were no infection related AESIs, and the SAE of DVT was also an AESI.

Population 2 has completed stage 1 but has not completed stage 2 and thus data remain blinded. For this population, five TESAEs have been reported (each occurring in one participant): neutropenia, gammopathy, influenza pneumonia, invasive ductal carcinoma of breast, and post-acute COVID-19 syndrome. The blinded investigator has assessed the invasive ductal carcinoma of breast to be related to the investigational product. AESIs of significant or opportunistic infections include herpes zoster (grade 2, considered unrelated to the investigational product) and esophageal candidiasis (moderate severity, considered related to the investigational product, but did not lead to its discontinuation).

No events of anaphylaxis or grade 3 or higher infusion-related reactions have been observed in either population. Pregnancy was reported in one participant during the treatment period: no associated adverse event was reported, and the participant elected to terminate the pregnancy.

1.4.1.5 *VIB4920.P2.S1*

VIB4920.P2.S1 is a single-arm, prospective, open-label pilot trial examining the efficacy, safety, and tolerability of dual costimulation blockade with VIB4920 and belatacept for prophylaxis of allograft rejection in kidney transplant. Adult recipients of a renal allograft from a deceased, living unrelated or HLA non-identical living related donor (n=23) received VIB4920 1500 mg IV on post-op day 1, post-op day 3 or 4, then every 2 weeks for 12 weeks, and then every 4 weeks for 36 weeks. Participants also received belatacept (10 mg/kg IV on post-op day 1, post-op day 3 or 4, and weeks 2, 4, 8 and 12; then 5 mg/kg IV every 4 weeks from week 16 to week 48), thymoglobulin, and corticosteroids. Enrollment has been completed, and the trial is ongoing with 13 participants having completed study treatment.

Thus far, 16 SAEs have been reported among 9 participants including ileus and subcapsular renal hematoma (1 participant), bacteremia and acute cholecystitis (1 participant); arteriovenous fistula site complication, hypervolaemia and urinary tract infection (1 participant); positive cytomegalovirus test and urosepsis (1 participant); ureteric stenosis, post-procedural urine leak and diabetic foot infection (1 participant); and post-procedural urine leak, *Clostridium difficile* infection, increased serum creatinine, and depression suicidal (each in 1 participant). Of the 16 SAEs, cytomegalovirus infection and urosepsis were assessed as related to study drug.

1.4.2 Clinical Efficacy Data for VIB4920

1.4.2.1 *D5100C00001*

In the single ascending dose study D5100C00001, T cell dependent antibody responses to keyhole limpet hemocyanin (KLH) were inhibited in a dose-dependent manner and showed statistically significant suppression at doses of 300, 1000, and 3000 mg compared with placebo. A 78% and 86% reduction in anti-KLH IgG levels was observed compared to placebo at day 43 in the 1000 and 3000 mg cohorts, respectively. Increases in total soluble CD40L were observed after VIB4920 administration, indicating binding of VIB4920 to soluble CD40L and target engagement. The incidence and titers of anti-drug antibodies (ADA) decreased with increasing doses of VIB4920. [9, 10]

1.4.2.2 *D5100C0002*

In multiple ascending dose study D5100C0002, 57 subjects with adult-onset RA taking a stable dose of methotrexate were treated with multiple ascending doses of VIB4920 (75, 500, 1000, or 1500 mg) or placebo every 2 weeks for 7 doses. VIB4920 was generally well tolerated. VIB4920 at the higher doses (1000 mg and 1500 mg) significantly reduced disease activity quantified by DAS28-CRP score. At week 12 (day 85), the adjusted mean change from the baseline of DAS28-CRP (SE) was −2.3 (0.3) in VIB4920 1500 mg group, −2.2 (0.3) in VIB4920 1000 mg group, −1.2 (0.3) in VIB4920 500 mg group, 0.1 (0.4) in VIB4920 75 mg group, and −1.0 (0.3) in the placebo group. Improvement in the DAS28-CRP was observed for the 1000 mg and 1500 mg doses compared to placebo: 75% of patients in the 1500 mg group and 50% of patients in 1000-mg dose group achieved a DAS28-CRP score of 3.2 or less at week 12 (day 85), indicating that they were in low disease activity or clinical remission at the primary endpoint assessment, compared to 13.4% of patients in the placebo group. The improvement in response at Day 85 was maintained until the end of the study at day 169. Serum levels of rheumatoid factor were decreased in the 500 mg, 1000 mg, and 1500 mg groups with reductions starting at day 29. The pharmacodynamic (PD) effect plateaued at doses of 500 mg and higher. ADA results were similar to the single ascending dose study, with no patients in the 1500 mg group developing ADA, and ADA levels did not appear to impact the PK or PD or VIB4920 levels at steady state. [9, 10]

1.4.2.3 *MIDORA (VIB4920.P2.S3)*

In the MIDORA study, each of the VIB4920 dosing groups showed a statistically significant and clinically meaningful improvement from baseline in DAS28-CRP score through Day 113 versus placebo. A similar magnitude of improvement from baseline in DAS28-CRP was observed at Day 113 in each of the VIB4920 dose groups. Significant reduction in DAS28-CRP score from baseline to Day 309 was also observed in each VIB4920 dose group versus placebo. The treatment effect, as measured by DAS28-CRP score, was maintained beyond Day 113 through end of study. These DAS28-CRP score findings were supported by favorable effects on multiple components of the composite score.[9]

1.4.2.4 *ALISS (VIB4920.P2.S2)*

In the ALISS study, subjects with moderate-to-severe systemic disease activity (Population 1) had statistically significant greater improvement in baseline ESSDAI at Day 169 in the dazodalibep group compared to placebo (-6.3 vs -4.1, p = 0.0167). Positive trends in secondary and exploratory endpoints were observed. Subjects with moderate-to-severe symptomatic burden, but low systemic disease activity (Population 2) had a statistically significant greater improvement in baseline ESSPRI at Day 169 in dazodalibep group compared to placebo (-1.80 vs -0.53, p = 0.0002). Statistical significance difference was noted in multiple key secondary endpoints, including FACIT-F.[9]

1.4.2.5 *VIB4920.P2.S1*

The study is ongoing, with 13 out of 23 participants having completed study treatment.

2. STUDY HYPOTHESES AND OBJECTIVES

2.1 HYPOTHESES

1. Temporary blockade of the CD40-CD40L pathway in patients with active RA combined with ongoing TNFi therapy will improve disease activity, restore immune homeostasis, and lead to sustained disease control.

2. Temporary blockade of the CD40-CD40L pathway in patients with active RA combined with ongoing TNFi therapy will be safe and well tolerated in patients with active RA.

2.2 PRIMARY OBJECTIVE

To determine if the addition of a 12-week course of treatment with VIB4920 (also known as dazodalibep and HZN-4920) to background disease-modifying RA therapy with a TNFi in patients with moderately-to-highly active rheumatoid arthritis (RA) improves clinical disease control compared to background disease-modifying RA therapy with a TNFi and without the addition of VIB4920.

2.3 SECONDARY OBJECTIVES

1. To determine if the addition of a 12-week course of treatment with VIB4920 to background disease-modifying rheumatoid arthritis (RA) therapy with a TNFi in participants with moderately-to highly active RA sustains clinical disease control compared to background disease-modifying RA therapy with a TNFi without the addition of VIB4920.

2. To compare the safety and tolerability of adding a 12-week course of VIB4920 in participants with moderately-to highly active RA receiving background disease-modifying RA therapy with a TNFi to continuing background disease-modifying RA therapy with a TNFi but without the addition of VIB4920 and to switching from a TNFi to a 12-week course of VIB4920 while maintaining other background therapy.

3. To assess the quality of life during and after treatment in participants with moderately-to-highly active RA who receive a 12-week course of treatment with VIB4920 added to background disease-modifying rheumatoid arthritis (RA) therapy with a TNFi, continue background disease-modifying rheumatoid arthritis (RA) therapy with a TNFi but without the addition of VIB4920, or switch from a TNFi to VIB4920 while continuing other background disease-modifying RA therapy.

2.4 EXPLORATORY OBJECTIVES

1. To explore in patients with moderately-to-highly active RA receiving background disease-modifying therapy with a TNFi, if switching from a TNFi to a 12-week course of treatment with VIB4920 improves clinical disease control compared to continuing background disease-modifying RA therapy with a TNFi but without adding VIB4920 or adding a 12- week course of VIB4920 to background disease-modifying RA therapy with a TNFi.

2. To determine how the addition of a 12-week course of VIB4920 to a TNFi affects blood B cell and T cell activation and cytokine production in participants with moderately-to highly active RA compared to those who continue background disease-modifying RA therapy with a TNFi without the addition of VIB4920, or switch from a TNFi to VIB4920 and continue other background disease-modifying RA therapy.

3. To determine how the addition of VIB4920 to a TNFi affects the development of anti-drug antibodies to VIB4920 and TNFi compared to use of VIB4920 without TNFi and use of TNFi without VIB4920.

4. To compare the drug levels of VIB4920 in the VIB4920 with TNFi and VIB4920 without TNFi study arms.

5. To compare the drug levels of TNFi in the VIB4920 with TNFi and VIB4920 placebo with TNFi arms.

6. To explore in participants who meet the primary endpoint at week 16 if circulating fibroblast and activated B cell gene signatures from whole blood obtained weekly at home predict RA flare.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY DESIGN

This study is a phase 2, multi-site, prospective, randomized, placebo-controlled, three-arm [two arms double-blinded, one arm evaluator-blinded (participant is aware of his/her treatment status, but evaluator is not)] trial of VIB4920 in 104 adults with seropositive RA in the United States. Individuals will be eligible if they have moderate or high disease activity (Simplified Disease Activity Index [SDAI] ≥ 17, Section 3.2.1) despite treatment with a TNFi for at least 12 weeks. All FDA-approved TNFi (including biosimilars) administered subcutaneously and utilizing FDA-approved dosing regimens are permitted. Other csDMARDS are permitted (Section 7.1.2) and will be maintained at the same dose. Study participation is divided into two phases: the study drug administration period (from week 0 to week 12) and the post-administration observation period (from week 12 to week 40). The schematic for the study is presented in Figure 1. Study Schematic and the Schedule of Events for the study drug administration period is provided in Appendix 1.

Participants will be randomized in a 2:1:1 fashion into one of the following three study arms:

1. VIB4920 with TNFi (n≈52): Participants will receive VIB4920 in a blinded fashion intravenously at a dose of 1500 mg at weeks 0, 2, 4, 8, and 12 and continue all background disease-modifying RA therapy (e.g., methotrexate, hydroxychloroquine, etc.), including the TNFi, through the study period.

2. VIB4920 placebo with TNFi (n≈26): Participants will receive VIB4920 placebo in a blinded fashion intravenously at weeks 0, 2, 4, 8, and 12 and continue all background disease-modifying RA therapy, including the TNFi, through the study period.

3. VIB4920 without TNFi (n≈26): Participants will stop TNFi after randomization to this arm and receive VIB4920 in an evaluator-blinded fashion intravenously at a dose of 1500 mg at weeks 0, 2, 4, 8, and 12 while maintaining all other background disease-modifying RA therapy through the study period. This arm is evaluator-blinded (evaluator not aware of treatment status), with the participant aware of treatment status due to not using a TNFi placebo while participating in this study.

Three arms are included in this study to assess the efficacy of adding VIB4920 to background disease modifying RA therapy including TNFi and replacing TNFi with

VIB4920, as well as the safety of this combination of biologic agents compared to either agent alone.

Participants will be assessed for the primary endpoint, achievement of low disease activity (defined as SDAI ≤ 11), at week 16. Participants will then be followed until week 40 while they continue their other disease-modifying treatments to assess for sustained clinical response and safety. Participants randomized to receive VIB4920 after stopping their TNFi should not restart their TNFi after week 12.

Participants who achieve the primary endpoint at week 16 will be eligible to undergo weekly blood sampling and RAPID3 evaluation at home. This weekly blood sampling will be optional for eligible participants and will be obtained from week 16 through week 40 using a fingerstick method. This "dense sampling" approach will be used to explore transcriptional signatures that may be associated with increases in disease activity (see Schedule of Events provided in Appendix 2). Participants who do not achieve the primary endpoint or elect not to participate in the optional dense sampling collection will be followed from week 16 to week 40 using the Schedule of Events provided in Appendix 3. A blinded study evaluator will assess disease activity and adverse events for all participants the entire duration of the study.

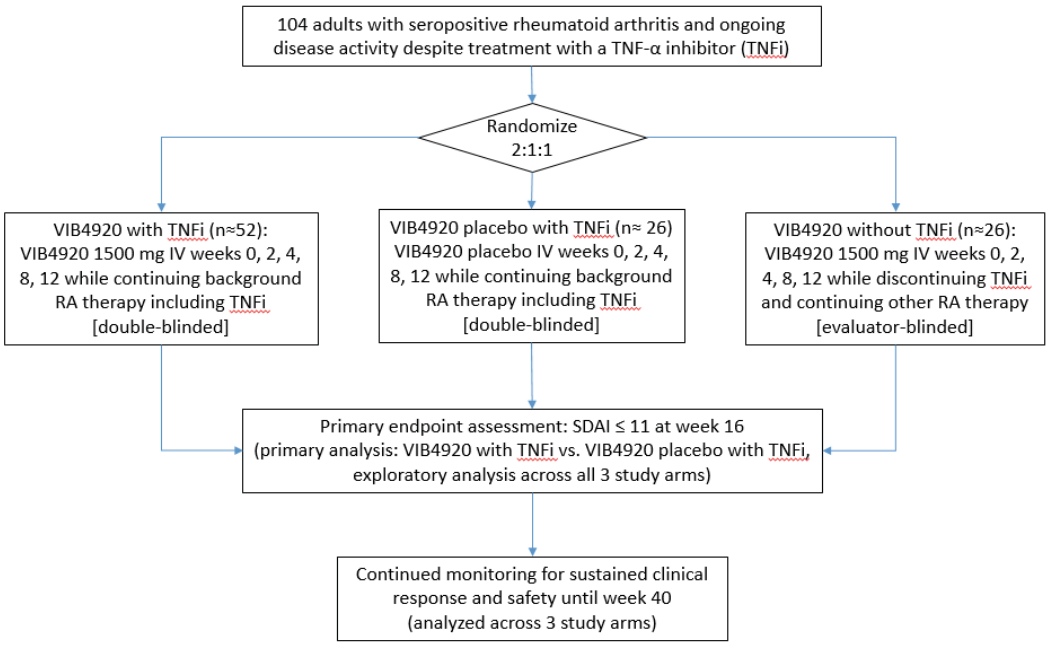

Figure 1. Study Schematic

From week 12 onward, participants with persistent or worsening disease activity (including those whose RA improved and subsequently worsened) may receive additional

treatment to manage their RA (Section 7.4) at the discretion of their rheumatologist. Participants whose treatment for RA is changed or increased due to persistent or worsening disease activity will be followed through week 40 according to an alternate monitoring schedule (Section 6.6, Appendix **4**).

3.2 DEFINITION OF DISEASE ACTIVITY MEASURES

RA disease activity and severity are being assessed by the following measures in this study: the Simplified Disease Activity Index (SDAI); Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP); ACR20, ACR50, and ACR70; and the Routine Assessment of Patient Index Data 3 (RAPID3). The SDAI is being used for the primary and the key secondary endpoint assessments since the definition of remission is more stringent than that of the DAS28-CRP. [17] The DAS28-CRP and ACR20/ACR50/ACR70 are being assessed given their widespread use as disease activity measures in RA clinical trials and to facilitate comparison with other studies. The RAPID3 relies solely on patient self-reported measures and thus can be used to assess disease activity at home without input from a health care provider. While a 44 joint count is being performed, only the joints specified in the 28 joint count (Appendix 5) will be used to calculate the SDAI and DAS28-CRP.

3.2.1 Simplified Disease Activity Index (SDAI)

The SDAI is calculated using the following formula [18]:

SDAI = TJC28 + SJC28 + PaGH + PrGH + CRP

based on the following assessments:

- TJC28: Number of tender joints (0-28)
- SJC28: Number of swollen joints (0-28)
- CRP: C-reactive protein concentration (mg/dl)
- PaGH: Patient global health assessment (from 0=best to 10=worst, Appendix 6).
- PrGH: Healthcare provider global health assessment (from 0=best to 10=worst, Appendix 6)

Categories of disease activity are defined using the thresholds presented in Table 1.

Table 1. Categories of disease activity defined by the SDAI

Disease state	SDAI score
Remission	≤ 3.3
Low disease activity	> 3.3 - ≤11
Moderate disease activity	>11- ≤26
High disease activity	>26

3.2.2 Disease Activity Score-28 for Rheumatoid Arthritis with CRP (DAS28-CRP)

The DAS28-CRP is calculated using the following formula [19]:

DAS28-CRP = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.36 * ln(CRP+1) + 0.014 * PaGH + 0.96

based on the following assessments:

- ∞ TJC28: number of tender joints (0-28)
- ∞ SJC28: number of swollen joints (0-28)
- ∞ CRP: C-reactive protein concentration (mg/l)
- ∞ PaGH: Patient global health assessment (from 0=best to 100=worst, Appendix 6)

Categories of disease activity are defined by the thresholds presented in Table 2.

Table 2. Categories of disease activity defined by the DAS28-CRP

Disease state	DAS28-CRP score
Remission	<2.6
Low disease activity	2.6 - ≤3.2
Moderate disease activity	>3.2 - ≤5.1
High disease activity	>5.1

3.2.3 ACR20, ACR50, and ACR70 response

The definitions of ACR20, ACR50, and ACR70 responses are shown in Table 3. This study will utilize the Health Assessment Questionnaire - Disability Index (HAQ-DI, Appendix 7, [20]) as the assessment of functional ability and the C-reactive protein (CRP) as the inflammatory marker for the assessment of these responses. [21, 22] The patient global assessment, physician global assessment, and pain assessment scale are provided in Appendix 6.

Table 3. Definitions of ACR20, ACR50, and ACR70 Responses

	% improvement from baseline needed to achieve:		
	ACR20 response	**ACR50 response**	**ACR70 response**
Tender joint count	At least 20%	At least 50%	At least 70%
Swollen joint count	At least 20%	At least 50%	At least 70%
Patient global assessment **Physician global assessment** **Assessment of functional ability (HAQ-DI)** **Pain assessment** **C-reactive protein**	At least 20% in 3 out of these 5 measures	At least 50% in 3 out of these 5 measures	At least 70% in 3 out of these 5 measures

3.2.4 Routine Assessment of Patient Index Data 3 (RAPID3)

The patient reported items in the RAPID3 for the assessment of disease activity and its scoring are provided in Appendix 8. The categories of disease severity are defined by the thresholds presented in Table 4. [23, 24]

Table 4. Categories of disease severity defined by the RAPID3

Disease state	RAPID3 score
Remission	<3
Low disease severity	3.1 – 6.0
Moderate disease severity	6.1 – 12
High disease severity	12.1-30

3.3 PRIMARY ENDPOINT

The primary endpoint is the proportion of participants achieving low disease activity as defined by a SDAI ≤ 11 at week 16. Participants who escalate their disease-modifying therapy or take any prohibited medications for treatment of RA prior to week 16 are considered to have failed the primary endpoint. The primary analysis will compare the primary endpoint between the two blinded study arms: VIB4920 with TNFi and VIB4920 placebo with TNFi.

3.4 SECONDARY ENDPOINTS

All secondary endpoints will be assessed across all three study treatment arms. For efficacy endpoints listed under A-D below, participants who escalate their disease-modifying therapy or take prohibited medications for treatment of their RA prior to the specified timepoint(s) are considered to have failed that secondary endpoint.

Secondary efficacy endpoints:

A. Sustained remission (key secondary endpoint).

1. Proportion of participants who achieve sustained remission defined by SDAI ≤ 3.3 at all available disease activity assessments between week 16 and week 40.

B. Low disease activity by DAS28-CRP.

2. Proportion of participants achieving low disease activity defined by DAS28-CRP ≤ 3.2 at week 16.

C. Remission.

3. Proportion of participants achieving remission defined by SDAI ≤ 3.3 at week 16.
4. Proportion of participants achieving remission defined by DAS28-CRP < 2.6 at week 16.

D. ACR20/50/70 endpoints.

5. The proportion of participants achieving an ACR20 response at week 16.
6. The proportion of participants achieving an ACR50 response at week 16.
7. The proportion of participants achieving an ACR70 response at week 16.
8. The proportion of participants achieving an ACR20 response at week 40.
9. The proportion of participants achieving an ACR50 response at week 40.
10. The proportion of participants achieving an ACR70 response at week 40.

E. Time to low disease activity or remission. For participants who fail to achieve low disease activity or remission prior to escalating their disease-modifying therapy or taking a prohibited medication for treatment of RA, we will assume low disease activity and remission is not achievable within 40 weeks.

11. Time to first occurrence of low disease activity as defined by SDAI ≤ 11.
12. Time to first occurrence of low disease activity as defined by DAS28-CRP ≤ 3.2.
13. Time to first occurrence of remission as defined by SDAI ≤ 3.3.

14. Time to first occurrence of remission as defined by DAS28-CRP < 2.6.

F. Time to loss of low disease activity or remission. Participants who escalate their disease-modifying therapy or take prohibited medications for treatment of their RA will be considered to have lost the low disease activity or remission response.

15. Time to loss of low disease activity defined by SDAI > 11 for the subset of individuals achieving low disease activity by the SDAI criteria at week 16.
16. Time to loss of low disease activity defined by DAS28-CRP > 3.2 for the subset of individuals achieving low disease activity by the DAS28-CRP criteria at week 16.
17. Time to loss of remission defined by SDAI > 3.3 for the subset of individuals achieving remission by the SDAI criteria at week 16.
18. Time to loss of remission defined by DAS28-CRP ≥ 2.6 for the subset of individuals achieving remission by the DAS28-CRP criteria at week 16.

G. Longitudinal trends.

19. Longitudinal trends in SDAI from week 0 to week 40.
20. Longitudinal trends in DAS28-CRP from week 0 to week 40.

H. HAQ-DI and PROMIS-29.

21. Change in HAQ-DI from week 0 to week 16.
22. Change in HAQ-DI from week 0 to week 40.
23. Change in PROMIS-29 from week 0 to week 16.
24. Change in PROMIS-29 from week 0 to week 40.

Secondary safety endpoints:

1. Incidence of grade 2 or higher adverse events.
2. Incidence of serious adverse events.
3. Incidence of adverse events of special interest (AESI, Section 12.2.4).

3.5 EXPLORATORY ENDPOINTS

All exploratory endpoints will be assessed across all three study treatment arms.

1. Total sCD40L
2. Anti-drug antibodies to VIB4920

3. Anti-drug antibodies to the prescribed TNFi
4. Plasma levels of VIB4920
5. Blood levels of the prescribed TNFi
6. Peripheral blood gene expression signatures as predictors of disease flare (determined by a change in RAPID3 score) using the dense blood sampling method described above.
7. Routine Assessment of Patient Index Data 3 (RAPID3)

Other mechanistic assays are described in Section 9.2.

3.6 RANDOMIZATION, STRATIFICATION, AND BLINDING/MASKING

3.6.1 Randomization and Stratification

Participants who provide written informed consent and meet the eligibility criteria will be randomly assigned in a 2:1:1 fashion to the following treatment groups: (1) VIB4920 with TNFi, (2) VIB4920 placebo with TNFi, and (3) VIB4920 without TNFi. Per Hey and Kimmelman [25], unequal randomization can be used in early-phase trials to explore aspects of treatment (e.g., co-intervention) to determine clinical utility, and to provide additional safety information. In this early-phase study, unequal randomization is being utilized to investigate the clinical efficacy of combination therapy (VIB4920 with TNFi) and enable a more robust assessment of a sustained clinical response, a key secondary endpoint, as an indicator of tolerance. In addition, a larger sample size for the VIB4920 with TNFi arm will provide additional statistical power for monitoring adverse events, such as infections, which are of special interest in this study.

Randomization will be stratified based on the level of disease activity as assessed by SDAI at study screening (moderate disease activity vs. high disease activity as described in Table 1). Randomization will be accomplished through a password-protected, web-based, randomization system maintained by the Division of Allergy, Immunology, and Transplantation (DAIT) Clinical Data and Safety Management Center (CDSMC).

3.6.2 Blinding

For participants randomly allocated to receive VIB4920 with TNFi or VIB4920 placebo with TNFi, blinding will be maintained for all study participants and trial personnel throughout the study, with the exception of the study site pharmacist. For participants randomly allocated to the VIB4920 without TNFi arm, participants and the study site pharmacist will be notified of their treatment assignment. Unblinded trial personnel will also be aware of their treatment assignment. Evaluators assessing clinical efficacy and safety will remain blinded for the duration of the study.

3.6.3 Procedure for Unblinding / Unmasking

Before the study is complete, the blind for an individual participant in the VIB4920 with TNFi or VIB4920 placebo with TNFi study arms should only be broken when

appropriate medical management of the participant necessitates knowledge of treatment assignment.

In the event of a medical emergency, when the immediate knowledge of the actual treatment is essential for the management of the participant, the site investigator or designee can automatically obtain the participant's treatment assignment from the randomization system. The site investigator is encouraged to discuss the emergency unblinding with the National Institute of Allergy and Infectious Diseases (NIAID) Medical Monitor prior to unblinding the participant, if possible.

If the randomization system is not available, the site investigator can contact the CDSMC Client Support Services to obtain treatment assignment information. For more information and other unblinding pathways, please refer to the study Manual of Procedures (MOP).

As soon as possible, the site investigator will provide a full account of unblinding to the NIAID Medical Monitor, Protocol Chair, and the CDSMC of the unblinding event. The NIAID Medical Monitor will then notify the Data and Safety Monitoring Board (DSMB). A full account of the event will be recorded, including the date and time of the unblinding, the names of the individual(s) who made the decision, the reason(s) for unblinding, the participant(s) affected, individual(s) who were unblinded, and individual(s) who were notified.

Unblinding the treatment of an individual participant or subgroups of participants for unplanned interim analyses to support DSMB reviews and final analyses will require written approval from NIAID.

The final study report will contain any instances of intentional unblinding in the VIB4920 with TNFi or VIB4920 placebo with TNFi study arms prior to completion of the study along with the reason(s) for unblinding. Unintentional unblinding, including that of blinded evaluators in the VIB4920 without TNFi study arm, will also be recorded.

4. SELECTION OF PARTICIPANTS

4.1 RATIONALE FOR STUDY POPULATION

This study will recruit individuals with seropositive RA who have had an inadequate response to a TNFi. We chose this study population because patients with persistent disease activity despite treatment with a TNFi (with or without methotrexate or other csDMARD) are at risk for progressive joint damage and would be candidates for a change in disease-modifying therapy. We are specifically enrolling patients with active disease that are receiving a TNFi since our central scientific hypothesis is that combining TNF-α inhibition with an agent that interferes with a dysregulated adaptive immune response, in this case a drug targeting the CD40L-CD40 pathway, will improve disease control and lead to a sustained clinical benefit (Section 1.2). Individuals will need to have moderate or high disease activity, as well as a sufficient number of tender and swollen

joints that would warrant a change in treatment strategy. Patients with clinical or laboratory features associated with an increased risk for infection will not be eligible for this trial.

4.2 INCLUSION CRITERIA

Individuals who meet all of the following criteria at screening are eligible for enrollment as study participants:

1. Participant or legally authorized representative must be able to understand and provide informed consent
2. Adults ≥ 18 years of age
3. Diagnosed with RA by fulfilling the ACR/EULAR 2010 Classification Criteria for RA ≥ 6 months prior to screening (Appendix 9)
4. Documented positive test for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (ACPA)
5. SDAI ≥ 17
6. At least 4 tender and 4 swollen joints by a 44 joint count (Appendix 5)
7. Receiving treatment with an FDA-approved TNFi (including biosimilars) that is dosed subcutaneously at an FDA-approved dosing regimen for at least 12 weeks.
8. Willing to continue or discontinue treatment with their current TNFi at the same dose depending upon study arm assignment
9. If treated with leflunomide, sulfasalazine, or hydroxychloroquine, must be taking a stable dose for at least 12 weeks
10. If treated with methotrexate, must be taking a stable dose for at least 12 weeks. The following exceptions are permitted within the 12 weeks prior to screening:
    a. Holding methotrexate after COVID-19 vaccination as per American College of Rheumatology guidance (https://rheumatology.org/)
    b. Holding methotrexate for 1 or 2 weeks after influenza vaccination
11. All participants who engage in sexual activity that could lead to pregnancy must agree to use abstinence or an FDA-approved contraception for the duration of the study to prevent pregnancy (Section 7.5)

4.3 EXCLUSION CRITERIA

Individuals who meet any of these criteria at screening are not eligible for enrollment as study participants:

1. Inability or unwillingness to give written informed consent or comply with the study protocol
2. Prior or ongoing systemic inflammatory or autoimmune disease (other than RA and secondary Sjögren's syndrome) requiring or potentially requiring other systemic immunomodulatory therapy during the 40-week study period

3. Use of glucocorticoid and/or disease-modifying therapies as specified below:
    a. Prior treatment with any B cell depleting therapy (e.g., rituximab)
    b. Treatment with other biologic therapy (i.e., not targeting TNF-α), including abatacept, tocilizumab, or sarilumab within the previous 12 weeks
    c. Treatment with a JAK inhibitor within the previous 12 weeks
    d. Concurrent use of methotrexate and leflunomide in combination
    e. Prednisone > 10 mg a day or equivalent glucocorticoid use within the previous 4 weeks
    f. Intramuscular, intra-articular, or intravenous glucocorticoids within the previous 4 weeks
    g. Other immunomodulatory medications within the previous 12 weeks except for methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine
4. Lack of any subjective or objective clinical response (i.e., complete non-responder) to treatment with the current TNFi, in the opinion of the study investigator based on available documentation in the medical record and/or history provided by the patient and/or referring rheumatologist
5. Use of an investigational agent including VIB4920 in the past 30 days or 5 half-lives, whichever is longer
6. History of a severe allergy, hypersensitivity reaction, or infusion reaction to any component of the VIB4920 formulation
7. History of Felty's syndrome
8. History of interstitial lung disease with FVC < 70% predicted, DLCO < 70% predicted, or requiring supplemental oxygen
9. Arterial or deep venous thromboembolism including pulmonary embolism in the prior two years
10. Infection:
    a. Evidence of current or prior infection with hepatitis B, as indicated by a positive test for the hepatitis B surface antigen (HBsAg) or a positive test for the hepatitis B core antibody (HBcAb)
    b. Positive HCV serology unless treated with an anti-viral regimen resulting in a sustained virologic response (undetectable viral load 24 weeks after cessation of therapy)
    c. Evidence of HIV infection
    d. Evidence of active tuberculosis, untreated or incompletely treated latent tuberculosis, or recent close contact with a person who has active tuberculosis

e. Positive QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT-TB test without history of previous treatment for active or latent TB

f. Indeterminate QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test which remains indeterminate on repeat testing, and any of the following additional required screening which indicates an increased risk of TB infection:

   i. History of tuberculosis exposure

   ii. History of travel to an area where tuberculosis is endemic

   iii. Findings on chest radiograph suggestive of prior exposure to tuberculosis (e.g., granulomas or apical scarring) obtained at screening or within the past 3 months

   iv. Positive purified protein derivative (PPD) skin test for tuberculosis obtained in the past 3 months, either obtained at screening or within the past 3 months

   v. Prior history of a positive QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, T-SPOT.TB, or purified protein derivative (PPD) test without history of previous treatment for latent TB

g. Symptoms of presumed or documented SARS-CoV-2 infection in the past 30 days

h. More than one episode of herpes zoster in the past 12 months

i. An opportunistic infection in the past 12 months

j. Acute or chronic infection, including current use of suppressive systemic anti-microbial therapy for chronic or recurrent bacterial or fungal infection, hospitalization for treatment of infection in the past 60 days, or parenteral anti-microbial (including anti-bacterial, anti-viral, or anti-fungal agents) use in the past 60 days for infection

k. History of bronchiectasis with recurrent pulmonary infections

11. History of a primary immunodeficiency disorder
12. Vaccination with a live vaccine within the past 30 days
13. Women who are pregnant or breast-feeding
14. White blood cell (WBC) count $< 3.0 \times 10^3/\mu l$
15. Absolute neutrophil count $< 1.5 \times 10^3/\mu l$
16. Hemoglobin < 9 g/dL
17. Platelet count $< 100 \times 10^3/\mu l$
18. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2x the upper limit of normal (ULN)

19. History of malignant neoplasm within the last 5 years, except for basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma *in situ* of the uterine cervix treated locally
20. Current, diagnosed mental illness or current, diagnosed or self-reported drug or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements
21. Any new or uncontrolled condition occurring within the past 12 weeks which, in the judgment of the investigator, could interfere with participation in the trial (e.g., diabetes mellitus with HbA1c ≥ 9.0%, myocardial infarction, or stroke)
22. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study
23. Inability to comply with study and follow-up procedures

4.4 IDENTIFICATION OF PARTICIPANTS FOR "DENSE SAMPLING"

Participants who achieve the primary endpoint at week 16 will be eligible to participate in the "dense sampling" collection, where participants undergo weekly fingerstick blood sampling and RAPID3 evaluation at home (Section 3.1). To identify participants eligible to participate in the dense sampling protocol, a participant's SDAI will be estimated at the week 16 visit by assuming that the CRP is 0. If the participant's estimated SDAI is ≤11 and the participant is willing to participate in the dense sampling protocol (as indicated on the informed consent document), the participant will undergo fingerstick blood collection at the week 16 visit and be instructed on the study procedures for home fingerstick blood collection and RAPID3 assessment. Once the SDAI is calculated using the CRP result from the week 16 visit, the study staff will inform the participant whether to continue the dense sampling procedures at home.

5. KNOWN AND POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS

5.1 RISKS OF INVESTIGATIONAL PRODUCT AS CITED IN THE INVESTIGATOR'S BROCHURE

All potential risks are considered important potential risks in the investigator's brochure (version 9.0). The following important potential risks are considered to warrant precautions and/or special monitoring:

1. Anaphylaxis, serious allergic reactions, infusion-related, and type III hypersensitivity reactions: While infusion reactions have not been observed in clinical studies of VIB4920, they may occur. The risks of hypersensitivity or infusion-related reactions are considered to be the highest after the first two doses of VIB4920.

2. Serious or severe infections including bacterial, viral, and opportunistic infections: One opportunistic infection was observed when VIB4920 was administered IV weekly at a dose of 300 mg/kg to cynomolgus monkeys for 6 months, and changes suggesting potential systemic infection were observed in another animal treated with VIB4920 150 mg/kg (Section 1.3.1.1).

   In clinical studies, no severe or serious infections have been observed in the phase 1 studies D5100C00001 and D5100C00002. In D5100C00002, there were 4 reports of herpes simplex, and none were serious: oral herpes (500 mg and 1000 mg), nasal herpes (1500 mg), and herpes simplex (1500 mg). Two instances of SARS-CoV-2 infection occurred during the MIDORA study:

   - One participant receiving VIB4920 1500 mg for 2 doses developed COVID-19 pneumonia (Grade ≥ 3 severity) that the investigator felt was not related to study treatment, who died of unknown cause during the study
   - One participant receiving VIB4920 3000 mg for one dose who reported a SARS-CoV-2 infection (Grade ≥ 3 severity). This treatment-emergent AESI was not considered by the investigator to be related to study treatment, was a treatment-emergent SAE, and led to discontinuation of study treatment.

No opportunistic infections were reported in the MIDORA study.

5.1.1 Other potential risks:

1. Exposure in utero: no embryo-fetal studies have been conducted to date.
2. Drug-drug interactions: No formal drug-drug interaction studies have been conducted with VIB4920.
3. Drug overdose: No clinical data regarding VIB4920 overdose are available.
4. Impact on vaccine response: Participants who obtain a vaccination while receiving VIB4920 may have a decreased or suboptimal response to vaccination.

5.2 RISKS OF INVESTIGATIONAL PRODUCT CITED IN MEDICAL LITERATURE

Studies DC5100C0001 and DC5100C0002 have been published [10], and the risks presented for VIB4920 in this publication are summarized in Section 1.4.1.

5.3 RISKS OF OTHER PROTOCOL SPECIFIED MEDICATIONS

In this study, participants may be at an increased risk of infection. Treatment with a TNFi is associated with an increased risk of serious infections and the use of VIB4920, a CD40L antagonist, may further increase the risk for serious infections. The other background DMARDs, and low doses of prednisone in some cases, will be maintained for the 40-week duration of the study and also may increase infection risk.

During the 12-week treatment phase, participants randomized to the VIB4920 with TNFi arm will be exposed to two biologic agents targeting innate and adaptive immune pathways, which has an unknown risk for serious infections. The combination of VIB4920 with TNFi has not been studied in pre-clinical animal models or previously in patients with RA. Previous studies of two biologic DMARDs used concurrently indicate that the combination may be associated with an increase in serious adverse events, including infection, compared to monotherapy. The rates of infection vary depending on the study and the nature of the biologic agents. Examples of this increase in risk include the following:

- In a 6-month, double-blind, randomized, clinical trial comparing etanercept 25 mg twice weekly, etanercept 25 mg once weekly plus anakinra 100 mg daily, and etanercept 25 mg twice weekly plus anakinra 100 mg daily in patients with active RA, combination therapy failed to provide any significant benefit over etanercept alone and was associated with a 3.7 – 7.4 % incidence of serious infections, or nearly double the rate of serious infections compared with etanercept treatment alone. [26]

- In a 1-year randomized, controlled, clinical trial of abatacept in combination with a background biologic DMARD or a conventional DMARD, such as methotrexate, use of abatacept with a biologic DMARD (predominately a TNFi) was associated with a higher number of serious infections compared to use of placebo with a biologic DMARD (6/103 vs. 1/64). [27]

- In a study of 121 RA patients taking etanercept that were randomized to receive abatacept or placebo, participants in the combination group experienced higher rates of SAEs (16.5 % vs. 2.8%) and serious infections (3.5% vs. 0%) compared to placebo. [28]

However, other clinical trials did not show a significantly increased risk of serious infection with combination biologic DMARD therapy:

- In a placebo-controlled clinical trial of patients with active RA treated with methotrexate and a TNFi (etanercept or adalimumab), 33 patients adding rituximab (500 mg IV x 2) to their regimen were compared to 18 patients receiving placebo. During the 24 weeks of the trial, one serious infection occurred in the rituximab group, and none was reported in the placebo group. [29]

- In a randomized clinical trial evaluating bimekizumab, an anti-IL-17A/F antibody, as add-on therapy, patients with RA and an inadequate response to certolizumab pegol were treated for 12 weeks with certolizumab pegol plus bimekizumab or certolizumab pegol alone and then followed through week 40. At week 20, the DAS28-CRP remission rate was higher in the certolizumab pegol plus bimekizumab group (n=21, 45.7%) compared with certolizumab pegol

alone (n=7, 29.2%). Although infections and infestations were higher in the bimekizumab than the placebo group (50% vs. 22.2%), serious infections were reported in one patient in each treatment group. [30]

- An unpublished trial (NCT00845832) comparing rituximab 500 mg IV x 2 in combination with tocilizumab 2 mg/kg IV every 4 weeks or tocilizumab 4 mg/kg IV every 4 weeks to tocilizumab 8 mg/kg IV every 4 weeks alone was stopped early after 24 participants had enrolled in the clinical trial. Among the enrolled participants, one subject in the rituximab plus tocilizumab 2 mg/kg IV every 4 weeks group was reported to have had a serious infection (pneumonia).

A recent meta-analysis of 6 studies utilizing combination biologic DMARDs for the treatment of RA has found an increased risk of serious infection with combination biologic therapy. In this analysis, 410 individuals who received combination therapy were compared to 213 patients receiving monotherapy, with a median follow-up of 9.5 months. When compared to monotherapy, the participants in the combination group had an increased incidence of SAEs (14.9% vs 6.0%, OR 2.51, 95% CI 1.29–4.89). In the subgroup receiving full doses of both biologic DMARDs, the use of combination therapy was associated with an increase in serious infections compared to monotherapy (6.7% vs 0.6%, OR 5.58, 95% CI 1.25–24.90). This meta-analysis did not include the most recent study by Glatt et al. [30]

The absolute risk attributable to combination biologic therapy may be difficult to estimate from these studies. The duration of follow-up varied across clinical trials, and the cumulative number of serious infections would be expected to increase the longer subjects were followed whether or not they were receiving combined biologic DMARD therapy. Moreover, the discontinuation rates were not the same across treatment groups, resulting in differences between groups in drug exposure. The risk of serious infections from combination biologic DMARD therapy as estimated by an odds ratio, while informative, should be also considered in terms of absolute risk. A sense of absolute risk may be ascertained from the percent of participants in the trial that had a serious infection as shown in Figure 2 below.

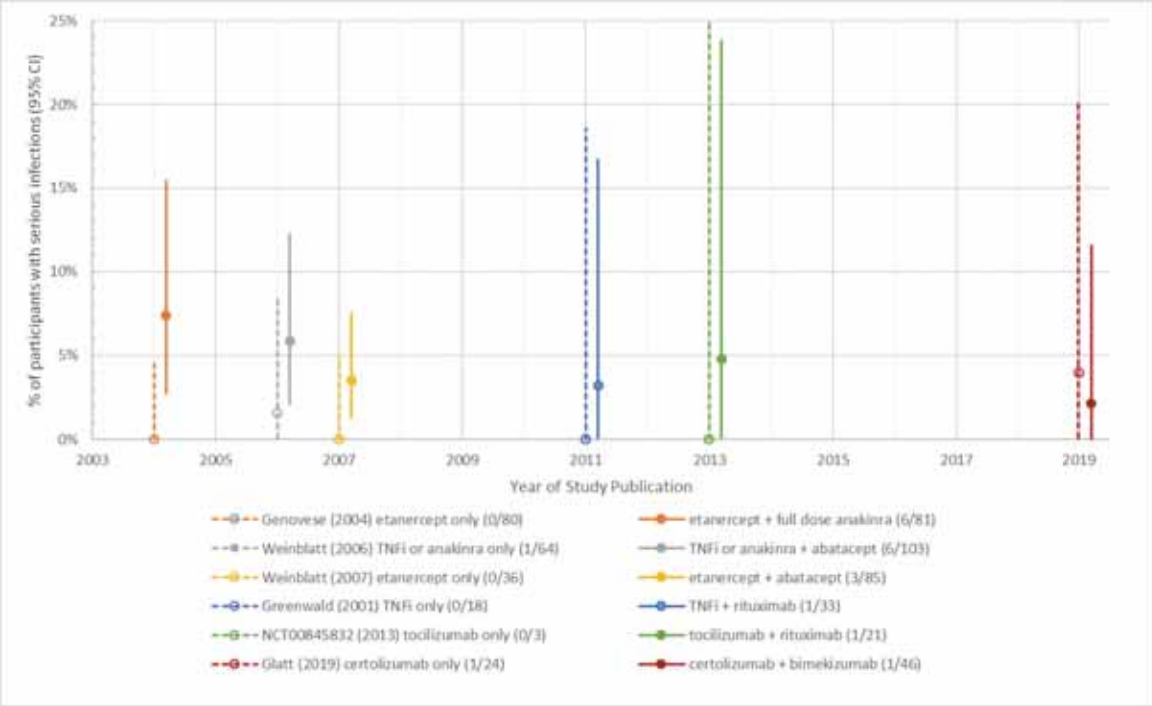

Figure 2. Percent of participants with serious infections in RA trials using two biologic agents.

The types of serious infections have been similar in participants receiving combination biologic DMARDs as in those receiving TNFi alone and include pneumonia, urinary infections, cellulitis, herpes zoster, and gastroenteritis. Importantly, no unusual or opportunistic infections or deaths were reported in the patients receiving dual biologic therapy.

The observed safety outcomes from these studies over the past two decades suggest a trend towards fewer serious infections in the most recently conducted trials. This trend could be explained by an evolution of study populations in the more recent trials towards those with a lower disease burden and thus, a lower risk of infection. The older trials enrolled subjects with an average disease duration of 10-12 years, while the more recent trials enrolled patients with a disease duration in the 7-year range. Tender and swollen joint counts in the earlier trials were in the range of 30 and 20, respectively, compared with 20-26 and 11-16, respectively, in the clinical trial investigating bimekizumab add-on therapy. In support of this notion, a registry study has found a time trend of a decreasing rate of serious infections associated with biologic DMARD therapy in recent years [31].

Given the potential increased risk of infection with concurrent use of two biologic agents, this study is employing the following measures to mitigate infection risk:

1. Utilizing a short duration of VIB4920 therapy, with the final dose of VIB4920 administered at week 12.

2. Requiring participants to have been treated with a TNFi for at least 12 weeks prior to enrollment. Thus, participants who develop serious infections early after initiation of a TNFi, when the risk for serious bacterial infection is highest, will not be enrolled in the trial. [32]

3. Excluding participants at high risk of infection. The standard exclusions for hepatitis B, hepatitis C, HIV, and TB are included. In addition, participants with the following conditions are also excluded: any opportunistic infection in the past 12 months, more than 1 episode of herpes zoster in the past 12 months, history of bronchiectasis with recurrent pulmonary infections, primary immunodeficiency, leukopenia, neutropenia, or uncontrolled diabetes mellitus (Section 4.3).

4. Assessing participants every 2 weeks for infection from weeks 0-16, either through in-person study assessments or contacting participants by telephone to inquire about infections (Appendix 1).

5. Suspending study treatment if the participant develops an infection the investigator judges to be significant (Section 6.4.2).

6. Convening an *ad hoc* DSMB review if observed rate of grade 3 or higher infections is higher than anticipated in the VIB4920 with TNFi arm, the VIB4920 without TNFi arm, or in the two VIB4920 arms pooled together (Section 12.8.2.2).

Lastly, this study will allow us to evaluate the risk of infection associated with combination of TNFi and VIB4920 therapy, by examining the rate of serious infections across all study arms (VIB4920 with TNFi arm, VIB4920 placebo with TNFi, and VIB4920 without TNFi).

5.4 RISKS OF STUDY PROCEDURES

The risks of the study procedures are as follows:

1. Study drug administration: Infusion reactions have not been observed with infusions of VIB4920; however, a low risk of infusion reaction may exist. Symptoms of an infusion reaction may include urticaria, angioedema, hypotension, hypoxia, or death.

2. Intravenous line placement: Low risk of infiltration, infection, or bruising at the venipuncture site.

3. Blood draw: Low risk of hemorrhage, hematoma, or infection at the venipuncture site.

4. Questionnaires: Low risk of discomfort due to questions that may be sensitive in nature.

5.5 POTENTIAL BENEFITS

The results of the multiple ascending dose trial suggest that patients with active RA treated with VIB4920 will have improved disease control, as evidenced by the higher rates of low disease activity and clinical remission observed in patients receiving VIB4920 compared to placebo. Participants in this trial may benefit by experiencing an improvement in joint pain and swelling during the VIB4920 treatment period, which may persist beyond the period of drug administration in view of the sustained clinical improvement following VIB4920 treatment in the previous phase 1b study.

The combination of a CD40L antagonist with a TNFi represents an innovative therapeutic approach not previously investigated in clinical trials. This combination may suppress adaptive and innate immunity in tandem and more profoundly downregulate pathologic immune responses, and may lead to sustained disease control. The knowledge gained from this study may provide a new approach for inducing sustained clinical remission in RA and advance novel tolerance-inducing strategies that may allow tapering or withdrawal of a TNFi.

6. INVESTIGATIONAL AGENT

6.1 INVESTIGATIONAL AGENTS: VIB4920 AND VIB4920 PLACEBO

6.1.1 VIB4920

VIB4920 is also known as dazodalibep and HZN-4920. These names are interchangeable in this protocol.

6.1.1.1 *Formulation, Packaging, Labeling, and Storage*

VIB4920 is an investigational fusion protein designed to bind to CD40L and is being developed by AMGEN Inc. It is not yet approved for any clinical indication.

VIB4920 is a clear to opalescent, colorless to yellow liquid, free from or practically free from visible particles. VIB4920 is supplied as a sterile liquid in a glass vial with a nominal fill volume of 5.0 mL, stoppered with siliconized 20 mm Teflon-coated elastomeric stopper, and sealed with flip-off cap overseal. Each vial contains 500 mg of VIB4920 at 100 mg/mL in 10 mM sodium phosphate buffer, 250 mM sucrose, and 0.02% (weight/volume) poloxamer 188, pH 7.4.

VIB4920 will be provided by the drug manufacturer, AMGEN Inc., in unlabeled vials. VIB4920 vials will be labeled and packaged specific to this clinical trial by the designated DAIT/NIAID Clinical Product Center under contract. The labeled and packaged vials will be distributed to investigational site pharmacies by the Clinical Product Center.

It is stored at 2°C to 8°C (36°F to 46°F). VIB4920 should not be allowed to freeze. VIB4920 should not be shaken.

6.1.1.2 *Dosage, Preparation, Administration, and Monitoring*

6.1.1.2.1 Dosage

VIB4920 will be administered at a dose of 1500 mg as an intravenous infusion at weeks 0, 2, 4, 8, and 12 (Section 3.1).

6.1.1.2.2 Preparation

VIB4920 will be prepared by the unblinded site pharmacist. To prepare the dose, VIB4920 should be removed from refrigerated storage conditions and allowed to equilibrate in the carton for 15 minutes but no longer than 2 hours prior to preparation. VIB4920 vials should be inspected prior to preparation to ensure that there are no particles and the color is not different from the description in Section 6.1.1.1.

Three vials of VIB4920 containing 5 mL each will be used to prepare a dose of 1500 mg VIB4920. 15 ml will be removed from a 250 mL bag of 0.9% normal saline supplied from site pharmacy stock and replaced with 15 mL VIB4920 (5 mL from each of 3 vials). The contents of the bag should be mixed gently by inverting but should not be shaken. If discoloration or particles are observed, the bag should not be administered.

The diluted investigational product VIB4920 can be stored for a maximum of 24 hours at 2-8°C from the initial puncture of the VIB4920 vial or for a maximum of 4 hours at room temperature from the initial puncture of the VIB4920 vial.

The investigational product will be covered by an opaque bag before being given to blinded study personnel for administration.

6.1.1.2.3 Administration

VIB4920 should not be administered on the same days as the TNFi. If VIB4920 and TNFi are scheduled to be administered on the same day, then the TNFi should be administered the day before or day after VIB4920 administration and maintained on that treatment schedule. Participants will be administered VIB4920 in a clinical trial facility and monitored for evidence of an infusion reaction. VIB4920 infusions should be administered by trained medical personnel prepared to manage anaphylaxis, severe hypersensitivity reactions, and infusion-related reactions. Appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions must be immediately available, and study personnel trained to recognize and treat these reactions must be immediately available.

VIB4920 will be administered via an infusion pump using an infusion line containing a low-protein binding 0.2 to 0.22 micrometer in-line filter. The infusion should be administered over a minimum of 90 minutes. The infusion will be slowed down or discontinued if there is evidence of an infusion reaction. The infusion will be discontinued if there is evidence of an anaphylactic reaction (Appendix 11). Once the infusion bag is empty, the IV tubing should be flushed with 0.9% normal saline with the same volume used to prime the IV tubing. This flush should be administered at the same rate as VIB4920 administration.

6.1.1.2.4 Monitoring

Vital signs will be monitored:

- ∞ Prior to the infusion
- ∞ Approximately every 30 minutes (+/- 5 minutes) during treatment administration
- ∞ Approximately every 30 minutes (+/- 5 minutes) for 2 hours after the completion of the first 3 infusions, and for 1 hour after completion of the remaining infusions.

Participants should be monitored for infusion or hypersensitivity reactions per Section 6.4.

After completion of each infusion, the IV line should remain in the participant for at least 2 hours after the completion of the first 3 infusions and for at least 1 hour after the completion of the remaining infusions.

6.1.2 VIB4920 Placebo

6.1.2.1 *Formulation, Packaging, and Labeling*

VIB4920 placebo consists of a 250 mL bag of 0.9% normal saline and will be supplied from the site pharmacy stock in 250 mL bags.

6.1.2.2 *Dosage, Preparation, and Administration*

6.1.2.2.1 Dosage

VIB4920 placebo will also be administered as an intravenous infusion at weeks 0, 2, 4, 8, and 12 as described in Section 3.1.

6.1.2.2.2 Preparation

VIB4920 placebo will be supplied from site pharmacy stock by the unblinded site pharmacist.

The infusion bag should be covered by an opaque bag before given to blinded study masked prior to delivery to the site personnel responsible for administration.

6.1.2.2.3 Administration

VIB4920 placebo will be administered according to the instructions provided for VIB4920 in Section 6.1.1.2.3.

6.1.2.2.4 Monitoring

Vital signs will be monitored according to the instructions in section 6.1.1.2.4.

6.2 DRUG ACCOUNTABILITY

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator is required to maintain adequate records of all investigational drug storage and disposition. For all DAIT-sponsored clinical trials, these responsibilities are delegated to the site's pharmacist of record (PoR). The PoR must maintain all records related to storage and disposition of VIB4920 vials including:

1. Ensure drugs are stored in a secured area, with access limited to authorized pharmacy personnel and stored under appropriate temperature range as specified in the protocol and pharmacy manual.

2. Date and quantity of the drug received.

3. Date and quantity of the drug dispensed.

    a. A drug dispensing log will be kept current for each drug and participant. These logs will contain the drug information, identification of each participant, the date, and quantity of drug dispensed. Please see pharmacy manual for more detailed information.

4. Detailed accountability of any unused (un-dispensed) VIB4920 vials for return to the DAIT/NIAID investigational drug distributor.

    a. All remaining unused and/or expired VIB4920 vials will be returned to DAIT/NIAID investigational drug distributor during study and after study termination.

All records regarding drug disposition will be maintained by the study site's investigational pharmacy and available for inspection.

6.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH INVESTIGATIONAL AGENT

Study treatment will be administered at the study sites by trained medical staff. Compliance, therefore, will be monitored by the site and documented on the electronic case report form (eCRF).

6.4 TOXICITY MANAGEMENT

6.4.1 Infusion or hypersensitivity reactions

Participants will be monitored for infusion or hypersensitivity reactions, and will receive VIB4920 or VIB4920 placebo in a clinical trial facility with personnel, medications, and equipment immediately available to treat these types of reactions. Antihistamine (e.g., diphenhydramine or cetirizine) and/or acetaminophen can be administered per institutional guidelines prior to VIB4920 infusion to help prevent infusion reactions, at the discretion of the site investigator. Administration of glucocorticoids prior to VIB4920 infusion to help prevent infusion reactions is not permitted (Section 7.3).

Administration of study treatment will be permanently discontinued if the participant develops a grade 3 or greater hypersensitivity, anaphylactic (Appendix 11), or infusion reaction.

6.4.2 Infection

Clinical assessments for signs of infection will be performed at each study visit. Participants will also be contacted by telephone at study weeks 6, 10, and 14 to assess for infection. Participants will be given instructions on potential signs of infection and instructed to contact the site investigator if they have signs or symptoms of an infection.

VIB4920/VIB4920 placebo will be suspended if the participant develops an infection that is grade 2 or greater where systemic treatment (e.g., antibiotic, antifungal or antiviral) is indicated, or if the investigator judges it to be significant. The site investigator and the participant's treating physician will determine if other DMARD therapies should continue or be suspended.

If the infection resolves, VIB4920 or VIB4920 placebo may be restarted at the next scheduled dose at the investigator's discretion.

6.4.3 Liver Chemistry Abnormalities

Participants will be monitored for drug induced liver injury. Abnormalities in liver chemistries have not been observed in participants receiving VIB4920 but they remain possible. If liver chemistries are found to be abnormal in a participant, they should be repeated in 1-2 weeks for confirmation. If liver chemistry abnormalities are confirmed, then the dosing of VIB4920 or VIB4920 placebo should be adjusted as shown in Table 5.

Table 5. Dose Modification for Liver Chemistry Abnormalities

ALT/AST	Action
< 3xULN	Maintain dosing.
3-5xULN or 1.5-3x baseline if baseline abnormal, with serum total bilirubin < 2x ULN	Suspend study treatment at first occurrence. Recheck ALT/AST prior to the next expected dose and if AST and ALT < 3xULN (<1.5-3x baseline if baseline abnormal), resume treatment per study schedule. Permanently discontinue study treatment if ALT or AST ≥ 3xULN a second time.
≥ 3xULN with serum total bilirubin ≥ 2xULN (Hy's Law), regardless of baseline values	Discontinue study treatment.
≥ 5xULN, regardless of baseline values	Discontinue study treatment.

6.5 DISCONTINUATION OF STUDY DRUG ADMINISTRATION

Study drug administration (week 0 to week 12) will be discontinued for the following reasons:

1. A toxicity management discontinuation criterion is met for VIB4920 (Section 6.4).
2. The participant experiences a grade 3 or greater AE that the investigator judges to be possibly related or related to study treatment.
3. The participant receives a prohibited disease-modifying or other systemic immunosuppressive drug, or has an increase in dose of a disease-modifying drug compared with the dose at baseline, except as permitted in Section 7.1.2
4. The participant receives a live-attenuated vaccine.
5. The participant becomes pregnant.
6. The participant requests that further study treatment be halted.
7. The investigator believes that continuing study treatment is no longer in the best interest of the participant.

Participants who meet these criteria will continue follow-up per the Schedule of Events presented in Appendix 1, and then continue post-drug administration follow-up per Appendix 3, unless the participant fulfilled criterion #3. Participants who fulfill criterion #3 will complete a treatment modification visit (Appendix 1) and enter alternate monitoring per Section 6.6.2 (Table 6, Appendix 4).

Participants who have study drug administration discontinued because of an adverse event will be followed until recovery from or stabilization of the adverse event. Participants who have study drug administration discontinued due to pregnancy will be followed using the alternate monitoring schedule (Appendix 4) to ascertain pregnancy outcomes.

If administration of study drug is discontinued, the NIAID Medical Monitor will be notified.

6.6 ALTERNATE MONITORING SCHEDULE

6.6.1 Participants with persistent disease activity that may require a change in disease-modifying therapy

From week 12 to week 40, a participant may be considered for a change in disease modifying treatment regimen (e.g., change from one TNFi to another TNFi [not including a change to its respective biosimilar], an increase in dose of a current disease-modifying medication, a switch to another disease-modifying drug, an increase in glucocorticoid dose, or use of a prohibited disease-modifying medication listed in Section 7.3) if either of the following occurs:

1. The participant has an SDAI > 26 at week 12 or later, which is confirmed at a study visit (scheduled or unscheduled) in the next 2-4 weeks

2. The participant has an SDAI > 11 at week 16 or later, and his/her SDAI has decreased by less than 50% from baseline, and both are confirmed at a study visit (scheduled or unscheduled) in the next 2-4 weeks.

Participants who fulfill any of these criteria above will be treated at the discretion of the participant's rheumatologist/treating physician.

It is expected that most participants who fulfill either of these two criteria will change their disease-modifying treatment regimen (i.e., switch or escalate their disease-modifying therapy). Participants who change their disease-modifying treatment will complete a treatment modification visit (Appendix 2 or Appendix 3) and enter alternate monitoring (Appendix 4). The alternative schedule of events consists of fewer visits and assessments to reduce the burden to participants who change DMARD therapy during the study while maintaining the ability to collect safety and efficacy data through week 40, recognizing the interpretation of these data may be confounded by medication changes. Alternate monitoring includes assessment of adverse events including AESIs; recording of concomitant medications at weeks 2, 4, 8, 12, 16, 24, 32, and 40; and disease activity assessments at weeks 16 and 40, if those visits have not already occurred. More frequent assessments can occur, as clinically indicated. However, a minority of participants who fulfill either of the two criteria above may, in consultation with their treating rheumatologist, choose not to change their disease-modifying therapy. These participants will continue with assessments according to the Schedule of Events in Appendix 2 or Appendix 3, depending on whether the participant achieves the primary endpoint and participates in dense sampling collection at home.

Table 6 summarizes the participant follow-up based on whether his/her disease modifying treatment regimen for RA is escalated or switched during the study.

If a participant enters alternate monitoring, the NIAID Medical Monitor will be notified.

6.6.2 Participants who escalate disease-modifying therapy or receive treatment with a prohibited medication

If the participant receives a prohibited disease-modifying or other systemic immunosuppressive drug, or has an increase in dose of a disease-modifying drug (including prednisone) compared with the dose at baseline (except as permitted in Section 7.1.2), regardless of whether criteria 1 or 2 are met in Section 6.6.1, the participant will complete a treatment modification visit (Appendix 1, Appendix 2, or Appendix 3) and will no longer follow the Schedule of Events presented in Appendix 1, Appendix 2, or Appendix 3. Instead, the participant will enter alternate monitoring and follow the Schedule of Events presented in Appendix **4** and Table 6. Alternate monitoring includes assessment of adverse events including AESIs; recording of concomitant medications at weeks 2, 4, 8, 12, 16, 24, 32, and 40; and disease activity assessments at weeks 16 and 40, if those visits have not already occurred. If a participant enters alternate monitoring, the NIAID Medical Monitor will be notified.

Table 6 summarizes the participant follow-up based on whether his/her disease modifying treatment regimen for RA changes or the participant uses a prohibited treatment for RA during the study.

Table 6. Participant's follow-up based on the status of their RA treatment regimen during the study

Description	Follow-Up Monitoring Actions
Participant's disease modifying RA treatment remains unchanged from randomization or the prednisone dose is decreased (Section 7.1.2.2) during the course of the study	Participant follows their current Schedule of Events per Appendix 1, Appendix 2, or Appendix 3
Participant's disease modifying treatment is escalated for any reason, the DMARD agent is changed, or the participant uses a prohibited treatment for RA (Section 7.3)	Participant completes a treatment modification visit per their current Schedule of Events (Appendix 1, Appendix 2, or Appendix 3). Participant enters alternate monitoring and is followed per Appendix 4.

7. OTHER MEDICATIONS

7.1 CONCOMITANT MEDICATIONS

7.1.1 Protocol Mandated

A participant randomized to the VIB4920 with TNFi or VIB4920 placebo with TNFi arms is required to continue the prescribed subcutaneous TNFi and maintain the same dose (the dose at study entry) until week 40 unless the TNFi is changed for persistent or worsening disease activity (Section 6.6.1), the participant experiences an adverse effect from TNFi use, or the participant exits the study (Section 11.2).

Participants randomized to VIB4920 without TNFi are required to stop TNFi use at randomization (week 0).

For all participants, changes in disease-modifying therapy may be considered after week 12 in the setting of persistent or worsening disease activity per Section 6.6.1.

7.1.2 Other Permitted Concomitant Medications

7.1.2.1 *Disease Modifying Anti-rheumatic Drugs (DMARDS)*

The following DMARDs are permitted at study entry. Their dose must be maintained at the same dose for the duration of the study unless the dose is reduced or the medication is stopped due to toxicity.

1. Methotrexate: up to 25 mg oral or subcutaneous weekly. Methotrexate may be held for 1 week after COVID-19 or influenza vaccination. Maintaining the same route of administration is strongly encouraged during study participation. However, a change in the route of administration is not considered a change in DMARD therapy as long as the administered dose remains the same. If methotrexate is held for a vaccination, the dates that methotrexate is held should be recorded on the appropriate eCRF.

2. Leflunomide: up to 20 mg oral daily. Participants cannot receive methotrexate and leflunomide concurrently.

3. Hydroxychloroquine: up to 400 mg oral daily.

4. Sulfasalazine: up to 3 g oral daily.

7.1.2.2 *Glucocorticoids*

Oral prednisone is permitted up to 10 mg oral daily (or equivalent dose of other oral glucocorticoid) at study entry. The prednisone dose cannot be tapered prior to the assessment of the primary endpoint at week 16. Prednisone can be tapered between weeks 16 to 30 if the participant is in remission (SDAI $\leq$ 3.3). Prednisone can be tapered at the investigator's discretion and according to patient preferences, but it is recommended to be not faster than decreasing the daily dose by 2.5 mg every two weeks for individuals taking prednisone 5-10 mg/day, and not faster than 1 mg every 2 weeks for individuals taking prednisone 1-5 mg/day.

One course of oral prednisone can be used to treat conditions other than RA, provided the dose does not exceed 40 mg daily and the duration is $\leq$ 2 weeks (Section 7.3). This course of prednisone cannot occur within weeks 12-16 or weeks 36-40.

One intra-articular or bursa injection of glucocorticoids is permitted after the assessment of the primary endpoint between weeks 16-32, provided the dose does not exceed 40 mg of triamcinolone (or equivalent dose of other injectable glucocorticoid).

7.1.2.3 *Other Medications*

Use of non-steroidal anti-inflammatory medications is permitted.

While not prohibited, use of herbal remedies is discouraged and should be discussed with the site investigator.

COVID-19 vaccines are permitted and strongly recommended to be given prior to initiation of study treatment if they have FDA emergency use authorization or are FDA-approved.

Medications to prevent or treat COVID-19 infection are also permitted if they have FDA emergency use authorization or are FDA-approved.

Participants should be instructed not to take any new medications or over-the-counter products without first consulting with the site investigator unless the medications are prescribed by a healthcare provider for another medical condition that develops or worsens during the study. In that case, the new medications should be reported as soon as possible to the site investigator.

7.2 PROPHYLACTIC MEDICATIONS

No prophylactic medications are required by this protocol.

It is recommended that participants be up-to-date with their recommended vaccinations at least 2 weeks prior to study entry, since VIB4920 may decrease responses to vaccinations. Prior to study participation, it is strongly recommended that participants receive the seasonal influenza vaccination and any new COVID-19 vaccine when available.

It is recommended that participants do not receive non-live vaccines (except for seasonal influenza) from the start of screening (Visit -1) to 8 weeks from the last dose of study drug treatment.

If the participant receives a COVID-19 vaccine during the study period, the type of vaccine and the date(s) of administration must be included in the source documentation and list of concomitant medications. Methotrexate may be held for 1 week after vaccination (Section 7.1.2.1).

7.3 PROHIBITED MEDICATIONS AND PROCEDURES

The following medications and procedures are prohibited:

- Any investigational drug or treatment other than VIB4920
- Live-attenuated vaccines
- Concurrent use of methotrexate and leflunomide in combination
- Injection of corticosteroids into joints or bursae, except as permitted after the assessment of the primary endpoint and between weeks 16-32 (Section 7.1.2.2)
- Intravenous glucocorticoids, unless used to treat infusion reactions
- Intramuscular injections of glucocorticoids

- ∞ Oral prednisone at doses or duration greater than described in Section 7.1.2
- ∞ Addition of a new treatment or increase in dose of current disease modifying therapy to treat RA except as specified in the protocol (Section 7.1)
- ∞ Plasmapheresis or plasma exchange
- ∞ Any other medication that fulfills exclusion criteria (Section 4.3)

7.4 RESCUE MEDICATIONS

Participants who meet any of the criteria in Section 6.6.1 may be considered for a change in his/her disease modifying treatment regimen for RA. These participants will be treated at the discretion of their rheumatologist/treating physician. If a participant is treated with a prohibited medication or their RA treatment regimen changes as described in Section 6.6, the participant will complete a treatment modification visit as per their current Schedule of Events (Appendix 1, Appendix 2, or Appendix 3), and will enter alternate monitoring (Appendix **4**).

7.5 CONTRACEPTION AND AVOIDING PREGNANCY

All participants who engage in sexual activity that could lead to pregnancy must use an acceptable method of contraception to avoid pregnancy during the period from 2 weeks prior to the administration of the first dose of the study drug until the end of the study (week 40). Participants who exit the study prior to week 40 should continue contraception for 24 weeks after the last dose of study medication.

Acceptable forms of contraception include consistent and correct use of combined estrogen and progestogen contraceptives, progestin-only contraceptives, intrauterine hormone releasing systems or devices with <1% failure rate, bilateral tubal occlusion, male partner sterilization, or double barrier methods (e.g., condom and occlusive cap with spermicidal agent) or complete abstinence. For study participants relying on a sterile male partner, documentation of azoospermia must occur prior to the participant's entry into the study (for female participants relying on a sterile male partner, this must be their only partner).

Periodic abstinence and withdrawal are not acceptable methods of contraception.

The investigator is responsible for ensuring participants understand how to properly use these methods of contraception. The allowed contraceptive products are only effective when used consistently, correctly, and in accordance with the product label.

8. STUDY PROCEDURES / ASSESSMENTS

8.1 ENROLLMENT

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study

procedures. Participants who sign consent and meet the eligibility criteria will be randomly assigned to a study treatment group (VIB4920 with TNFi, VIB4920 placebo with TNFi, or VIB4920 without TNFi), in a 2:1:1 fashion. A participant is enrolled into the study when the informed consent form is signed.

8.2 SCREENING/BASELINE VISIT

8.2.1 Screening Visit

The purpose of the screening period is to confirm eligibility to continue in the study. Screening of study participants will take place at Visit -1. Participants will be assessed for the eligibility criteria listed in Sections 4.2 and 4.3.

8.2.2 Baseline Visit

Baseline is defined as Week 0 (Visit 0).

8.3 STUDY ASSESSMENTS

The study assessments to be performed at each study visit are listed in the Schedules of Events: Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

8.3.1 General Assessments

- Informed consent: Written informed consent will be obtained before any study assessments or procedures are performed.
- Eligibility criteria: Eligibility for study participation will be assessed during the screening period.
- Demographics: age, sex, race, and ethnicity.
- Medical history: A history will be taken to determine if the participant has had any clinically significant diseases or medical procedures other than the disease under study.
- Rheumatoid arthritis history, including date of diagnosis and previous treatments.
- Comprehensive physical examination includes the following body systems: musculoskeletal, respiratory, cardiovascular, gastrointestinal, skin, neurologic and renal/urinary.
- Limited physical examination focuses on the musculoskeletal exam and body systems relevant to the participant's clinical complaints and clinical status at the study visit.
- Adverse events: Participants will be assessed for AEs. All adverse events will be graded, recorded on the case report forms (CRFs), and reported per Section 12.
- Concomitant medications: All concomitant medications and their indications will be recorded.

- Vital signs: Height and weight will be obtained at screening (V-1); weight, temperature, blood pressure, respiration, and pulse will be obtained at all visits. Temperature, blood pressure, respiration, and pulse will be obtained prior to VIB4920/VIB4920 placebo infusion, approximately every 30 minutes (+/- 5 minutes) during study drug administration, and approximately every 30 minutes (+/- 5 minutes) during the subsequent observation period.

8.3.2 Clinical Assessments

i. Laboratory Assessments: Central Laboratory

- Hematology: CBC with differential
- Chemistry: Creatinine, total bilirubin, AST, ALT, alkaline phosphatase, and albumin
- Inflammatory marker: C-reactive protein
- HIV (RNA or antibody)
- Hepatitis B (surface antigen, core antibody)
- Hepatitis C (RNA or antibody)
- Tuberculosis testing: QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test
- Rheumatoid factor (RF)
- Anti-citrullinated peptide antibodies (ACPA)
- Serum pregnancy (for women with childbearing potential)

ii. Laboratory Assessments: Local Laboratory

- STAT urine pregnancy (for women with childbearing potential)

iii. Other Assessments

- PPD skin test for participants with an indeterminate QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test, if not performed within the past 3 months
- AP and lateral chest radiograph for participants with an indeterminate QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test, if not performed within the past 3 months

8.3.3 Disease Specific Assessments

Completed by the blinded evaluator:

- Tender and swollen joint count (Appendix 5): 44 joint count

- ∞ Health care provider global health assessment (Appendix 6)

Completed by the participant:

- ∞ Patient global health assessment (Appendix 6)
- ∞ Pain assessment (Appendix 6)
- ∞ Health Assessment Questionnaire – Disability Index (HAQ-DI) [33] (Appendix 8)
- ∞ PROMIS-29 Profile [34] (Appendix 9)
- ∞ RAPID3 (Appendix 7)

8.3.4 Mechanistic Assessments

The following samples will be collected for mechanistic assessments.

Clinic collection:

- ∞ Plasma PK, anti-drug antibody, and sCD40L assays
- ∞ Serum PK assays
- ∞ Peripheral blood mononuclear cells (PBMCs)
- ∞ Serum
- ∞ Whole blood DNA
- ∞ Whole blood RNA
- ∞ Whole blood RNA-microcontainer (training)

Home collection after week 16 and through week 40 by participant (Appendix 2):

- ∞ Whole blood RNA-microcontainer

Section 9 provides a detailed discussion of the mechanistic assays to be performed.

8.3.5 Study Drug Administration

- ∞ Intravenous infusion of study treatment (VIB4920 or VIB4920 placebo)

8.4 TREATMENT MODIFICATION VISIT

Participants who switch or escalate their immunosuppression or use a prohibited medication to treat their rheumatoid arthritis (Section 6.6) will complete the assessments outlined for the treatment modification visit per their current Schedule of Events (Appendix 1, Appendix 2, or Appendix 3) and then enter alternate monitoring (Appendix 4).

8.5 STUDY DISCONTINUATION VISIT

Participants who withdraw from the study (Section 11.2) will be asked to complete the assessments outlined in the discontinuation visit (DV) in their current Schedule of Events (Appendix 1, Appendix 2, Appendix 3, or Appendix 4).

8.6 UNSCHEDULED VISITS

If a participant experiences worsening disease activity, any potential toxicity, or develops other concerns between regularly scheduled visits, the participant should contact study personnel and may be asked to return to the study site for an "unscheduled" visit for further assessment. Assessments obtained during an unscheduled visit are outlined in each of the Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4). Some assessments for an unscheduled visit may be omitted at the discretion of the investigator if not indicated.

8.7 VISIT WINDOWS

Study visits should take place within the time limits specified below:

Baseline/Visit 0 must occur within 6 weeks of Visit –1. All other scheduled study visits must occur within the time limits specified in Table 7 below:

Table 7. Visit Windows

Visit	Time point(s)	Visit Window
Appendix 1. Schedule of Events: Screening and Study Drug Administration		
Screening - Visit -1	Within 6 weeks of Day 0	
Baseline - Visit 0	Day 0	n/a
Visits 1-7	Weeks 2 – up to but not including week 16	+/- 3 days
Appendix 2. Schedule of Events: Post-Drug Administration with Dense Sampling Collection		
Visits 8, 9, 10, …14	Every 4 weeks from week 16 to week 40	+/- 7 days
Dense sampling collection (whole blood RNA microcontainer collection and RAPID3 assessment at visits 8, 8.1, 8.2, 8.3, 9, 9.1, etc.)	In clinic at week 16 At home every week from week 17 to week 40	+/- 7 days +/- 1 days
Treatment Modification or Study Discontinuation visit	As needed	As per window for next scheduled in-person visit
Appendix 3. Schedule of Events: Post-Drug Administration without Dense Sampling Collection		

Visits 8, 9, 10, …14	Every 4 weeks from week 16 to week 40	+/- 7 days
Treatment Modification or Study Discontinuation visit	As needed	As per window for next scheduled in-person visit
Appendix 4. Schedule of Events: Alternate Monitoring		
M1-M2	Weeks 2 and 4	+/- 3 days
M3-M8	Weeks 8 to 40	+/- 7 days
Study Discontinuation visit	As needed	As per window for next scheduled in-person visit

9. MECHANISTIC ASSAYS

In this study, serial blood specimens will be collected to interrogate mechanisms of tolerance induction and maintenance. The objectives are to determine how the addition of VIB4920 to TNF-α inhibition affects the frequencies, phenotypes, and functional profiles of relevant T cell, B cell and myeloid cell populations in blood, and to quantify soluble mediators in serum and plasma associated with RA and the blockade of CD40-CD40L signaling. These studies will explore immune signatures that correlate with clinical response outcomes. Mechanistic studies will address multiple questions but will be prioritized based on the amount of blood available.

9.1 MECHANISTIC HYPOTHESES

The CD40-CD40L pathway plays a critical role in the mechanisms of T cell activation and has long been investigated as a promising therapeutic target in RA, as well as other immune-mediated diseases. CD40-CD40L interactions also stimulate B cell differentiation, germinal center formation, and antibody isotype switching. This pathway appears to be active in patients with RA. Synovial tissue from patients with both early and established RA show increased levels of CD40L gene expression that positively correlate with disease activity (DAS28-ESR). [7] CD40L expression is higher on the surface of CD4+ T cells obtained from blood and synovial tissue of patients with RA compared to healthy controls. [6, 35] Therefore, this trial will test the hypothesis that the addition of VIB4920 to TNFi therapy in patients with RA and ongoing disease activity will effectively inhibit activation of effector T cells by blocking a key costimulatory pathway and thereby result in improved disease control. This hypothesis will be explored by comparing the mechanistic results across the three study arms.

9.2 PROPOSED MECHANISTIC ASSAYS

9.2.1 Peripheral Blood Cells

Flow cytometry, mass cytometry, CITE-seq, single cell or bulk RNAseq, ATACseq, and DNA methylation sequencing may be done at ITN laboratories to determine how the addition of VIB4920 to a TNFi affects the frequency, phenotype, gene expression, and functional status of specific immune cell populations in viably cryopreserved PBMC. In

addition, functional status of various cell subsets may be examined by *in vitro* culture. To investigate oligoclonality of purified T cells and B cells, we may sequence DNA and/or RNA encoding the T cell receptor and B cell receptor, respectively. Proposed immunophenotyping panels will be finalized and validated by the ITN prior to starting batched analysis. Profiles of circulating cells may be compared between the baseline and various time points following treatment. Additional comparisons may be made between treatment groups to evaluate the effect of treatment on specific cell phenotypes and profiles and to identify phenotypes and/or profiles that correlate with clinical outcomes. The following cellular parameters may be interrogated to determine the effects of VIB4920 or VIB4920 placebo in RA patients that have responded inadequately to TNF-α inhibition:

1. Frequency, phenotype, gene expression, and functional profile of CD4+CD27-HLA-DR+ [36], CD4+ CXCR5-PD1hi Tph, [37] Tfh, [38-40] or other T cells [38] in blood
2. Frequency, phenotype, gene expression, and functional profile of CD14+ myeloid subsets in blood [38, 41]
3. Frequency, phenotype, gene expression, and functional profile of ABCs, [38] memory B cells, and other B cell subsets (i.e. CD21-/low) [42] in blood.
4. Expression level and frequency of CD40 and CD40L proteins in relevant myeloid, B cell and T cell populations in blood
5. Oligoclonality of T cells and B cells in blood, as measured by T cell receptor and B cell receptor sequencing
6. Epigenetic profile of purified cell subsets, such as T cells and B cells
7. Frequency, phenotype, gene expression, and functional profile of other relevant hematopoietic or non-hematopoietic cells in blood

9.2.2 Serum and Plasma Assays

In RA, the differential responses to TNFi therapy may be partly explained by the cellular heterogeneity of synovial tissue among individuals with the clinical phenotype that defines this disease. An analysis of synovial tissue samples from patients with established RA reveals subgroups of myeloid, lymphoid, and mixed phenotypes that correlate with circulating levels of sICAM and CXCL13. [11] This hypothesis was further explored in the ADACTA trial comparing the clinical efficacy of adalimumab, an anti-TNF-α antibody, with tocilizumab, an anti-IL-6R antibody. Patients with high serum sICAM levels and low CXCL13 levels in the ADACTA trial and by inference, with the myeloid phenotype, showed the best response to adalimumab therapy; whereas, patients with high serum CXCL13 levels and low sICAM levels, characteristic of the lymphoid phenotype, benefited more from tocilizumab therapy. These predictive biomarkers of differential treatment response have been reproduced in another RA cohort. [13]

Participant serum and plasma will be collected and stored for longitudinal analyses using validated platforms to determine how addition of VIB4920 or VIB4920 placebo affects RA in patients that have responded inadequately to TNFi therapy. Soluble factors that may be examined include:

- Levels of antibodies or autoantibodies, such as rheumatoid factor and anti-cyclic citrullinated peptide antibody (ACPA)
- Levels of sCD40L
- Levels of anti-drug antibodies targeting VIB4920, adalimumab, etanercept, or other relevant TNFi, if assays are available
- Levels of VIB4920
- Levels of adalimumab, etanercept, or other relevant TNFi as applicable
- Levels of CXCL13, sICAM, and any other relevant soluble mediators (e.g., IL-21, IL-10, IL-2, IL-17A, IFNγ, etc.)

Levels of soluble immune parameters may be compared between the baseline and time points following treatment. Comparisons may be made between treatment groups to evaluate the effect of the therapeutic intervention on changes in circulating levels of soluble immune parameters. In addition, we may determine the relationship between baseline sICAM and CXCL13 levels and treatment response. The impact of coadministration of TNFi and VIB4920 on the drug levels of VIB4920 and the TNFi may be assessed using parameters such as AUC, Cmax, and $t_{1/2}$ (half-life). Finally, levels of soluble immune parameters may also be evaluated for associations with frequency, phenotype, and/or functional profile of circulating cells, such as T cell, B cell and myeloid populations.

9.2.3 Whole Blood Assays

9.2.3.1 *RNA*

Systemic treatment with biologic medications has been shown to modulate gene expression in autoimmune disease; therefore, whole blood can be used to evaluate changes in the transcriptional signatures of circulating immune cells related to the experimental intervention, namely VIB4920. Whole blood will be collected and may be used to evaluate gene expression profiles before, during, and after treatment. Gene expression of molecules found to be modulated by treatment in blood leukocytes may be investigated in whole blood using quantitative methods.

The results from the PRIME study indicate that weekly sampling of whole blood to identify key transcriptional signatures together with measurement of patient reported disease activity by RAPID3 may be used to identify indicators of disease flares in RA. [43] In this current study, whole blood will be collected in clinic at week 16 and then weekly at home (“dense sampling collection”) from week 17 through week 40 using the methods described in the PRIME study [43] by participants who achieve the primary endpoint at week 16 (SDAI ≤ 11). These samples will be used to examine gene expression signatures of various cell types and their changes over time, as well as to explore whether the circulating fibroblast and activated B cell gene signatures detected shortly before a disease flare as assessed by RAPID3 in the PRIME study also precede an

RA flare in those participants in the current trial who achieve the primary endpoint at week 16.

9.2.3.2 *DNA*

Specific *CD40* alleles are associated with RA risk and B cells homozygous for the *CD40* risk allele display increased surface expression of CD40 compared to their non-risk allele counterparts. [8] Thus, genetic differences may, in part, determine response to CD40L blockade with VIB4920. DNA will be collected from all consenting participants, and ITN may perform genotyping or sequencing of relevant disease- or immune-associated genes, such as HLA Class I/II alleles, genes with reported associations to RA, or genes related to the CD40L-CD40 pathway to investigate correlations with disease activity and therapeutic response. Similarly, whole blood may be used to examine epigenetic status of relevant disease- or immune-associated genes and to investigate relationships between epigenetics and disease activity or therapeutic response.

9.3 FUTURE / UNPLANNED STUDIES

Specimens collected and stored during the trial may be used in future assays to reevaluate biological responses as research tests are developed over time. Reevaluations or new assays will only be performed on samples of participants who have consented for future research. Participant consent will be obtained for future use of samples, including specific consent for future studies of genetic material.

10. BIOSPECIMEN STORAGE

A major priority of the Immune Tolerance Network, in partnership with the National Institute of Allergy and Infectious Diseases of the NIH, USA, is the development of novel immunoassays in order to better understand mechanisms of tolerance and to develop biomarkers to predict the development and maintenance of clinical tolerance. As in all Immune Tolerance Network-funded clinical trials, informed consent will be obtained from all participants for their samples to be stored for use in future studies. For consenting participants, biological specimens collected in this trial will be stored long-term in order to re-evaluate biologic responses as new research tools to study tolerance become available. The specimens will therefore be stored at the ITN sample repository for a minimum of 10 years. Residual specimens may be used by the investigators for development of new immunologic assays or for cross-trial comparisons. Although specimens in this protocol are described in the context of assays to be performed, it should be noted that not necessarily all assays will be performed for all participants at each time point. Decisions to perform assays will be made based on statistical and scientific planning, hypotheses to be tested, and technologies available. Finally, clinical outcomes will be taken into account to determine the potential value of the assays. For example, if a clinical effect fails to occur, it may be decided that there is minimal value in performing certain mechanistic assays. The ITN sample sharing policy will apply for the provision of samples to study or outside investigators (www.immunetolerance.org).

11. CRITERIA FOR PARTICIPANT AND STUDY COMPLETION AND PREMATURE STUDY TERMINATION

11.1 PARTICIPANT COMPLETION

A participant is considered to have completed the study if the participant is enrolled and completes the last visit at Week 40 (Visit 11).

11.2 PREMATURE TERMINATION OF STUDY PARTICPATION

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up". Study investigators will contact participants who fail to maintain contact with the investigator through telephone, mail and emergency contacts. Participants will be considered lost to follow-up if these attempts to reestablish contact with the participant have failed. Additional details are provided in the MOP.
3. The participant dies.
4. The investigator no longer believes participation is in the best interest of the participant.

Participants who are prematurely terminated from the study will undergo the follow-up procedures described in Section 11.4.

11.3 PARTICIPANT REPLACEMENT

Randomized participants will be replaced if they do not receive any amount of study medication.

11.4 FOLLOW-UP AFTER PREMATURE TERMINATION OF STUDY PARTICIPATION

Participants who terminate study participation as described in Section 11.2 will be asked to return for a final visit where the assessments outlined in the discontinuation visit (DV) in their current Schedule of Events (Appendix 1, Appendix 2, Appendix 3, or Appendix 4) will be performed. Other than follow-up for adverse events as described in Section 12.4.3, no additional follow-up will be requested from participants after premature termination of study participation. Participants will be advised to continue contraception for 24 weeks after the last dose of VIB4920.

11.5 STUDY STOPPING RULES

There are no pre-specified study stopping rules for this study. If any of the safety criteria described in Section 12.8.2.2 are met, an *ad hoc* DSMB review will occur. After review

of the data, the DSMB will make recommendations regarding the study conduct and/or continuation.

A non-binding interim analysis for futility will be conducted as per Section 13.5.1. The DSMB may make recommendations regarding study continuation after reviewing the results of the interim analysis.

12. SAFETY MONITORING AND REPORTING

12.1 OVERVIEW

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, Reporting of Serious Adverse Events and Adverse Events) to the sponsor (DAIT/NIAID). Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies *with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice,* 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.).

12.2 DEFINITIONS

12.2.1 Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (21 CFR 312.32 (a)).

12.2.1.1 *Suspected Adverse Reaction (SAR)*

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in current investigator's brochure for VIB4920 or is not listed at the specificity, severity, or rate of occurrence that has been observed.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

12.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID), it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor (DAIT/NIAID), its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.2.4 Adverse Event of Special Interest

The following are considered Adverse Events of Special Interest (AESI) and must be reported to the IND Sponsor within 24 hours, according to the procedure for SAE reporting described in Section 12.5.1:

- ∞ Anaphylaxis and grade 3 or higher hypersensitivity reactions
- ∞ Grade 3 or higher infusion reactions
- ∞ AST or ALT > 3xULN with serum total bilirubin > 2xULN (Hy's Law)
- ∞ Grade 3 or higher infection
- ∞ Opportunistic infections including but not limited to reactivation of latent viral infections, invasive fungal infections, and TB
- ∞ Malignant neoplasm

- Immune complex disease

12.3 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

12.3.1 Grading of Liver Chemistry Abnormalities

For this study, liver chemistry abnormalities will be graded using protocol specific criteria, and are defined relative to the upper limit of normal (ULN) as follows:

- Aspartate aminotransferase [AST] increased
  - Grade 1: > ULN – 3.0x ULN
  - Grade 2: > 3.0x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Alanine aminotransferase [ALT] increased
  - Grade 1: > ULN – 3.0x ULN
  - Grade 2: > 3.0x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Alkaline phosphatase [ALP] increased
  - Grade 1: > ULN – 2.5x ULN
  - Grade 2: > 2.5x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Blood bilirubin increased
  - Grade 1: > ULN – 1.5x ULN
  - Grade 2: > 1.5x ULN - 3.0x ULN
  - Grade 3: > 3.0x ULN - 10.0x ULN
  - Grade 4: > 10.0x ULN

12.3.2 Grading of Other Adverse Events

For all other adverse events not related to liver chemistry abnormalities, the study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chair, ITN Clinical Trial Physician, and the NIAID Medical Monitor, and has been deemed appropriate for the population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe adverse event.

Grade 4 = life-threatening adverse event or urgent intervention indicated.

Grade 5 = death.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

12.3.3 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen (VIB4920 or VIB4920 placebo) will initially be determined by the site investigator and recorded on the appropriate AE/SAE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID (sponsor). The relationship of an adverse event to the study therapy regimen (VIB4920 or VIB4920 placebo) will be determined using the descriptors and definitions provided in Table 8.

Table 8. Attribution of Adverse Events

Code	Descriptor	Relationship to the investigational product
Unrelated Category		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
Related Categories		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4 COLLECTION AND RECORDING OF ADVERSE EVENTS

12.4.1 Collection Period

Adverse events will be collected from the time of participant signs informed consent until a participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3 Recording Adverse Events

All grades of adverse events (AEs), with the exception of laboratory Grade 1 AEs, will be collected and recorded on the AE eCRF. The investigator will record AEs and SAEs (Section 12.2) on the appropriate AE eCRF regardless of the relationship to study treatment.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, it stabilizes in the case of a chronic condition, or the participant declines further contact or is lost to follow-up.

12.5 REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST

12.5.1 Reporting of Adverse Events

This section describes the responsibilities of site investigators to report AEs to the study sponsor via the CDSMC. Timely reporting of AEs is required.

Unless otherwise noted below in Section 12.5.2 for SAEs and AESIs, AEs must be recorded on the AE/SAE eCRF within five (5) days of discovery of the event. Whenever possible, a diagnosis should be provided, rather than compilation of signs/symptoms, with grade of the event dictated by highest grade of the sign/symptom component.

12.5.2 Reporting of Serious Adverse Events and Adverse Events of Special Interest to Sponsor

This section describes the responsibilities of the site investigator to report SAEs and AESIs to the sponsor (DAIT/NIAID) via the eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all SAEs (see Section 12.2.3, *Serious Adverse Event)* and AESIs (see Section 12.2.4, *Adverse Events of Special Interest)*, regardless of relationship or expectedness, within 24 hours of discovering the event.

For SAEs and AESIs, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF should be updated and submitted. Every time the AE/SAE eCRF is submitted, it should be electronically signed by the investigator or sub-investigator.

For additional information regarding SAE and AESI reporting, contact Rho Product Safety (CDSMC):

Rho Product Safety
2635 East NC Highway 54
Durham, NC 27713

Toll-free - (888) 746-7231
SAE Fax Line: 1-888-746-3293
Email: rho_productsafety@rhoworld.com

12.5.3 Reporting to Health Authority

After an adverse event requiring 24-hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

12.5.3.1 *Annual Reporting*

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Adverse events of special interest (AESIs)
- Pregnancies

12.5.3.2 *Expedited Safety Reporting*

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction [SUSAR]** (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report to FDA and all participating investigators any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: **Any findings from studies that suggests a significant human risk**

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g., mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.4 Reporting of Adverse Events to IRB/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by DAIT/NIAID or designee to all participating institutions for site IRB/IEC submission.

12.6 PREGNANCY REPORTING

The investigator shall be informed immediately of any pregnancy in a study participant or a partner of a study participant. A pregnant participant shall be instructed to stop taking study medication. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to DAIT/NIAID all pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to DAIT/NIAID when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study participant.
Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Sex
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, and 5 minutes after birth, if available
- Any abnormalities

While pregnancy itself is not considered to be an AE or SAE, pregnancy outcomes such as miscarriage or termination must be reported as an SAE to the sponsor as described above, in Section 12.5.2, *Reporting of Serious Adverse Events and Adverse Events of Special Interest to Sponsor*. In addition, if the pregnancy results in a congenital abnormality or birth defect, a separate SAE report must be submitted to the Sponsor, DAIT/NIAID, using the SAE reporting procedures described above.

12.7 REPORTING OF OTHER SAFETY INFORMATION

An investigator shall promptly notify the IRB as well as DAIT/NIAID when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

12.8 REVIEW OF SAFETY INFORMATION

12.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the Statistical and Clinical Coordinating Center (SCCC) compiling new and accumulating information on AEs, SAEs, AESIs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the SCCC (See Sections 12.5.2, *Reporting of Serious Adverse Events*, and 12.6, *Pregnancy Reporting*).

12.8.2 DSMB Review

12.8.2.1 *Planned DSMB Reviews*

The NIAID Autoimmune Data and Safety Monitoring Board (DSMB) will review safety data and make recommendations regarding the continuation, termination, or modification of the study. The DSMB shall review safety data 6 months after the first participant is treated and then at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner.

12.8.2.2 *Ad hoc DSMB Reviews*

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- ∞ Any death which is possibly related or related to study treatment.
- ∞ A grade 3 or higher SAE of the same preferred term that is possibly related or related to study treatment in two or more of the participants who have received a study treatment.
- ∞ The observed rate of grade 3 or higher infections is higher than anticipated in the VIB4920 with TNFi arm, the VIB4920 without TNFi arm, or in the two VIB4920 arms pooled together, as indicated in Table 9. This rule will be monitored for each treatment arm separately and for both VIB4920 treatment arms pooled together by an unblinded statistician.

Table 9. Infection rule for triggering an ad hoc DSMB review.

This rule is to be evaluated separately for each of the VIB4920 study arms and across both VIB4920 study arms pooled together[1].

Number of Grade 3 or higher infections observed in the group of interest	Total number of participants treated in the group of interest
2	≤11
3	12-22
4	23-34
5	35-47
6	48-60
7	61-73
8	74-78

[1] Based on the expectation that the underlying risk of severe infection is 2-3% in the VIB4920 placebo with TNFi arm and that an increase to 6% in the VIB4920 with TNFi arm, the VIB4920 without TNFi arm, or in the VIB4920 arms pooled together might be of concern. See Section 13.5 for details.

- A grade 2 or higher thromboembolic event in 2 or more participants who have received any assigned study treatment.
- Two grade 4 (life-threatening) infusion reactions, including anaphylaxis, that occur during administration of study treatment, or in the first 24 hours after each study treatment.
- Any event which in the opinion of the Protocol Chair or Medical Monitor merits DSMB review.

The DSMB will review the data within 2 weeks of the event being identified. If the DSMB has not reviewed the data within 2 weeks, a temporary halt in enrollment will be implemented. Participants already in screening may continue with screening assessments but will not begin treatment. Participants already enrolled in the trial will continue as planned, pending completion of the DSMB *ad hoc* review.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation. The DSMB will also advise as to the subsequent frequency of reporting for any criterion which triggered an *ad hoc* review.

13. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

13.1 OVERVIEW

ITN092AI is a randomized, placebo-controlled, three-arm (two arms double-blinded, one arm evaluator-blinded) trial in which participants with RA taking a TNFi will be randomized to receive a 12-week course of VIB4920 with TNFi, VIB4920 placebo with TNFi, or VIB4920 without TNFi. The primary objective is to determine if the addition of a 12-week course of treatment with VIB4920 to a TNFi in patients with RA who have had an inadequate response to a TNFi results in improved clinical disease control. The study also aims to evaluate safety and assess the durability of clinical response.

13.2 ENDPOINTS

Primary, secondary, and exploratory endpoints are listed in Sections 3.3, 3.4, and 3.5.

13.3 MEASURES TO MINIMIZE BIAS

This study has a randomized placebo-controlled, prospective design with blinding and well-defined entry criteria. Participants and site personnel who manage participants will be blinded to treatment assignment for the VIB4920 with TNFi and VIB4920 placebo with TNFi arms throughout the trial. Assessments of disease activity and adverse events will be performed by a blinded study assessor for all 3 treatment groups. In addition, site personnel, including investigators, will not have access to any mechanistic data until completion of the study.

13.4 ANALYSIS PLAN

13.4.1 Analysis Populations

Safety sample (SS): All participants who receive any amount of VIB4920 or VIB4920 placebo. The safety analyses will be based on the actual treatment the participants receive.

Modified Intent to treat (mITT) sample: All randomized participants who receive any amount of VIB4920 or VIB4920 placebo. The efficacy analyses will be based on the mITT sample according to the group to which the participants are assigned.

Per protocol (PP) sample: All participants in the mITT sample with no protocol deviations that impact efficacy assessments, who received at least 80% of the total planned cumulative dose of the expected study treatment, and for whom the primary endpoint can be evaluated either by completing the week 16 SDAI or by failing prior to Week 16 due to increased disease activity requiring a change in RA medications. The reported major deviations will be reviewed during a masked data review after the last participant's primary endpoint visit to determine which participants should be excluded from the per-protocol population.

13.4.2 Primary Analysis of Primary Endpoint

The primary endpoint is the proportion of participants achieving low disease activity, as defined by a SDAI ≤ 11 at week 16. In addition, participants who take prohibited medications as treatment for RA prior to week 16 will be considered to have failed the primary endpoint. A participant's SDAI status at week 16 will be used for the analysis of the primary endpoint for participants who temporarily or permanently discontinue VIB4920 and/or TNFi, but do not take prohibited medications and continue study follow-up through Week 16. These participants will not be considered to have failed the primary endpoint unless their SDAI is > 11.

The primary analysis of the primary endpoint will be performed on the mITT sample utilizing participants in the VIB4920 with TNFi and VIB4920 placebo with TNFi arms and is designed to test the following hypotheses:

- Null hypothesis: The proportion achieving low disease activity at week 16 does not differ between the VIB4920 with TNFi and VIB4920 placebo with TNFi groups.
- Alternate hypothesis: The proportion achieving a low disease activity at week 16 differs between the VIB4920 with TNFi and VIB4920 placebo with TNFi groups.

The proportion of mITT participants achieving low disease activity at week 16 will be estimated for the VIB4920 with TNFi and VIB4920 placebo with TNFi groups. Groups will be compared using a two-sided Fisher's Exact test evaluated using a Type 1 error rate of α=0.10.

Intercurrent Events. For the primary analysis of the primary endpoint, we assume all participants for whom the SDAI cannot be evaluated at Week 16 (e.g., due to missed visit or failure due to taking any prohibited medications for treatment of RA prior to Week 16) would have failed the primary endpoint.

13.4.3 Supportive Analyses of the Primary Endpoint

At a minimum, the following sensitivity analyses for the primary analyses will be performed:

- An analysis comparing treatment group estimates from a logistic regression adjusting for baseline SDAI score.
- An analysis analogous to the primary analysis, where all participants for whom disease activity cannot be evaluated (by SDAI or failure) are dropped from the analysis.
- An analysis analogous to the primary analysis, where the difference in response (e.g., SDAI $\leq$ 11) at Week 16 will be evaluated between treatments in all randomized patients regardless of whether a participant took prohibited medications as treatment for RA or not. We assume all participants for whom the SDAI cannot be evaluated at Week 16 (e.g., due to missed Week 16 visit) would have failed the primary endpoint.
- An analysis analogous to the primary analysis using the PP participants in the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups.

13.4.4 Analyses of Secondary Endpoints

13.4.4.1 *Efficacy*

All secondary inferential analyses are considered supportive; p-values for the test of differences among groups will be presented without adjustment for multiple comparisons. The mITT population for the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups will be used for all secondary efficacy analyses. The null hypothesis proposes that there are no differences in the secondary endpoints between the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups. The alternative hypothesis proposes that there are differences between the two groups. Unless specified otherwise, data will not be imputed for analyses of secondary endpoints.

The following analyses are planned to support the primary objective to evaluate the impact of treatment on control of disease.

1. For secondary endpoints that are defined as proportions achieving low disease activity, remission, sustained remission, or ACR response, where participants who escalate their disease-modifying therapy or take prohibited medications as treatment for RA prior to the endpoint are failures, analyses will be analogous to that described for the analysis of the primary endpoint.

   Intercurrent Events. We assume all participants for whom the endpoint cannot be evaluated at the timepoint of interest (e.g., due to a missed visit or participant took any prohibited medications for treatment of RA prior to the timepoint of interest) would have failed the endpoint.

2. For secondary endpoints that are defined as time to first occurrence of low disease activity (e.g., SDAI ≤ 11; DAS28-CRP ≤ 3.2) or remission (e.g., SDAI ≤ 3.3; DAS28-CRP < 2.6), the cumulative incidence of achieving the response endpoint by time t will be computed using the Kaplan-Meier product limit estimator and plotted for each treatment group in the mITT population. The log-rank test will be used to evaluate differences in response rates between the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups over the entire course of the study.

   Intercurrent Events. For participants who fail to achieve the response endpoint (low disease activity or remission) prior to taking a prohibited medication for treatment of RA or prior to exiting the study prematurely due to an AE related to treatment, or high disease activity (Section 3.2), we will assume low disease activity is not achievable within 40 weeks (i.e. data is censored at 40 weeks rather than point of departure, so they are counted in the denominator throughout the study). For participants who leave the study for reasons unrelated to study treatment or disease, data will be censored at the last observed disease assessment.

3. To evaluate sustained clinical control, a secondary efficacy objective, we want to estimate how long the response is maintained. For subsets of individuals who achieve low disease activity (e.g., SDAI ≤ 11; DAS28-CRP ≤ 3.2) or remission (e.g., SDAI ≤ 3.3;

DAS28-CRP < 2.6) at some point during the study, a secondary endpoint is defined for time to loss of that response. For each, the probability of retaining the response for at least t weeks will be computed and plotted as a Kaplan-Meier curve for the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups. Descriptive statistics will be used to summarize the duration of response. Assuming sufficient numbers of low disease activity responders in each treatment arm, the log-rank test will be used to evaluate differences in failure rates between treatment groups over the entire course of the study.

Intercurrent Events: Participants who escalate their disease-modifying RA therapy or take a prohibited medication for the treatment of RA, or exit the study for reasons related to study treatment or disease will be deemed failures (i.e., loss of low disease activity) at the time of these events. For participants who leave the study prior to failure for reasons unrelated to study treatment or disease, data will be censored at the last observed disease assessment.

4. Longitudinal trends for SDAI and DAS28-CRP scores will be explored using repeated measures or mixed models that account for within-participant correlation, under the assumption that data are missing at random. No modifications will be made for participants who escalate their disease-modifying RA therapy or take a prohibited medication for the treatment of RA. Covariates will include treatment, time, and treatment by time interaction.

5. To evaluate HAQ-DI and PROMIS-29 scores and their change from Week 0 to Week 16 and from Week 0 to Week 40, analysis of covariance (ANCOVA) will be used. The ANCOVA model will include the HAQ-DI or PROMIS-29 score at Week 16 (or Week 40) as the response and the HAQ-DI or PROMIS-29 score at Week 0 and treatment as covariates. No modifications will be made for participants who escalate their disease-modifying RA therapy or take a prohibited medication for the treatment of RA.

13.4.4.2 *Safety*

AEs and SAEs will be tabulated by MedDRA Preferred Term and System Organ Class for all 3 treatment arms. Comparisons of incidence and incidence rates of serious infections between arms will be descriptive and include estimates of differences (or ratios) along with confidence intervals.

13.4.5 Exploratory Analysis

Although the primary efficacy analysis will compare VIB4920 with TNFi to VIB4920 placebo with TNFi, we will explore differences in primary and secondary efficacy endpoints among all 3 treatment arms in exploratory analyses.

In general, descriptive statistics and/or data plots will be used to gain an understanding of the nature of exploratory endpoints. Inferential analyses will be considered to evaluate hypotheses generated by the descriptive analyses. Additional exploratory analyses may also be considered based on results of planned analyses.

13.4.6 Descriptive Analyses

Descriptive statistics will be provided by each of the three treatment groups for participant disposition, baseline and demographic characteristics, and use of concomitant medications. Continuous measures will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

13.5 INTERIM ANALYSES

13.5.1 Futility

One interim analysis for futility is planned for the study once the week 16 SDAI low disease activity outcome is known for the first 52 participants (half of the target sample size). The interim analysis will only include participants in the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups. If the proportion of participants in the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups who have achieved low disease activity (SDAI $\leq$ 11) at week 16 is such that at the interim analysis it is unlikely the study will reach statistical significance, the study may be stopped. A conditional power analysis will be performed using the observed frequency of participants with low disease activity in the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups and assuming the pattern of the remaining participants follows the original design assumptions. If the conditional power is less than 20%, the DSMB may recommend the study be terminated. This futility analysis is designed to be non-binding, so the DSMB may elect not to recommend terminating the trial after considering all of the data, even if the conditional power is less than 20%.

Simulation studies suggest that, because the conditional power threshold is low, the planned futility analysis has negligible impact on power. No adjustment to the sample size is necessary.

Although the conditional power analysis assesses the week 16 SDAI low disease activity outcome for subjects in the VIB4920 with TNFi and VIB4920 placebo with TNFi treatment groups only, additional figures and descriptive statistics for other disease activity and safety measures for all three treatment arms will be included in the report to the DSMB.

The interim analysis report will be reviewed by the DSMB but will not be available to the study management team or AMGEN Inc.

13.5.2 Safety and Data Quality

In addition to reviewing futility analysis results, the DSMB will review interim data on participant accrual, participant disposition, safety, site performance, and data quality during routine planned DSMB reviews. Moreover, the DSMB will review safety data on an *ad hoc* basis if an event of sufficient concern arises. Events that would trigger an *ad hoc* DSMB review are listed in Section 12.8.2.2. Specifically, the triggering event for grade 3 or higher infections warrants explanation (Table 9). The underlying risk of severe

infection in the VIB4920 placebo with TNFi treatment arm is estimated to be 2-3%. [44, 45] An increase in risk to 6% or more in the VIB4920 with TNFi arm, the VIB4920 without TNFi arm, or in the two VIB4920 arms pooled together might be of concern. If the true rate of infections is <6%, then observing the number of infections, k, indicated in Table 9 in the VIB4920 with TNFi arm, the VIB4920 without TNFi arm, or the two VIB4920 arms pooled together would be unlikely, where "unlikely" is deemed Pr (≥ k infections) < 15%. This rule will be monitored by a statistician in an unblinded fashion.

13.6 STATISTICAL HYPOTHESES

The statistical hypotheses for the primary analysis is provided in Section 13.4.2, Statistical Hypotheses of Primary Endpoint.

13.7 SAMPLE SIZE CONSIDERATIONS

For the primary analysis, we are interested in comparing the proportions of participants achieving low disease activity based on SDAI by week 16 in the VIB4920 with TNFi and VIB4920 placebo with TNFi arms. In two randomized clinical trials where biologic therapies were added to TNFi use and compared with placebo for treatment of RA patients with an inadequate response to TNFi, the placebo response rates were 11% at 24 weeks and 29% at 8 weeks [29, 30] based on DAS28-CRP. Assuming response rates for low disease activity based on SDAI and DAS28-CRP would be similar, a 20-25% response at week 16 for the VIB4920 placebo with TNFi arm is a reasonable expectation for this study. If the underlying VIB4920 placebo with TNFi response is 20% and the VIB4920 with TNFi response is at least 53%, then a study of 78 participants randomized 2:1 to VIB4920 with TNFi and VIB4920 placebo with TNFi, respectively, will provide at least 84% power using a 2-sided Fisher's Exact test at α=0.10. If the underlying VIB4920 placebo with TNFi rate of low disease activity is actually 25%, then the study would achieve at least 85% power if the rate of low disease activity in the VIB4920 with TNFi arm is ≥ 59%. For the secondary per-protocol analysis, if the sample size drops to 69 (12% loss), the power is still >79% for a VIB4920 placebo with TNFi low disease activity rate of 20% and a VIB4920 with TNFi low disease activity rate of at least 53%. Compared to the 20-25% response rate expected in the VIB4920 placebo with TNFi arm, a 53-59% response rate in the VIB4920 with TNFi arm represents a clinically meaningful improvement. The planned sample size represents a compromise between feasibility and ability to detect a meaningful improvement, which is an appropriate approach for this stage of development.

A key secondary analysis is to compare proportions of participants achieving sustained remission between weeks 16 and 40 in the VIB4920 with TNFi and VIB4920 placebo with TNFi arms. In the VIB4920 placebo with TNFi arm, a reasonable assumption is that the underlying sustained remission rate will be ≤ 5%. At 5%, power will be at least 80%, if the underlying sustained remission rate in the VIB4920 with TNFi arm is at least 30%, using a 2-sided Fisher's Exact test at α=0.10.

The total planned sample size is 104, randomized 2:1:1 to VIB4920 with TNFi, VIB4920 placebo with TNFi, and VIB4920 without TNFi, respectively. Only the VIB4920 with TNFi and VIB4920 placebo with TNFi arms will be included in the primary analysis. The primary reason for including the VIB4920 without TNFi arm is to collect preliminary data on safety. If the underlying probability of a serious infection is at least 6%, then the chance of observing at least one case among 26 participants is at least 80%. That chance increases to >90% if the underlying probability of an event is at least 9%. The width of the Clopper-Pearson 95% confidence interval for an estimated percent is at a maximum (± 20%) for estimates of 50%. Table 10 displays confidence limits for events occurring in <20% of participants, assuming 26 participants in the VIB4920 without TNFi arm. Comparisons of events and incidence rates between arms will be descriptive and include estimates of differences (or ratios) along with confidence intervals.

Table 10. 95% Confidence Limits for events occurring in <20% of participants

Participants with events	LCL	Estimate	UCL
0	0.0%	0.0%	13.2%
1	0.1%	3.8%	19.6%
2	0.9%	7.7%	25.1%
3	2.4%	11.5%	30.2%
4	4.4%	15.4%	34.9%
5	6.6%	19.2%	39.4%

14. IDENTIFICATION AND ACCESS TO SOURCE DATA

14.1 SOURCE DATA

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2 ACCESS TO SOURCE DATA

The site investigators and site staff will make all source data available to the DAIT/NIAID, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to the identity of individuals.

15. QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management. Quality control (QC)

procedures will be implemented beginning with the data entry system and QC data checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

16. PROTOCOL DEVIATIONS

16.1 PROTOCOL DEVIATION DEFINITIONS

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program’s research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2 REPORTING AND MANAGING PROTOCOL DEVIATIONS

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

17. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

17.1 STATEMENT OF COMPLIANCE

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2 INFORMED CONSENT PROCESS

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the FDA 1572 will review the consent document and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

18. PUBLICATION POLICY

The ITN policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ITN website at http://www.immunetolerance.org.

19. REFERENCES

1. Hunter, T.M., et al., *Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014.* Rheumatol Int, 2017. **37**(9): p. 1551-1557.
2. Aletaha, D. and J.S. Smolen, *Diagnosis and Management of Rheumatoid Arthritis: A Review.* JAMA, 2018. **320**(13): p. 1360-1372.
3. Myasoedova, E., et al., *Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995-2007 versus 1985-1994: a population-based study.* J Rheumatol, 2011. **38**(6): p. 983-9.
4. Hellgren, K., et al., *Rheumatoid Arthritis and Risk of Malignant Lymphoma: Is the Risk Still Increased?* Arthritis Rheumatol, 2017. **69**(4): p. 700-708.
5. Scott, I.C., et al., *The frequency of remission and low disease activity in patients with rheumatoid arthritis, and their ability to identify people with low disability and normal quality of life.* Semin Arthritis Rheum, 2019. **49**(1): p. 20-26.
6. Berner, B., et al., *Increased expression of CD40 ligand (CD154) on CD4+ T cells as a marker of disease activity in rheumatoid arthritis.* Ann Rheum Dis, 2000. **59**(3): p. 190-5.
7. Guo, Y., et al., *CD40L-Dependent Pathway Is Active at Various Stages of Rheumatoid Arthritis Disease Progression.* J Immunol, 2017. **198**(11): p. 4490-4501.
8. Raychaudhuri, S., et al., *Common variants at CD40 and other loci confer risk of rheumatoid arthritis.* Nat Genet, 2008. **40**(10): p. 1216-23.
9. Horizon_Therapeutics, *Investigators Brochure VIB4920 Dazodalibep*. 2023.
10. Karnell, J.L., et al., *A CD40L-targeting protein reduces autoantibodies and improves disease activity in patients with autoimmunity.* Sci Transl Med, 2019. **11**(489).
11. Dennis, G., Jr., et al., *Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics.* Arthritis Res Ther, 2014. **16**(2): p. R90.
12. Gabay, C., et al., *Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial.* Lancet, 2013. **381**(9877): p. 1541-50.
13. Folkersen, L., et al., *Integration of known DNA, RNA and protein biomarkers provides prediction of anti-TNF response in rheumatoid arthritis: results from the COMBINE study.* Mol Med, 2016. **22**: p. 322-328.
14. McInnes, I.B., C.D. Buckley, and J.D. Isaacs, *Cytokines in rheumatoid arthritis - shaping the immunological landscape.* Nat Rev Rheumatol, 2016. **12**(1): p. 63-8.
15. Tanaka, T., M. Narazaki, and T. Kishimoto, *IL-6 in inflammation, immunity, and disease.* Cold Spring Harb Perspect Biol, 2014. **6**(10): p. a016295.
16. Nicholson, S.M., et al., *The enhanced immunopharmacology of VIB4920, a novel Tn3 fusion protein and CD40L antagonist, and assessment of its safety profile in cynomolgus monkeys.* Br J Pharmacol, 2020. **177**(5): p. 1061-1076.
17. Anderson, J.K., et al., *Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA).* Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**: p. S14-36.
18. Smolen, J.S., et al., *A simplified disease activity index for rheumatoid arthritis for use in clinical practice.* Rheumatology (Oxford), 2003. **42**(2): p. 244-57.
19. Wells, G., et al., *Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in*

patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis, 2009. **68**(6): p. 954-60.
20. Bruce, B. and J.F. Fries, *The Stanford Health Assessment Questionnaire: dimensions and practical applications.* Health Qual Life Outcomes, 2003. **1**: p. 20.
21. Felson, D.T., et al., *American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis.* Arthritis Rheum, 1995. **38**(6): p. 727-35.
22. Felson, D.T., et al., *Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent?* Arthritis Rheum, 1998. **41**(9): p. 1564-70.
23. Pincus, T., Y. Yazici, and M.J. Bergman, *RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care.* Rheum Dis Clin North Am, 2009. **35**(4): p. 773-8, viii.
24. Pincus, T., et al., *RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than ninety seconds.* Arthritis Care Res (Hoboken), 2010. **62**(2): p. 181-9.
25. Hey, S.P. and J. Kimmelman, *The questionable use of unequal allocation in confirmatory trials.* Neurology, 2014. **82**(1): p. 77-9.
26. Genovese, M.C., et al., *Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate.* Arthritis Rheum, 2004. **50**(5): p. 1412-9.
27. Weinblatt, M., et al., *Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study.* Arthritis Rheum, 2006. **54**(9): p. 2807-16.
28. Weinblatt, M., et al., *Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial.* Ann Rheum Dis, 2007. **66**(2): p. 228-34.
29. Greenwald, M.W., et al., *Evaluation of the safety of rituximab in combination with a tumor necrosis factor inhibitor and methotrexate in patients with active rheumatoid arthritis: results from a randomized controlled trial.* Arthritis Rheum, 2011. **63**(3): p. 622-32.
30. Glatt, S., et al., *Efficacy and safety of bimekizumab as add-on therapy for rheumatoid arthritis in patients with inadequate response to certolizumab pegol: a proof-of-concept study.* Ann Rheum Dis, 2019. **78**(8): p. 1033-1040.
31. Ranza, R., et al., *Changing rate of serious infections in biologic-exposed rheumatoid arthritis patients. Data from South American registries BIOBADABRASIL and BIOBADASAR.* Clin Rheumatol, 2019. **38**(8): p. 2129-2139.
32. Crawford, M. and J.R. Curtis, *Tumor necrosis factor inhibitors and infection complications.* Curr Rheumatol Rep, 2008. **10**(5): p. 383-9.
33. Pincus, T., et al., *Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire.* Arthritis Rheum, 1983. **26**(11): p. 1346-53.
34. Cella, D., et al., *The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008.* J Clin Epidemiol, 2010. **63**(11): p. 1179-94.
35. MacDonald, K.P., et al., *Functional CD40 ligand is expressed by T cells in rheumatoid arthritis.* J Clin Invest, 1997. **100**(9): p. 2404-14.
36. Fonseka, C.Y., et al., *Mixed-effects association of single cells identifies an expanded effector CD4(+) T cell subset in rheumatoid arthritis.* Sci Transl Med, 2018. **10**(463).
37. Rao, D.A., et al., *Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis.* Nature, 2017. **542**(7639): p. 110-114.
38. Zhang, F., et al., *Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry.* Nat Immunol, 2019. **20**(7): p. 928-942.

39. Arroyo-Villa, I., et al., *Constitutively altered frequencies of circulating follicullar helper T cell counterparts and their subsets in rheumatoid arthritis.* Arthritis Res Ther, 2014. **16**(6): p. 500.
40. Deng, J., et al., *Signal Transducer and Activator of Transcription 3 Hyperactivation Associates With Follicular Helper T Cell Differentiation and Disease Activity in Rheumatoid Arthritis.* Front Immunol, 2018. **9**: p. 1226.
41. Firestein, G.S. and I.B. McInnes, *Immunopathogenesis of Rheumatoid Arthritis.* Immunity, 2017. **46**(2): p. 183-196.
42. Thorarinsdottir, K., et al., *CD21(-/low) B cells associate with joint damage in rheumatoid arthritis patients.* Scand J Immunol, 2019. **90**(2): p. e12792.
43. Orange, D.E., et al., *RNA Identification of PRIME Cells Predicting Rheumatoid Arthritis Flares.* N Engl J Med, 2020. **383**(3): p. 218-228.
44. Downey, C., *Serious infection during etanercept, infliximab and adalimumab therapy for rheumatoid arthritis: A literature review.* Int J Rheum Dis, 2016. **19**(6): p. 536-50.
45. Burmester, G.R., et al., *Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis.* Ann Rheum Dis, 2017. **76**(2): p. 414-417.
46. Sampson, H.A., et al., *Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium.* J Allergy Clin Immunol, 2006. **117**(2): p. 391-7.

APPENDIX 1. SCHEDULE OF EVENTS: SCREENING AND STUDY DRUG ADMINISTRATION

Phase of trial	**Screening**	**STUDY DRUG ADMINISTRATION**									
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**		
Visit	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**U[1]**	**TM/DV[2]**
GENERAL ASSESSMENTS											
Informed Consent	x										
Eligibility criteria	x										
Demographics (age, sex, ethnicity)	x										
Medical history	x										
Rheumatoid arthritis history	x										
Comprehensive physical exam	x	x								x	x
Vital signs	x	x[3]	x[3]	x[3]		x[3]		x[3]		x	x
Randomization		x									
Limited physical exam			x	x		x		x			
Adverse events		x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Telephone assessment of changes since prior visit					x		x		x		

[1] Unscheduled visit

[2] Treatment Modification or Study Discontinuation visit. If treatment modification or intent to discontinue the study is identified during an in-person visit, convert that visit to a Treatment Modification Visit or Study Discontinuation visit. .If treatment modification or intent to discontinue the study is identified between in-person visits, then schedule the Treatment Modification or Study Discontinuation Visit for the next scheduled in-person visit

[3] Vitals monitored per Section 6.1.1.2.4

Phase of trial	Screening	STUDY DRUG ADMINISTRATION									
Week		0	2	4	6	8	10	12	14		
Visit	-1	0	1	2	3	4	5	6	7	U[1]	TM/DV[2]
DISEASE SPECIFIC ASSESSMENTS											
Tender and swollen joint count[4]	x	x	x	x		x		x		x	x
Patient global health assessment (PaGH)	x	x	x	x		x		x		x	x
Health care provider global health assessment (PrGH)[4]	x	x	x	x		x		x		x	x
Pain assessment		x								x	x
Health Assessment Questionnaire – Disability Index (HAQ-DI)		x								x	x
PROMIS-29 Profile		x								x	x
STUDY DRUG ADMINISTRATION											
VIB4920 or VIB4920 placebo		x	x	x		x		x			
CLINICAL LABORATORY ASSESSMENTS (Central Lab)											
Hematology (CBC, differential, and platelet count)	x	x		x		x		x		x	x
Serum chemistry (AST, ALT, bilirubin, alkaline phosphatase, albumin, creatinine)	x	x		x		x		x		x	x
Inflammatory marker (C-reactive protein)	x	x	x	x		x		x		x	x
HIV (RNA or antibody)	x										
Hepatitis B (core antibody, surface antigen)	x										
Hepatitis C (RNA or antibody)	x										

[4] Assessed by blinded evaluator

Phase of trial	Screening	STUDY DRUG ADMINISTRATION									
Week		0	2	4	6	8	10	12	14		
Visit	-1	0	1	2	3	4	5	6	7	U[1]	TM/DV[2]
Tuberculosis Testing - QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus, or T-SPOT.TB test[5]	x										
Serum pregnancy[6]	x										
Rheumatoid Factor (RF)	x									x	x
Anti-citrullinated peptide antibodies (ACPA)	x									x	x
STAT urine pregnancy[6]		x	x	x		x		x		x	x
MECHANISTIC ASSESSMENTS											
Plasma PK pre-infusion assays[7]		x	x	x		x		x			
Serum PK pre-infusion assays[7]		x	x	x		x		x			
Plasma PK post-infusion [7]		x						x			
Plasma anti-drug antibody and sCD40L Assays[8]		x	x	x		x		x			
PBMCs[8]		x		x				x			x
Serum[8]		x		x				x			x
Whole blood RNA[8]		x		x				x			x
Whole blood DNA[8]		x		x				x			x

[5] For participants with indeterminate QuantiFERON-TB Gold, QuantiFERON-TB Gold Plus or T-SPOT.TB tests: 1) PPD skin test, if not performed within the past 3 months; 2) AP and lateral chest radiograph, if not performed within the past 3 months

[6] For women with childbearing potential; test provided by Central Lab but performed locally

[7] Plasma and serum samples for PK collected pre-infusion and within 15 min +/- 5 min minutes post-infusion

[8] Collected prior to infusion

APPENDIX 2. SCHEDULE OF EVENTS: POST-DRUG ADMINISTRATION WITH DENSE SAMPLING COLLECTION

Phase of trial	POST-ADMINISTRATION OBSERVATION WITH DENSE SAMPLING														
Week	16	17, 18, 19	20	21, 22, 23	24	25, 26, 27	28	29, 30, 31	32	33, 34, 35	36	37, 38, 39	40		
Visit	8	8.1, 8.2, 8.3	9	9.1, 9.2, 9.3	10	10.1, 10.2, 10.3	11	11.1, 11.2, 11.3	12	12.1, 12.2, 12.3	13	13.1, 13.2, 13.3	14	U[1]	TM/DV[2]
GENERAL ASSESSMENTS															
Comprehensive physical exam	x												x	x	x
Vital signs	x		x		x		x		x		x		x	x	x
Limited physical exam			x		x		x		x		x				
Adverse events	x		x		x		x		x		x		x	x	x
Concomitant medications	x		x		x		x		x		x		x	x	x
DISEASE SPECIFIC ASSESSMENTS															
Tender and swollen joint count[3]	x		x		x		x		x		x		x	x	x
Patient global health assessment (PaGH)	x		x		x		x		x		x		x	x	x
Health care provider global health assessment (PrGH)[3]	x		x		x		x		x		x		x	x	x
Pain assessment	x												x	x	x
RAPID3 assessment (for dense sampling collection)	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Health Assessment Questionnaire Disability Index (HAQ-DI)	x												x	x	x
PROMIS-29 Profile	x												x	x	x

[1] Unscheduled visit

[2] Treatment Modification or Study Discontinuation visit. If treatment modification or intent to discontinue the study is identified during an in person visit, convert that visit to a Treatment Modification Visit or Study Discontinuation visit. If treatment modification or intent to discontinue the study is identified between in-person visits, then schedule the Treatment Modification or Study Discontinuation Visit for the next scheduled in-person visit

[3] Assessed by blinded evaluator

Phase of trial	POST-ADMINISTRATION OBSERVATION WITH DENSE SAMPLING														
Week	**16**	**17, 18, 19**	**20**	**21, 22, 23**	**24**	**25, 26, 27**	**28**	**29, 30, 31**	**32**	**33, 34, 35**	**36**	**37, 38, 39**	**40**		
Visit	**8**	**8.1, 8.2, 8.3**	**9**	**9.1, 9.2, 9.3**	**10**	**10.1, 10.2, 10.3**	**11**	**11.1, 11.2, 11.3**	**12**	**12.1, 12.2, 12.3**	**13**	**13.1, 13.2, 13.3**	**14**	**U[1]**	**TM/DV[2]**
CLINICAL LABORATORY ASSESSMENTS (Central Lab)															
Hematology (CBC, differential, and platelet count)	x				x				x				x	x	x
Serum chemistry (AST, ALT, bilirubin, alkaline phosphatase, albumin, creatinine)	x				x				x				x	x	x
Inflammatory marker (C-reactive protein)	x		x		x		x		x		x		x	x	x
Rheumatoid Factor (RF)	x												x	x	x
Anti-citrullinated peptide antibodies (ACPA)	x												x	x	x
MECHANISTIC ASSESSMENTS															
Plasma PK Assay	x		x		x		x		x		x		x		
Serum PK Assay	x		x		x		x		x		x		x		
Plasma ADA and sCD40L Assays	x		x		x		x		x		x		x		
PBMCs	x				x				x				x		x
Serum	x				x				x				x		x
Whole blood RNA	x				x				x				x		x
Whole blood RNA-microcontainer (clinic collection)	x														
Whole blood RNA-microcontainer (home collection for dense sampling collection)	x	x	x	x	x	x	x	x	x	x	x	x	x		
Whole blood DNA	x				x				x				x		x

APPENDIX 3. SCHEDULE OF EVENTS: POST-DRUG ADMINISTRATION WITHOUT DENSE SAMPLING COLLECTION

Phase of trial	POST-ADMINISTRATION OBSERVATION								
Week	16	20	24	28	32	36	40		
Visit	8	9	10	11	12	13	14	U[1]	TM/DV[2]
GENERAL ASSESSMENTS									
Comprehensive physical exam	x						x	x	x
Vital signs	x	x	x	x	x	x	x	x	x
Limited physical exam		x	x	x	x	x			
Adverse events	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x
DISEASE SPECIFIC ASSESSMENTS									
Tender and swollen joint count[3]	x	x	x	x	x	x	x	x	x
Patient global health assessment (PaGH)	x	x	x	x	x	x	x	x	x
Health care provider global health assessment (PrGH)[3]	x	x	x	x	x	x	x	x	x
Pain assessment	x						x	x	x
Health Assessment Questionnaire – Disability Index (HAQ-DI)	x						x	x	x
PROMIS-29 Profile	x						x	x	x
CLINICAL LABORATORY ASSESSMENTS (Central Lab)									
Hematology (CBC, differential, and platelet count)	x		x		x		x	x	x
Serum chemistry (AST, ALT, bilirubin, alkaline phosphatase, albumin, creatinine)	x		x		x		x	x	x

[1] Unscheduled Visit

[2] Treatment Modification or Study Discontinuation visit. If treatment modification or intent to discontinue the study is identified during an in person visit, convert that visit to a Treatment Modification Visit or Study Discontinuation visit. If treatment modification or intent to discontinue the study is identified between in-person visits, then schedule the Treatment Modification or Study Discontinuation Visit for the next scheduled in-person visit

[3] Assessed by blinded evaluator

Phase of trial	**POST-ADMINISTRATION OBSERVATION**								
Week	**16**	**20**	**24**	**28**	**32**	**36**	**40**		
Visit	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**U[1]**	**TM/DV[2]**
Inflammatory marker (C-reactive protein)	x	x	x	x	x	x	x	x	x
Rheumatoid Factor (RF)	x						x	x	x
Anti-citrullinated peptide antibodies (ACPA)	x						x	x	x
MECHANISTIC ASSESSMENTS									
Plasma PK Assays	x	x	x	x	x	x	x		
Serum PK Assays	x	x	x	x	x	x	x		
Plasma ADA and sCD40L Assays	x	x	x	x	x	x	x		
PBMCs	x		x		x		x		x
Serum	x		x		x		x		x
Whole blood RNA	x		x		x		x		x
Whole blood DNA	x		x		x		x		x

APPENDIX 4. SCHEDULE OF EVENTS: ALTERNATE MONITORING

Phase of trial	ALTERNATE MONITORING									
Week of Study	2	4	8	12	16	24	32	40		
Visit	M1	M2	M3	M4	M5	M6	M7	M8	U[1]	DV[2]
GENERAL ASSESSMENTS										
Vital signs	x	x	x	x	x	x	x	x	x	x
Limited physical exam	x	x	x	x	x	x	x	x	x	x
Adverse events[3]	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x
CLINICAL LABORATORY ASSESSMENTS (Central Lab)										
Hematology (CBC, differential, and platelet count)		x	x	x	x			x	x	x
Serum chemistry (AST, ALT, bilirubin, alkaline phosphatase, albumin, creatinine)		x	x	x	x			x	x	x
Inflammatory marker (C-reactive protein)					x			x	x	x
DISEASE SPECIFIC ASSESSMENTS										
Tender and swollen joint count[4]					x			x	x	x
Patient global health assessment (PaGH)					x			x	x	x
Health care provider global health assessment (PrGH)[4]					x			x	x	x
Pain assessment					x			x	x	x

Additional assessments are permitted, if indicated for participant monitoring.

[1] Unscheduled visit.

[2] Study Discontinuation visit. If intent to discontinue the study is identified during an in-person visit, convert that visit to a Study Discontinuation visit. If intent to discontinue the study is identified between in-person visits, then schedule the Study Discontinuation Visit for the next scheduled in-person visit.

[3] Adverse event monitoring will assess adverse events including AESIs.

[4] Assessed by blinded evaluator

APPENDIX 5. 28 AND 44 JOINT COUNT

The following joints are to be assessed for tenderness and swelling in the 44 joint count, as shown in Figure 3 with gray circles: sternoclavicular (2), acromioclavicular (2), shoulder (2), elbow (2), wrist (2), metacarpophalangeal (10), finger proximal interphalangeal (10), knee (2), ankle (2), and metatarsophalangeal (10) joints. Out of these 44 joints, assessment of the 28 joints indicated by X's on the figure (shoulder (2), elbow (2), wrist (2), metacarpophalangeal (10), finger proximal interphalangeal (10), and knee (2) joints) will be used to calculate the SDAI and DAS28-CRP.

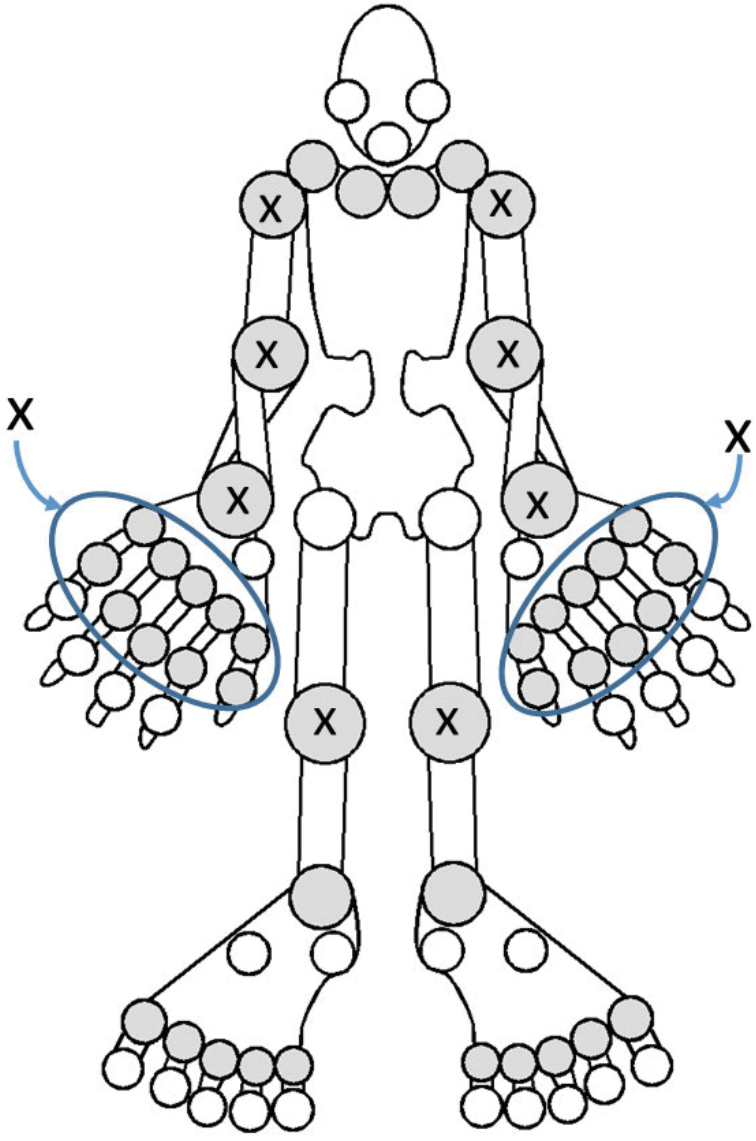

Figure 3. Joints assessed in a 44 and 28 joint count.

APPENDIX 6. PATIENT GLOBAL, PROVIDER GLOBAL, AND PAIN ASSESSMENT

1. Patient global assessment:

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:



The selected number will be multiplied by 10 to calculate the DAS28-CRP.

2. Provider Global Assessment:

Considering all the ways arthritis affects the patient, how well is the patient doing?



3. Pain assessment:

Choose a number between 0 and 10 that best describes your pain:



APPENDIX 7. HEALTH ASSESSMENT QUESTIONNAIRE DISABILITY INDEX (HAQ-DI)[1]

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Long-handled appliances for reach
- ☐ Long-handled appliances in bathroom
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Hygiene
- ☐ Reach
- ☐ Gripping and opening things
- ☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

No Pain **Severe Pain**

0 **100**

[1] The copyright of the HAQ-DI is held by Stanford University, School of Medicine. MAPI Research Trust is the authorized by Stanford University, School of Medicine, to provide the certified Spanish-translated version of the HAQ-DI is licensed from MAPI Research Trust.

APPENDIX 8. RAPID3 ASSESSMENT

The RAPID3 assessment can be found here, with a representation shown below:
https://www.rheumatology.org/Portals/0/Files/RAPID3%20Form.pdf

RAPID3

ROUTINE ASSESSMENT OF PATIENT INDEX DATA

The RAPID3 includes a subset of core variables found in the Multi-dimensional HAQ (MD-HAQ). Page 1 of the MD-HAQ, shown here, includes an assessment of physical function (section 1), a patient global assessment (PGA) for pain (section 2), and a PGA for global health (section 3). RAPID3 scores are quickly tallied by adding subsets of the MD-HAQ as follows:

1. PLEASE CHECK THE ONE BEST ANSWER FOR YOUR ABILITIES AT THIS TIME:

OVER THE LAST WEEK, WERE YOU ABLE TO:	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
a. Dress yourself, including tying shoelaces and doing buttons?	___ 0	___ 1	___ 2	___ 3
b. Get in and out of bed?	___ 0	___ 1	___ 2	___ 3
c. Lift a full cup or glass to your mouth?	___ 0	___ 1	___ 2	___ 3
d. Walk outdoors on flat ground?	___ 0	___ 1	___ 2	___ 3
e. Wash and dry your entire body?	___ 0	___ 1	___ 2	___ 3
f. Bend down to pick up clothing from the floor?	___ 0	___ 1	___ 2	___ 3
g. Turn regular faucets on and off?	___ 0	___ 1	___ 2	___ 3
h. Get in and out of a car, bus, train, or airplane?	___ 0	___ 1	___ 2	___ 3
i. Walk two miles or three kilometers, if you wish?	___ 0	___ 1	___ 2	___ 3
j. Participate in recreational activities and sports as you would like, if you wish?	___ 0	___ 1	___ 2	___ 3
k. Get a good night's sleep?	___ 0	___ 1.1	___ 2.2	___ 3.3
l. Deal with feelings of anxiety or being nervous?	___ 0	___ 1.1	___ 2.2	___ 3.3
m. Deal with feelings of depression or feeling blue?	___ 0	___ 1.1	___ 2.2	___ 3.3

1. a-j FN (0-10):

1=0.3 16=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

2. PN (0-10):

3. PTGE (0-10):

RAPID3 (0-30)

2. HOW MUCH PAIN HAVE YOU HAD BECAUSE OF YOUR CONDITION OVER THE PAST WEEK? PLEASE INDICATE BELOW HOW SEVERE YOUR PAIN HAS BEEN:

NO PAIN — PAIN AS BAD AS IT COULD BE

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

3. CONSIDERING ALL THE WAYS IN WHICH ILLNESS AND HEALTH CONDITIONS MAY AFFECT YOU AT THIS TIME, PLEASE INDICATE BELOW HOW YOU ARE DOING:

VERY WELL — VERY POORLY

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

CONVERSION TABLE

Near Remission (NR): 1=0.3; 2=0.7; 3=1.0
Low Severity (LS): 4=1.3; 5=1.7; 6=2.0
Moderate Severity (MS): 7=2.3; 8=2.7; 9=3.0; 10=3.3; 11=3.7; 12=4.0
High Severity (HS): 13=4.3; 14=4.7; 15=5.0; 16=5.3; 17=5.7; 18=6.0; 19=6.3; 20=6.7; 21=7.0; 22=7.3; 23=7.7; 24=8.0; 25=8.3; 26=8.7; 27=9.0; 28=9.3; 29=9.7; 30=10.0

HOW TO CALCULATE RAPID 3 SCORES

1. Ask the patient to complete questions 1, 2, and 3 while in the waiting room prior to his/her visit.
2. For question 1, add up the scores in questions A-J only (questions K-M have been found to be informative, but are not scored formally). Use the formula in the box on the right to calculate the formal score (0-10). For example, a patient whose answers total 19 would score a 6.3. Enter this score as an evaluation of the patient's functional status (FN).
3. For question 2, enter the raw score (0-10) in the box on the right as an evaluation of the patient's pain tolerance (PN).
4. For question 3, enter the raw score (0-10) in the box on the right as an evaluation of the patient's global estimate (PTGE).
5. Add the total score (0-30) from questions 1, 2, and 3 and enter them as the patient's RAPID 3 cumulative score. Use the final conversion table to simplify the patient's weighed RAPID 3 score. For example, a patient who scores 11 on the cumulative RAPID 3 scale would score a weighed 3.7. A patient who scores between 0–1.0 is defined as near remission (NR); 1.3–2.0 as low severity (LS); 2.3–4.0 as moderate severity (MS); and 4.3–10.0 as high severity (HS).

APPENDIX 9. 2010 ACR-EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

2010 Rheumatoid Arthritis Classification

THE 2010 ACR-EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

	Score
Target population (Who should be tested?): Patients who 1. have at least 1 joint with definite clinical synovitis (swelling)* 2. with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification) ††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification) ‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

APPENDIX 10. PROMIS-29 PROFILE

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA63	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
ANI	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.1

Fatigue

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Sleep Disturbance

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ability to Participate in Social Roles and Activities

		Never	Rarely	Sometimes	Usually	Always
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Pain Interference

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Intensity

	In the past 7 days…											
Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable

APPENDIX 11. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Adapted from the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network [46]