Cover Page for ClinicalTrials.gov

Document:
Protocol Version 3.0

Official Study Title:
A Clinical Utility Study of PrismRA Testing Therapeutic Response for Rheumatoid Arthritis (DRIVE)

Document Date:
October 20, 2022

A Clinical Utility Study of PrismRA Testing Therapeutic Response for Rheumatoid Arthritis (DRIVE)

Protocol Number: SCIPHER-RA-005

Version: 3.0
Date: 20-Oct-2022

Sponsor:
Scipher Medicine Corporation
221 Crescent Street, Suite 103A
Waltham, MA 02453

Contents

1 Key Personnel

Sponsor:	Sam Asgarian, MD Chief Medical Officer Scipher Medicine Corporation 221 Crescent Street, Suite 103A Waltham, MA 02453

2 Protocol Signature Page

Protocol Title: A Clinical Utility Study of PrismRA Testing Therapeutic Response for Rheumatoid Arthritis (DRIVE)
Protocol Version/ Date: 3.0, 20-Oct-2022
Sponsor Name: Scipher Medicine Corporation

Declaration of Principal Investigator
I confirm that I have read the above-mentioned protocol and its attachments and understand it. I agree to conduct the described study in compliance with all stipulations of the protocol, as well as all applicable research regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____

Principal Investigator Signature:_____

Date: _____

3 List of Abbreviations and Key Terms

Abbreviation or Specialist Term	Explanation
ACR	American College of Rheumatology
AE	Adverse Event
bDMARD	Biologic Disease Modifying Anti-Rheumatic Drug
CAP	College of American Pathologists
CBC	Complete Blood Count
CDAI	Clinical Disease Activity Index
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CRP	C-Reactive Protein
DAS	Disease Activity Score
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
DMARD	Disease Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Records
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Council for Harmonization
IL-1i	Interleukin-1 inhibitor
IL-6i	Interleukin-6 inhibitor
IL-17i	Interleukin-17 inhibitor
IL-23i	Interleukin-23 inhibitor
IQR	Interquartile Range
IRB	Institutional Review Board
JAKi	Janus Kinase inhibitor
MCID	Minimal Clinically Important Difference
MID	Minimal Important Difference
MOA	Mechanism of Action
MTX	Methotrexate
NSAIDs	Non-Steroidal Anti-Inflammatory Drug
PRO	Patient Reported Outcomes
PtGA	Patient Global Assessment

Abbreviation or Specialist Term	Explanation
RA	Rheumatoid Arthritis
RAPID3	Routine Assessment of Patient Index Data 3
RDCI	Rheumatic Disease Comorbidity Index
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	Standard of Care
TB	Tuberculosis
TNFi	Tumor Necrosis Factor Inhibitor
tsDMARD	Targeted small molecule Synthetic Disease Modifying Anti-Rheumatic Drug
UADE	Unanticipated Adverse Device Effect
US	United States

4 Definitions

Terms	Definition of Terms
DRIVE Study	The comparative effectiveness study of the PrismRA test comparing the clinical outcomes of patients in the PrismRA arm (trial) and the external control arm (observational).
Baseline	Assessments of patients as they enter the PrismRA arm. For the external control arm, the corresponding baseline CDAI assessment window is the 3-month period before the index date (defined as the time of study treatment initiation). For medical history all available data before the index date will be used in the external control arm.
Enrollment	The point at which the patient signs the informed consent form for the PrismRA arm. Not applicable for the external control arm.
PrismRA arm	Trial participants in the trial conducted by Scipher Medicine for whom PrismRA test is performed and the Investigator will use the PrismRA test results to inform the treatment decision.
External control arm	OM1 real-world data patients who received standard of care treatment for RA with TNFi or non-TNFi b/tsDMARDs without guidance from PrismRA test results.
Study Treatment	The b/tsDMARDs (FDA approved for RA) that is initiated at Visit 2 (See Section 8.5), informed by the PrismRA test in the PrismRA arm and as a part of standard of care in the external control arm. This study treatment (b/tsDMARDs) can be the very first b/tsDMARD for the patient or a subsequent b/tsDMARD after having used one or more TNFi bDMARDs (but not non-TNFi b/tsDMARDs).
Study Treatment Initiation	The point at which a study treatment (See “Study Treatment” above) is initiated to treat RA. This time point constitutes the index date (beginning of the follow-up) and is defined as Visit 2

Terms	Definition of Terms
RA Disease Activity	Disease activity is based on the CDAI score as follows: • Remission: CDAI ≤ 2.8 • Low: CDAI > 2.8 and ≤ 10.0 • Moderate: CDAI > 10.0 and ≤ 22.0 • High: CDAI > 22.0 For the PrismRA arm, the CDAI scores will be assessed by the Investigator. The CDAI scores for the external control arm in OM1 PremiOM RA consist of CDAI scores in structured EMR data, and CDAI scores estimated by machine learning based on unstructured data.[1]CDAI scores from all data sources will be used.

5 Introduction

5.1 Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation primarily involving the joints of the hands and wrists. RA typically presents with generalized morning stiffness and musculoskeletal pain followed by joint swelling and tenderness. Untreated RA often leads to progressive joint deformity and destruction with subsequent disability. The objectives of RA treatment are to stop disease progression, prevent irreversible joint destruction, and improve quality of life. Ideally, rheumatologists consult with their patients to decide whether disease remission (the absence of signs or symptoms of significant inflammatory disease) or low disease activity is the appropriate goal of treatment. After therapy is started, RA disease activity is measured regularly utilizing one of several validated tools (e.g., DAS, CDAI). Using the treat-to-target approach, therapeutic adjustments are made each visit to ensure continued progression to the agreed treatment target.

To achieve these treatment goals, there are an increasing number of advanced biologic and small molecule targeted therapies (e.g., b/tsDMARD) directed at specific components of the immune system involved in RA pathogenesis. Treatment options organized by mechanism of action (MOA) include tumor necrosis factor-α inhibitors (TNFi), Janus kinase inhibitors (JAKi), interleukin-6 inhibitors (IL-6i), interleukin-1 inhibitors (IL-1i), T cell co-stimulation inhibitors, and B cell modulators. For approval by the Food and Drug Administration (FDA), these agents are required report clinical trial data using ACR20, 50, and 70, defined as a 20%, 50%, and 70% improvement respectively in specific disease measures: swollen joint count, tender joint count, patient reported outcomes, physician reported outcomes and acute phase reactant measures[2]. Unfortunately, all of these agents report ACR50 response rates of only 25-40% at six months following treatment initiation[3-6]. Hence, two thirds of RA patients receiving their first b/tsDMARD fail to achieve ACR50, regardless of the MOA.

The goal of precision medicine is to match patients with a treatment MOA that most closely matches his or her individual disease biology to improve disease outcomes in a timely fashion. Precision medicine has been most successful in oncology where genetic (DNA) changes in patient tumors are analyzed in order to identify the best treatment options for each individual. However, DNA data alone is insufficient to determine individual treatment options in complex diseases such as RA. Scipher Medicine is using network medicine and artificial intelligence to

bring precision medicine to complex diseases through a combined analysis of gene expression (RNA) data, clinical metrics, and appropriate laboratory markers. PrismRA® is the first test developed using Scipher's network medicine approach.

PrismRA was developed because the majority of RA patients receive a TNFi therapy as their b/tsDMARD[7,8]. It is a molecular signature test designed to predict the likelihood that a RA patient will be a non-responder to TNFi therapies. From a single blood draw taken before the start of treatment, the PrismRA test assesses twenty-three (23) biomarkers that are integrated into a single predictive model that generates a score on a scale of one (1) to twenty-five (25) that represents the likelihood of non-response to TNFi therapies. In a prior PrismRA validation study, patients with a molecular signature of non-response were less likely to have an adequate response to TNFi therapies than those patients lacking the signature according to ACR50, ACR70, CDAI, and DAS28-CRP with significant odd ratios of 3.4-8.8 for targeted therapy naïve patients and 3.3-26.6 for TNFi-exposed patients[10].

5.2 Rationale

The objective of the DRIVE study is to establish the clinical utility of the PrismRA test in evaluating therapeutic response for patients with rheumatoid arthritis (RA).

6 Study Design

6.1 Study Type

This is a two-arm, multi-center United States (U.S.)-based study with a prospective, non-blinded intervention arm (PrismRA arm) and an observational external control arm designed to demonstrate the clinical utility of the PrismRA test in routine clinical care. The study will compare outcomes for RA patients with moderate to high disease activity whose treatment is informed by PrismRA test results (PrismRA arm) to outcomes among RA patients who receive the standard of care (SOC) not informed by PrismRA results (external control arm).

PrismRA arm:
In this arm, all patients will receive the PrismRA test. The Investigator will receive the PrismRA results and use those results to inform treatment selection by Visit 2. Patients may be followed indefinitely from the time of signing the informed consent and medical records release form unless the patient withdraws from the study, dies, or becomes lost to follow-up. Changes to the study b/tsDMARDs do not terminate follow-up. A patient can withdraw from the study at any time.

External control arm:
The observational external control arm will consist of comparable initiators of b/tsDMARDs in OM1's PremiOM RA dataset, in which the specific choice of TNFi or non-TNFi b/tsDMARDs was based on the treating physician's clinical judgement and was not informed by the PrismRA test results. Baseline as well as follow-up data will consist of data obtained at routine clinical encounters. The index date (start of follow-up) for this external control arm will be defined as the time of initiation of the study treatment (very first or subsequent b/tsDMARDs) and patients will be followed until week 24, death, or loss to follow-up, whichever occurs first. Changes to the

study b/tsDMARDs do not terminate follow-up. Controls may be sampled from time intervals contemporaneous with the trial (March 2022 and onward) as well as historical periods.

6.2 Study population

PrismRA arm:
This arm will enroll approximately 600 RA patients at approximately 33 clinical sites who are at least 18 years of age. All patients in the PrismRA arm will undergo PrismRA testing at their first study visit (Visit 1). See Patient Selection Criteria for details.

External control arm:
Patients with RA in the OM1 PremiOM RA Dataset will be selected based on the same eligibility criteria as in the PrismRA arm and adapted for real-world data availability where necessary. Patients in the external control arm will be balanced with patients in the PrismRA arm using a propensity score model developed with the primary goal of achieving balance in baseline characteristics between the comparison groups. The external control arm is expected to have at least 1,500 eligible patients after propensity score modeling, with no less than 750 patients having CDAI scores at both baseline and Week 24. The data from patients who initiated b/tsDMARDs in the contemporaneous period (March 2022 and onward) and if needed, the recent historical period (6-month to 3-year period prior to March 2022) will be used to maximize the size of the patient pool while minimizing confounding by the potential secular trends in treatment patterns. The smallest historical time window that can provide the planned number of external control arm patients comparable to the PrismRA arm patients will be used. The overlap in propensity score distributions between the external control and trial arms will inform the ultimate sample size.

The data source for the analysis is the OM1 PremiOM RA Dataset within the OM1's Real-World Data Cloud (OM1, Inc, Boston, MA, US). The OM1 Real-World Data Cloud is derived from deterministically linked, de-identified, individual-level health care claims, electronic medical record (EMR), and other data. EMR data are from sources geographically representative of the U.S. population and include medication history and prescription information, laboratory results, and diagnoses as documented by a physician. Additional medical and pharmacy claims data are linked to the clinical data to fill gaps in patients' clinical care. The medical and pharmacy claims contain billing and coding history on inpatient and outpatient encounters from acute care facilities, ambulatory surgery centers, and clinics. The OM1 Real-World Data Cloud includes data from January 2013 to present day.

To qualify for the OM1's PremiOM RA dataset, each patient must be at least 16 years old at the time of the qualifying diagnosis and meet *at least one* of the following conditions:

- At least two diagnosis codes for RA, at least 30 days apart, each coming from an encounter with a rheumatologist
- At least one inpatient RA diagnosis code
- At least two outpatient RA diagnosis codes, at least 30 days apart and within a year, regardless of physician specialty

- At least one outpatient RA diagnosis code and a prescription or fill for a DMARD and no diagnosis for any of the non-RA conditions for which those drugs may also be prescribed

Non-RA conditions are defined as juvenile idiopathic arthritis, psoriatic arthritis/psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, cryopyrin-associated periodic syndromes, renal transplant, malaria, systemic lupus erythematosus, giant cell arteritis, cytokine release syndrome, all cancers, hydatidiform mole.

7 Study Endpoints

7.1 Primary Endpoint

The proportion of patients with moderate or high disease activity at baseline who achieve a minimal important difference (MID) [11] in CDAI of ≥ 6 (baseline moderate) or ≥12 (baseline high) at 24 weeks after study treatment initiation.

7.2 Secondary Endpoint

Secondary endpoints include the following:

a) The proportion of patients with moderate or high disease activity at baseline who achieve **CDAI ≤ 10 (low disease activity (LDA))** or CDAI ≤ 2.8 (remission) at 12 and 24 weeks after study treatment initiation
b) The change in CDAI scores from baseline to 12 and 24 weeks among patients with moderate or high disease activity at baseline who initiate study treatment.
c) The proportion of patients with moderate or high disease activity at baseline who achieve an **MID in CDAI** of ≥ 6 and ≥12, respectively, 12 weeks after study treatment initiation
d) The proportion of patients with moderate or high disease activity at baseline who achieve a meaningful reduction (defined as ≥ 10 on the scale of 0–100) of **patient global assessment** (PtGA) compared to the baseline PtGA 12 and 24 weeks after study treatment initiation.
e) The proportion of patients with moderate or high disease activity at baseline who achieve a minimal clinically important difference (**MCID) in RAPID3** (≥ 3.8 on the scale of 0–30)[12]compared to the baseline RAPID3 at 12 and 24 weeks after study treatment initiation.
f) The proportion of patients with moderate or high disease activity at baseline who achieve an **MCID in patient pain visual analogue scale** [13](≥ 1.1 on the scale of 0–10) compared to the baseline pain at 12 and 24 weeks after initiation of a b/tsDMARD therapy.
g) The proportion of **treatment decisions** that were guided by PrismRA test results (in the PrismRA arm only)

7.3 Exploratory Endpoints

- The proportion of moderate to high disease activity patients that achieve **ACR50** therapeutic response 12 and 24 weeks after study treatment initiation (in the PrismRA arm only; analysis in the external control arm may only be descriptive in nature if the constructed ACR50 is not sufficiently available in real world data).

- The proportion of patients receiving **TNFi therapy** and non-TNFi b/tsDMARDs as the study treatment at the index date.
- The number of patients that **stop or change the study treatment** due to an intolerance during the 24-week follow-up period (in the PrismRA arm only; analysis in the external control arm may only be descriptive in nature if the reason for the study treatment discontinuation is not sufficiently available in real world data).

7.4 Patient Selection Criteria

7.4.1 Inclusion Criteria

Table 1 shows the inclusion criteria that will be used prospectively in the PrismRA arm and the best approximation for the selection of comparable patients in the observational external control arm.

Table 1. Inclusion criteria by study arm

	PrismRA arm	**External control arm**
1	Patient is eighteen years of age or older (≥ 18) at time of consent.	All patients are ≥ 18 years at the initiation of b/tsDMARDs (which can be the first ever b/tsDMARD or subsequent b/tsDMARDs).
2	Patient must meet the criteria for RA as defined by the 2010 ACR/EULAR classification at Visit 1.	Patients are in the OM1 PremiOM RA dataset (See Section 6.2 Study Population).
3	Patient has active, moderate to severe RA with a CDAI of >10 at Visit 1.	Patient has a CDAI of > 10 based on the most recent CDAI assessed during the 3-month period prior to the b/tsDMARDs initiation.
4	Patient has swollen and tender joint count of ≥ 2 each, as determined by CDAI assessment at Visit 1 using a 28-joint count.	Patient has swollen and tender joint counts of ≥ 2 each, based on the most recent joint counts assessed during the 3-month period prior to the b/tsDMARDs initiation.

5	Patient is eligible for treatment with <u>any</u> b/tsDMARD therapy at Visit 1 based on all of the following: • Investigator determination that patient satisfies clinical criteria • Patient consents to the use of non-csDMARD therapy during shared investigator-patient decision making • Absence of any financial or logistical limitations to the initiation of a b/tsDMARD therapy	Only patients who initiate a b/tsDMARD will be enrolled to ensure the treating rheumatologist determination of indication, patient consent, and financial/logistical feasibility. The list of b/tsDMARDs approved for RA includes the following: • TNFi (infliximab, etanercept, certolizumab pegol, golimumab, adalimumab) • IL-6i (tocilizumab, sarilumab) • IL-1i (anakinra) • T-cell co-stimulation inhibitor (abatacept) • B-cell depletion agent (rituximab) • JAKi (tofacitinib, baricitinib, upadacitinib) Biosimilars/generics of these b/tsDMARDs will also be included.
6	Concomitant treatments including but not limited to the following are permitted per standard of care: • csDMARDs (e.g., methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine) • Non-steroidal anti-inflammatory drugs (NSAIDs) • Corticosteroids • Prednisone (or equivalent) at a <u>stable ≤ 10 mg per day for at least 2 weeks prior to Visit 1</u> • Intra-articular or parenteral corticosteroids ≤ 2 weeks prior to Visit 1	Concomitant treatments per standard of care will be allowed and recorded.
7	Patient is willing and able to complete the informed consent process and comply with study procedures and visit schedule.	This criterion is not replicable with real world dispensing data and will not be used.
8	This additional point does not apply to the PrismRA arm.	Patients will have ≥ 1 CDAI measured in the 3-month period prior to the b/tsDMARD initiation to ensure patients from practices where CDAIs are routinely used and baseline CDAI is well defined in this 3-month window. There will be a further required ≥ 3 CDAI measurements in the 12-month period prior to the b/tsDMARD initiation. If possible to retain enough patients to fully match the PrismRA arm, there will be a

		required ≥ 4 CDAI measurements in the 12-month period prior to the b/tsDMARD initiation. To ensure sufficient medical history information and past b/tsDMARDs usage history, at least 12 months of enrollment in the database prior to the study treatment initiation will be required. All history information prior to 12 months will also be utilized.

7.4.2 Exclusion Criteria

Table 2 shows the exclusion criteria that will be used prospectively in the PrismRA arm and the best approximation for the selection of comparable patients in the observational external control arm.

Table 2. Exclusion criteria by study arm

	PrismRA arm	**External control arm**
1	Patient has any non-study limitation precluding patient receipt of the PrismRA test (e.g., financial, or logistical limitations).	The assumption will be made that patients who used b/tsDMARDs did not have such limitations that would have prevented the potential receipt of the PrismRA test had it been offered.
2	Concurrent treatment with an investigational product or use of an investigational product less than 4 weeks prior to Visit 1.	This criterion is not replicable with real world dispensing data and will not be used.
3	Patient cannot have participated in an observational study at least 4 weeks prior to Visit 1.	This criterion is not replicable in real-world data and will not be used.
4	The use of RA therapies outside of FDA-approved indication.	This criterion is not replicable with real-world dispensing data and will not be used.

5	Patient has been previously exposed to any non-TNFi b/tsDMARDs (FDA approved or experimental).	Patients who have been previously exposed to any non-TNFi b/tsDMARDs any time during their history prior to the study treatment initiation will be excluded. The list of non-TNFi b/tsDMARDs approved for RA includes the following: • IL-6i (tocilizumab, sarilumab) • IL-1i (anakinra) • T-cell co-stimulation inhibitor (abatacept) • B-cell depletion agent (rituximab) • JAKi (tofacitinib, baricitinib, upadacitinib) The list of non-TNFi b/tsDMARDs not currently approved for RA includes the following: • IL-23i (guselkumab, risankizumab, tildrakizumab, ustekinumab [IL-12/IL-23i]) • IL-17i (secukinumab, ixekizumab, brodalumab)
6	Women who are known to be pregnant or breast-feeding or plan to get pregnant during the study.	Patients who have relevant pregnancy-related codes in the past 12 months or during the 24-week follow-up will be excluded.
7	Patient is currently receiving systemic antimicrobial treatment for viral, bacterial, fungal, or parasitic infection at the time of Visit 1.	Patients who received antimicrobial medications in the 30-day period prior to the b/tsDMARD initiation will be excluded.

8	Patient has any active, chronic, or recurrent invasive infection (e.g., listeriosis and histoplasmosis) and/or a viral infection, that based on the Investigator's clinical assessment, makes the patient an unsuitable candidate for the study. This includes hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or human immunodeficiency virus (HIV).	Patients with the relevant diagnostic codes for chronic, or recurrent invasive infections any time prior to the study treatment initiation. This includes listeriosis, histoplasmosis, coccidioidomycosis, tuberculosis, non-tuberculosis mycobacterial infections, cryptococcosis, pneumocystis pneumonia, toxoplasmosis, HBV, HCV, varicella zoster virus (VZV), herpes simplex virus (HSV), HIV.
9	Patients with malignancy except non-melanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low risk or very low risk (per standard guidelines) localized prostate cancer under surveillance/watchful waiting (without intent to treat), or carcinoma in situ of any type (complete resected).	Patients with cancer diagnostic codes any time prior to the study treatment initiation will be excluded. This includes all malignancies except non-melanoma skin cancer. Allowing for localized and cured cancers is not replicable in real-world data and will not be attempted.
10	Patients who are unable to understand the protocol and unable to provide informed consent.	This criterion is not replicable in real-world data and will not be used.
11	Patients who are not indicated for PrismRA.	This criterion is not replicable in real-world data and will not be used. The assumption will be made that the careful replication of the above inclusion and exclusion criteria will ensure a comparable indication for PrismRA in the external control arm.
12	This point does not apply to the PrismRA arm.	Patients will be excluded if they have been cared for by rheumatologists who have participated in the PrismRA arm any time in the past to avoid including patients using PrismRA.

8 Study Procedures

8.1 Pre-Screening

PrismRA arm:
Prior to Visit 1, potential patient charts may be reviewed to determine eligibility for the study. At the discretion of the Investigator, pre-screening lab tests (i.e., Complete Blood Count (CBC), Clinical Metabolic Panel (CMP), Tuberculosis (TB), and/or C-reactive Protein (CRP)) may be ordered and analyzed per standard of care if the patient has not already received these lab tests within 3 months of the planned study Visit 1.

External control arm:
The entirety of data for each patient (no less than 12 months) prior to the study treatment initiation will be used to assess their medical history and past medication use and to determine their eligibility (see above). For variables required to be up to date at the time of the study treatment initiation, the most recent value within the 3-month period prior to the study treatment initiation will be used, unless otherwise stated (see Table 1, Table 2).

8.2 Screening and Enrollment

PrismRA arm:
At Visit 1, patients will complete the informed consent process. A written, signed informed consent form (ICF) must be obtained prior to the recording or collection of any data under this protocol. Upon signing the ICF, the patient will be considered enrolled into the study.

At the discretion of the Investigator, patients will also be asked to review and sign a medical records release form providing access to their medical records outside of the study. Sponsor or Sponsor designees may access patients' medical records upon study completion for only those patients that provide proper authorization.

Following patient consent, each patient will be assigned a unique study identification number that will be used to track their de-identified data throughout their participation in the study.

External control arm:
Screening/enrollment activities are not applicable for the external control arm of patients identified from real-world data.

8.3 Screen Failures

PrismRA arm:
Screen failures are defined as those patients who consent to participate in the clinical study but did not meet one or more criteria for participation in the study.

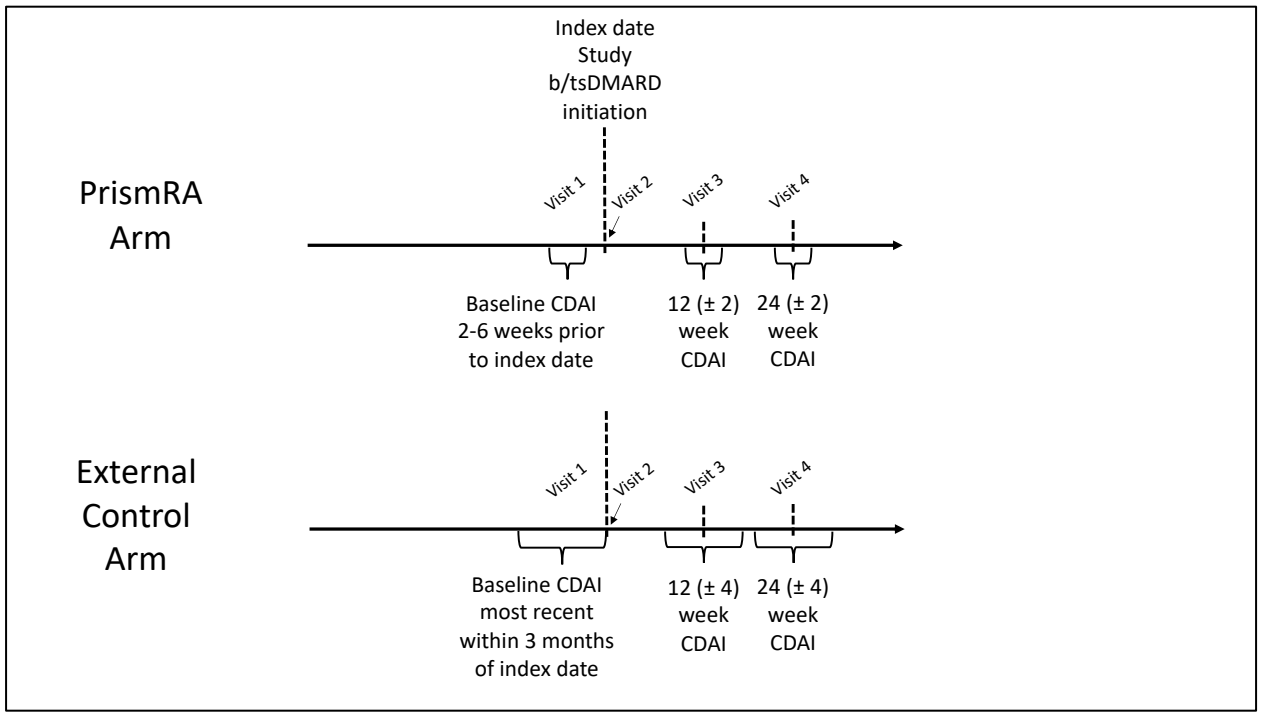
External control arm:
Non-initiators of b/tsDMARDs are considered screen failures and will not be in the analysis dataset.

8.4 Summary of Visits and Assessments

PrismRA arm:
Data will be collected at Screening/Baseline, Study Treatment Initiation (2–6 weeks after, and then at follow up visits approximately 12 weeks and 24 weeks after Study Treatment Initiation. The allowable time windows are explained in Section 8.5.

External control arm:
Data from clinical encounters over time will be used to provide information for (1) the baseline period (for CDAI assessment), (2) study treatment initiation time point; (3) the 12-week follow-up period; and (4) the 24-week follow-up period. The allowable time windows are explained in Section 8.5.

8.5 Schedule of Visits



PrismRA arm:
The timing for the follow-up visits (visits 3 and 4) should be projected based on the date of Study Treatment Initiation (index date).

External control arm:
The date of study treatment initiation constitutes the index date for the beginning of the follow-up. The 3-month period prior to the index date will be used to ascertain the baseline CDAI. The 12-week follow-up will be defined as the clinical encounter closest to the 12-week time point within the 12 (± 4) week visit window. The 24-week follow-up will be defined the visit closest to the 24-week time point within the 24 (± 4) week visit window. Depending on feasibility, we will

attempt follow-up windows, such as ± 6 week window, ± 3 week window, and ± 2 week window. Sensitivity analyses with different follow-up windows will be conducted as needed.

8.6 Schedule of Assessments

PrismRA arm:

Procedure	Visit 1 (Screening/ Baseline)	Visit 2 (Study Treatment Initiation)[7]	Visit 3 (12 Week Follow-up)	Visit 4 (24 Week Follow-up)
Visit Windows	N/A	2-6 weeks	±2 weeks	±2 weeks
Informed Consent	X			
Medical Records Release Form	X			
Eligibility Criteria	X			
RA Medical History	X			
Smoking[8]				X
Comorbidities[8]				X
Weight	X		X	X
28 Joint-Count for Tenderness & Swelling	X		X	X
PrismRA[1]	X			
CRP[2]	X		X	X
RF[3]				
Vectra DA[3]				
TB Test[4]				
Urine Pregnancy Test[5]				
Physician Global Assessment of Disease Activity	X		X	X
Patient Global Assessment of Pain	X		X	X
Patient Global Assessment of Disease Activity	X		X	X
Health Assessment Questionnaire	X		X	X
RAPID3 Assessment	X		X	X
Imaging[6]				
Targeted Therapy Questionnaire	X	X		
RX Adherence Check			X	X
Initiation or Change of Targeted Therapy		X		
Current RA Medications	X	X	X	X
Socioeconomic Status[8]				X

Abbreviations: CRP (C-Reactive Protein), N/A (Not Applicable), RA (Rheumatoid Arthritis), RF (rheumatoid factor), and RX (Treatment).
Note: At the discretion of the Investigator, pre-screening standard of care lab tests (e.g., CBC, CMP, and/or CRP) may be ordered if patient does not have lab tests within 3 months of Visit 1.
[1] PrismRA results will be provided to the Investigator based on the patient's assigned treatment selection arm. Investigators will receive the test results only for those patients in the informed treatment selection arm.
[2] Performed via standard lab practices utilizing the same local lab. Visit 1 results can be from a test within 3 months prior to Visit 1.
[3] If available, results can be provided from patient's medical records.
[4] If required by the Investigator, test can either be QuantiFERON Gold TB Test, local PPD TB test, or T-Spot.
[5] If required by the Investigator, a urine pregnancy test for child-bearing potential females should be completed.

[6] If available, results for imaging (e.g., X-rays, ultrasound, magnetic resonance imaging, or total sharp score) to be pulled from patient's medical records.
[7] PrismRA results must be received and reviewed prior to study treatment initiation for the PrismRA arm only.
[8] Smoking, comorbidities, and socioeconomic status information collected at Visit 4 reflects patient's status at Baseline.

External control arm:

No prospective data collection schedule is enforced, and the data collection is based on routine clinical encounters. Existing data will be mapped from these routine clinical encounters in the following manner.

Data Element	Baseline	Study Treatment Initiation	12 Week Follow-up	Visit 4 (24 Week Follow-up)
Visit Windows	3 months	(Precise index date)	±4 weeks	±4 weeks
Informed Consent	X			
Medical Records Release Form	X			
Eligibility Criteria	X			
RA Medical History	X			
Smoking	X			
Comorbidities	X			
Weight	X		X	X
28 Joint-Count for Tenderness & Swelling	X		X	X
PrismRA[1]	N/A			
CRP	X		X	X
RF	X			
Vectra DA	N/A			
TB Test	N/A			
Urine Pregnancy Test	N/A			
Physician Global Assessment of Disease Activity	X		X	X
Patient Global Assessment of Pain	X		X	X
Patient Global Assessment of Disease Activity	X		X	X
Health Assessment Questionnaire	X		X	X
RAPID3 Assessment	X		X	X
Imaging[6]	N/A			
Targeted Therapy Questionnaire	N/A			
RX Adherence Check (defined as continuation of the study treatment)			X	X
Initiation or Change of Targeted Therapy		N/A		
Current RA Medications	X		X	X
Socioeconomic Status[1]	X			

Abbreviations: CRP (C-Reactive Protein), N/A (Not Applicable), RA (Rheumatoid Arthritis), RF (rheumatoid factor), and RX (Treatment).
[1] Socioeconomic status information will be available for a subset of patients.

8.7 Specimen Collection

PrismRA arm:
Blood will be collected at Visits 1, 3, and 4. Blood will not be collected at Visit 2.
Blood will be collected in two 2.5 mL PAXgene tubes and one 8-10 mL serum separator tube for a total of 15 mL at Visit 1. Blood will be collected using the PrismRA sample collection kit at Visit 1 and processed according to the study sample collection process. Blood for the CRP test will be collected at Visits 1, 3, and 4 utilizing the same local lab and processed per standard lab practices.

Anticipated volume of blood to be drawn per patient over the scheduled study visits should not exceed 45 mL. If the initial blood draw in Visit 1 fails sample quality assessments, a patient may have an unscheduled study visit performed for an additional blood draw prior to Visit 2.

External control arm:
No specimen collection schedule is enforced, and the specimen collection is based on routine clinical encounters. OM1 does not handle specimens and utilizes the laboratory results only.

8.8 Study Treatment

PrismRA arm:
Patients are to initiate a b/tsDMARD or change to a study-indicated b/tsDMARD per clinical guidance of the Investigator on Visit 2.

External control arm:
b/tsDMARDs initiated by the treating physician according to the standard of care will be deemed as the study treatment. The study treatment can include the very first b/tsDMARD (new initiation) or subsequent b/tsDMARD (switch).

8.8.1 Randomization

No randomization will be performed for this study.

8.8.2 Stratification

There will be no stratification for this study.

8.8.3 Therapy, Dose, Modes of Administration

PrismRA arm:

- Dosage and selection of b/tsDMARD are at the Investigator's discretion but should be within the FDA approved label.
- Dose adjustments for a particular b/tsDMARD will be permitted only in accordance with the FDA approved label. Changes should be documented in the patient's medical records.

External control arm:

The selection and the initial dosage and dose adjustments are at the discretion of the treating physician and are assumed to be compatible with FDA approval.

8.8.4 Duration of Follow-up for Outcome Assessment

- 24 weeks from the index date, defined as the date of b/tsDMARDs initiation (See Section 8.5 for allowable time windows)

8.8.5 Medication Expenses and Reimbursement (PrismRA arm only)

- The Sponsor will not cover any b/tsDMARD medication costs associated with this study.
- Patients may be reimbursed for their time at the discretion of the Investigator.

8.9 Data Collection

PrismRA arm:
Patient data will be collected from clinical assessments, medical records, imaging, laboratory results, and surveys at screening/baseline, treatment initiation and follow-up visits and entered in the study database.

If a completed medical records release form is on file, comprehensive demographic, medical, and health information (if available) may be directly collected from the patient's electronic medical records by the Sponsor. Electronic Medical Records (EMR) data may be obtained indefinitely following a patient's enrollment unless the patient withdraws authorization.

Data from the PrismRA (Visit 1) samples will be stored at Scipher Medicine's Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathologists (CAP)-accredited laboratory.

External control arm:
In the external control arm, the existing data in OM1's PremiOM RA will be utilized. No new data collection will be performed.

8.10 Patient Follow-up

PrismRA arm:
In order to reduce the loss of patients to follow-up, all patients will be asked for their personal contact information and an alternate person's contact information. Patients may be directly contacted by the Investigator or Sponsor/designee in order to support study follow-up. The designated alternate contact person may also be directly contacted in the event the patient cannot be reached.

For patients who are lost to follow-up, Investigator or Sponsor/designee will search available health status databases to determine vital status and cause of death in case of mortality.

External control arm:

To ensure the availability of sufficient quality of data, at least one CDAI measurement during the baseline 3-month period prior to the index date (initiation of b/tsDMARDs) will be required. As needed, we will further require CDAI during the follow-up.

8.11 Patient Withdrawal/Completion

PrismRA arm:
Patients may withdraw from the study at any time without prejudice to their care.
The Investigator and/or the Sponsor may withdraw patients at any time who violate the study protocol or, to protect the subject for safety or administrative reasons at any time. It will be documented whether or not each patient completes the determined follow-up visits. Changes to the study treatment during follow-up as indicated by clinical practice does not constitute a protocol violation or withdrawal.

Early withdrawals will include, but are not limited to, those patients who consent to participate in the clinical study but fail to initiate a b/tsDMARD at Visit 2 within 6 weeks of Visit 1.

External control arm:
As existing data from routine clinical care will be utilized, this point does not apply.

9 Safety Assessments

9.1 Introduction to Safety Assessments

PrismRA arm:
There are no investigational therapies being evaluated per the protocol. For patients in the informed treatment selection arm, Investigators will receive the PrismRA test results and use the results to inform their treatment decision. PrismRA was developed and its performance characteristics determined by Scipher Medicine. The laboratory is certified under CLIA and accredited under CAP. This commercially available test is used for clinical purposes. It should not be regarded as investigational, or for research. The Investigator is expected to follow all aspects of the prescribing information when administering a pharmaceutical therapy in the course of the treatment of patients included in this study.

External control arm:
Data arise from routine clinical practice and are not subject to study-specific safety assessment.

9.2 Anticipated and Unanticipated Adverse Device Effects

PrismRA arm:
PrismRA is not expected to result in either anticipated or unanticipated adverse device effects (UADE) as it involves the analysis of ex-vivo blood samples from the participating patients.

This study does include a potential source of harm to the patient as a result of the venipuncture procedure, unrelated to the study device:

- Faintness, inflammation of the vein, bruising, temporary discomfort, and bleeding at the site of puncture may occur.
- Infection may also occur, though rare.

External control arm:
Data arise from routine clinical practice and do not involve the use of the PrismRA test. Thus, no study-relevant adverse device effect exists.

10 Statistical Considerations

Data collected throughout this study will be analyzed by Sponsor or its designee.

10.1 Sample size

The study is powered to detect a difference of 10% in the proportion of patients with improvement in CDAI from baseline to Week 24 by at least MID as defined in Section 7.1 between the PrismRA arm and the external control arm. Results are shown in Table 3. It is estimated that the attrition rate at Week 24 (defined as the proportion of patients with missing CDAI scores at Week 24 for any reason) can be up to 45% in the PrismRA arm and up to 50% in the external control arm. The sample sizes below have been inflated accordingly to account for the patient attrition mentioned above.

With a sample size of 600 in the trial arm and 1,500 in the external control arm, the study has 88% power to establish the superiority of the PrismRA intervention as compared to the standard of care by detecting a difference of 10% between the two study arms based on Fisher's exact test of independent proportions assuming the proportion of patients with improvement in CDAI by MID are 40% and 30% in the PrismRA arm and the external control arm, respectively.

Table 3. Study power for comparing proportion of patients with improvement in CDAI from baseline by at least MID between the two study arms

Sample size in the trial arm before attrition	Sample in the external control arm before attrition	Proportion of patients in the PrismRA arm with MID improvement in CDAI	Proportion of patients in the external control arm with MID improvement in CDAI	Study power	Alpha (two-sided)
600	1,000	0.45	0.35	80%	0.05
600	1,000	0.40	0.30	82%	0.05
600	1,000	0.35	0.25	85%	0.05
600	1,500	0.45	0.35	86%	0.05
600	1,500	0.40	0.30	88%	0.05
600	1,500	0.35	0.25	90%	0.05
600	2,000	0.45	0.35	88%	0.05

600	2,000	0.40	0.30	90%	0.05
600	2,000	0.35	0.25	92%	0.05

The sample size calculation was performed with SAS (version 9.4, Cary, NC).

10.2 Planned Interim Analysis of the PrismRA Arm

Data will be assessed by the Scipher Medicine team in one interim analysis when 50% of enrollees in the PrismRA arm have completed the treatment initiation visit. Refer to the study's SAP for additional details.

10.3 Baseline Analysis of the External Control Arm

The OM1 team will identify an eligible pool of patients for an external control arm in the OM1's PremiOM RA dataset.

The baseline study data from the PrismRA arm will be provided by the Scipher Medicine team in a format ready for analysis (fully quality controlled), with a corresponding dataset specification document to help the OM1 team understand the data.

From the pool of the study-eligible RA patients in the OM1 PremiOM RA dataset, the external control patients will be selected based on propensity scores. Analytic approaches which adjust for differences in patient baseline characteristics will be used. These approaches include but are not limited to propensity score weighting, matching and covariate adjustment in a multivariable regression model.

Baseline covariates including the following will be considered (defined in a 6-month window prior to the index date unless otherwise specified elsewhere).

Domain	**Variables**
Patient Characteristics	• Age (calculated from birth year) • Sex • Race/Ethnicity • Geography • Body mass index
Lifestyle	• Smoking (current, former, or never smoker)
Comorbidities (based on at least two diagnostic codes at least 30 days apart in the external control arm; based on an additional questionnaire in the PrismRA arm.)	• Lung disease • Myocardial infarction • Other cardiovascular • Stroke • Hypertension • Fractures spine, hip, or leg • Depression • Diabetes mellitus

	• Ulcer or stomach problem • Fibromyalgia The Rheumatic Disease Comorbidity Index (RDCI) will be derived.
RA Related	• Duration of RA (Defined as the number of days between the date of the first RA diagnosis code and the index date for the external control arm) • Seropositivity (rheumatoid factor or anti-citrullinated peptide antibody) • CDAI at baseline • Previous use of TNFi (yes, no)
Concurrent RA Medications	• Methotrexate • Folic acid • Non-methotrexate major csDMARDs (Sulfasalazine, Leflunomide, Hydroxychloroquine) • Glucocorticoids (with prednisone equivalent dose)

The choice of TNFi vs. non-TNFi b/tsDMARDs as the study treatment will be excluded from the list of potential propensity score variables, as this variable is temporally subsequent to the study's exposure variable (use or non-use of PrismRA in the trial arm and external control arm, respectively) and is considered a mediator of the potential benefit of PrismRA.

The baseline characteristics of patients will be compared across the PrismRA arm and the external control arm both before and after the propensity score modelling procedure in a table. In general, each continuous variable will be reported as mean, standard deviation (SD) or median, interquartile range (IQR), and range where appropriate. Each categorical variable will be summarized as a number and proportion. The baseline characteristics after propensity score modeling will be examined for improved covariate balance via the absolute standardized mean metric for each covariate.

Complete details regarding the planned analyses are available in the study SAP.

10.4 Planned Outcome Analysis

The previously stated outcome measures will be compared across the PrismRA arm and the external control arm after propensity score modelling. For all outcome measures, point estimates as well as two-sided 95% confidence intervals (CIs) will be provided. Hypothesis testing will be

two-sided with an alpha level of 5%. For proportion outcome measures, Pearson's χ^2 test will be utilized. For continuous outcome measures, unpaired t-test will be used.

Refer to the study's SAP for additional details.

10.5 Missing Data Handling

Missing data will be handled with two approaches: (1) minimizing the chance of missing data in the study design and conduct stages, and (2) handling missing data with statistical methods in the analysis phase.

The following measures will be taken to reduce missing data in the analysis datasets.

PrismRA arm:
Missing data will be minimized through rigorous conduct of data collection as described in Section 8.9. See below for the handling of missing follow-up data.

External control arm:
At least one observed CDAI in the 3-month period prior to the index date (b/tsDMARD initiation) will be required to ensure patients are selected from practices where CDAI are recorded as a part of routine care.

The following statistical methods will be considered in handling missing data in the analyses.

- For outcome measures, the appropriate methods depend on the magnitude of missing data, and whether data are assumed to be missing at random. This will be evaluated prior to the final analysis and will be evaluated for the PrismRA arm and the external control arm separately. Considerations will be given to multiple imputation, estimating the CDAI outcome (whether MID was achieved at Week 24) based on previous outcome measures and treatment status, and complete case analyses. A sensitivity analysis will be conducted to assess the robustness of the analysis results. Details will be provided in the SAP.

10.6 Data Reporting

10.6.1 Interim Analyses and Reporting

A single interim analysis will be conducted at the time that 50% of PrismRA arm patients (the first 300 patients enrolled) have completed Visit 2 or have dropped out of the study. All data available in the PrismRA arm at the time of the interim analysis will be included, but effectiveness of PrismRA will not be evaluated to protect the integrity of the study. Instead, the interim analysis will be restricted to baseline characteristics and data completeness analyses.

10.6.2 Final Analyses and Reporting

A final study report will be generated after all data collection is complete. The final report will encompass all planned analyses, including a description of the complete study population and study results, as described in the SAP.

11 Limitations

11.1 Data Recency

An ideal observational external control arm is fully contemporaneous to the single arm trial with prospective real-world data collection specifically tailored to the corresponding PrismRA arm[14]. The approach is based on retrospective real-world data collection (secondary use of routinely collected data). Due to the need to have enough patients for the propensity score process, the external control arm may have a mixture of contemporaneous external control patients (observed during the PrismRA arm study period) and historical external control patients (observed before the PrismRA arm study period). In the SOC for RA, an increasing uptake of late-comer b/tsDMARDs has been reported for the 2001–2015 time period [15]. The market uptake trend may have been less dramatic in the more recent time period due to the paucity of new FDA approvals (last FDA approval: upadacitinib in 2019) and market saturation. However, the recent announcement (September 2021) by the FDA of a boxed warning for JAK inhibitors' regarding cardiovascular safety may have had an influence. In the current study, the historical external control patients will be limited to those who initiated their index b/tsDMARDs with the 1-3 year period prior to the trial enrollment (March 2022; minimum years that allows sufficient propensity score model patients). This approach should minimize the potential impact of a secular trend in the SOC (particularly the increasing uptake of non-TNFi b/tsDMARDs) while allowing for sufficient power.

11.2 RA Patient Identification

External control arm:
The identification of RA patients in the external control arm is based on the claims algorithm implemented in OM1's PremiOM RA dataset rather than the 2010 ACR/EULAR classification criteria. The algorithm uses RA diagnostic codes as well as DMARDs use. The combination of RA diagnostic code and DMARD use has a high positive predictive value (86.2%-88.9% against physician diagnosis gold standard) [16] and is a well-accepted standard in the real-world data studies of RA. The OM1 claims algorithm likely has a higher positive predictive value as it incorporates further exclusion of patients with non-RA diagnoses for which DMARDs are indicated.

12 Data Handling and Record Keeping (Study Management)

PrismRA arm:
The design and conduct of the PrismRA arm will be governed by Scipher Medicine and its designees. OM1 will provide input to ensure the smooth execution of the subsequent analyses.

External control arm:
The design and execution of the observational external control arm and subsequent analyses will be performed by OM1, with the guidance, input, review, and approval of the Scipher Medicine

team. To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the principles outlined in the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research), and any applicable national guidelines.

12.1 Study Database

PrismRA arm:

Data will be collected into the study database through a secure, electronic database capture (EDC) system or an electronic data transfer via an encrypted secure sockets layer protocol to the Scipher Medicine data lake.

Electronic case report forms will be maintained in the EDC, and all relevant observations and data related to the protocol-defined assessments will be recorded. This will include, at minimum, demographics, medical history, physical examinations, laboratory results, clinical assessments, treatment information, and patient reported outcomes.

Prior to recording data in the paper CRF, Investigators and site staff will be trained on how to accurately capture data. Trained and qualified Investigators and site staff will be responsible for recording data in the paper CRFs.

The study database will be password protected and access will be provided only to trained and authorized personnel. Data collected into the study database may include protected health information (PHI). This PHI will not be shared beyond the Sponsor/designee or site without specific institutional review board (IRB) approval and additional patient consent.

External control arm:

An analytic dataset of eligible RA patients, built upon the underlying OM1 enterprise data warehouse, will be created for this study. The OM1 data warehouse is built on OM1 Origin Plus™, a scalable cloud computing platform with high availability and dependability. The analytic dataset will contain data ingested from multiple sources in multiple formats and will serve as a repository of centralized, standardized, normalized, and integrated data from the different sources. Where necessary and possible, data from disparate sources will be linked with other data that are attributed to a common patient creating a longitudinal record. Data will be standardized and normalized as necessary, for example, classifications of text documents such as lab reports and pathology reports. A detailed technical data management plan describing processes for transferring data, managing data quality, and maintaining data security will be developed and implemented for the study.

12.2 Inspection of Records

PrismRA arm:

Sponsor or its designee will be allowed to conduct site visits either remotely or at the Investigator's clinical research facilities for the purpose of monitoring any aspect of the study, as

applicable. The Investigator agrees to allow the Sponsor or its designee to inspect the facilities, patient medical records, source documents, and other records relative to study conduct. Source documents containing PHI will be protected and transferred to the Sponsor or its designee via a secure, HIPAA compliant portal. Study records containing patient health information will be maintained in a confidential manner.

12.3 Retention of Records

PrismRA arm:

All primary data collected as a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 6 years after the last approval of a marketing application in an International Council for Harmonization (ICH) region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 6 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country and region-specific requirements that may be more stringent than the 6 years included in ICH shall be followed.

The site will maintain an Investigator Site File (ISF), which will be maintained at the study site and in accordance with local and Federal regulations, as applicable. The site must keep this ISF current and available for review by the Sponsor, IRB, and/or regulatory bodies.

External control arm:

Based on recommendations from International Society for Pharmacoepidemiology Guidelines for GPP, all analysis datasets used for the final analysis will be archived for at least five years after the delivery of the final tables to Scipher Medicine unless specific requests are made during the report process.

12.4 Confidentiality (PrismRA arm Only)

12.4.1 Confidentiality of Records

PrismRA arm:

All study sites, laboratories, and parties supporting this study must comply with HIPAA, where applicable. All data and records generated throughout this study will be kept confidential in accordance with local and Federal policies and HIPAA on patient privacy.

At consent, personal identifying information, including patient name, birth date, and contact information, will be collected and stored on a secure and HIPAA-compliant research database.

Following consent, each patient will be assigned a unique study identification number that will be used to track their de-identified data.

Records that may have patient identifying information will be kept confidential in accordance with applicable guidelines, regulations, and laws.

External control arm:
The study utilizes a de-identification and secure patient key software tool to create statistically de-identified data sets and to create de-identified keys for patients. The tool generates tokens based on a patient's primary information (first name, last name, date of birth, and gender) and all study analysis performed will use the statistically de-identified data. Only a few limited data set data elements, including dates of service and date of death, will be part of the study data set. All parties will ensure protection of patient personal data and will not include patient identifiable information on any study forms, reports, publications, or in any other disclosures, except where required by law.

The database is housed on a secure cloud computing platform on which all OM1 technical operations, data processing, and storage are conducted. The global infrastructure is designed and managed according to security best practices as well as a variety of security compliance standards making it one of the most secure computing infrastructures in the world. The system also meets the standards of the ICH E6 (R2) guideline regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

12.4.2 Review of Records

Sponsor and/or its designee will review source documents (i.e., medical records, laboratory results) and data collected throughout the study. In addition, an auditor, IRB, FDA, or national or local regulatory authorities may access and review applicable source documents, records, and data. All patients will be notified of and consent to this possibility during the consenting process.

12.4.3 Study results

If any results of the study are published, the patient's identity will remain confidential.

12.4.4 Future Use of Data or Specimens

PrismRA arm:

Data collected throughout the study and subsequently de-identified will be used for future research and/or distributed to other investigators for future research.

PrismRA samples from patients processed at Scipher Medicine's CLIA-certified CAP-accredited laboratory will also be de-identified and used for future research and/or distributed to other investigators for future research. Future research will include extracting and sequencing DNA isolated from the blood samples, in addition to the RNA that is extracted and sequenced for PrismRA. Future research may also include discovering novel biomarkers for disease diagnosis, monitoring, or progression as well as discovering new disease mechanisms, therapeutic targets, and therapies for autoimmune disorders.

De-identified data may be stored indefinitely, and de-identified specimens may be stored for up to 10 years following study completion. The de-identified data and specimens may be shared with researchers/institutions outside of Scipher without additional informed consent from the subject or the legally authorized representative. This could include for-profit companies.

External control arm:

Patients in the external control arm are from the OM1 PremiOM RA dataset, owned and maintained by OM1. OM1 PremiOM RA data may be used for analyses in the future per agreement.

13 Ethics

13.1 Ethics Review

The protocol, ICF, and any advertisements must be approved or given a favorable opinion in writing by an IRB. The Investigator must submit written and dated verification of the IRB approval to Sponsor before he or she can enroll any patient into the study.

The Sponsor/designee or Investigator will inform the IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB upon receipt of amendments and annually, if required per local and IRB regulations.

Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

13.2 Ethical Conduct of the Study

The Sponsor, Investigators, study staff and designees will conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH, GCP, and other applicable local and federal laws, regulations, and guidelines.

14 Quality Control

14.1 Data Quality

PrismRA arm:

Site and data monitoring will occur in accordance with the clinical monitoring plan, if applicable. Data captured in the study database will be compared against the source data for completeness and accuracy. Discrepancies will be addressed and corrected, if required, by qualified site personnel.

eCRF data will also be routinely reviewed for timeliness, errors, accuracy, and omissions. Any data issues will be submitted to the site for further clarification. Qualified site personnel will address queries and correct data in the study database or paper source files.

14.2 Protocol Deviations

PrismRA arm:
Study sites and databases will be evaluated for protocol deviations.

At study completion, the number and type of protocol deviations will be analyzed by the study biostatistician to review the events by site to determine if the deviations could affect the integrity of the study data. The study biostatistician will report findings to the Sponsor.

15 Protocol revision history

Rev. #	Effective Date	Summary of Changes
3.0	20-Oct-2022	Change to an external control arm design and sample size adjustment.
2.0	04-Feb-2022	Change in study title, endpoints, clarification of study design, and general edits.
1.0	23-Jul-2021	Initial Release

16 References

1. Spencer AK, Bandaria J, Leavy MB, Gliklich B, Su Z, Curhan G, Boussios C. Validation of a machine learning approach to estimate Clinical Disease Activity Index Scores for rheumatoid arthritis. RMD Open. 2021 Nov;7(3):e001781. doi: 10.1136/rmdopen-2021-001781. PMID: 34819386; PMCID: PMC8614150.
2. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; **38**(6): 727-35.
3. Charles-Schoeman C, Burmester G, Nash P, et al. Efficacy and safety of tofacitinib following inadequate response to conventional synthetic or biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2016; 75(7): 1293-301.
4. Bykerk VP, Ostor AJ, Alvaro-Gracia J, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis* 2012; **71**(12): 1950-4.
5. Fleischmann R, van Adelsberg J, Lin Y, et al. Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors. *Arthritis Rheumatol* 2017; **69**(2): 277-90.
6. Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008; **67**(4): 547-54.
7. Jin Y, Desai RJ, Liu J, Choi NK, Kim SC. Factors associated with initial or subsequent choice of biologic disease-modifying antirheumatic drugs for treatment of rheumatoid arthritis. *Arthritis Res Ther* 2017; **19**(1): 159.
8. Curtis JR, Zhang J, Xie F, et al. Use of oral and subcutaneous methotrexate in rheumatoid arthritis patients in the United States. *Arthritis Care Res (Hoboken)* 2014; **66**(11): 1604-11.
9. Mellors TW, Johanna; Ameli, Asher; Jones, Alex; et al. Clinical validation of a blood-based predictive test for stratification of response to anti-TNF therapies in rheumatoid arthritis patients. Network and Systems Medicine Volume 3.1, 2020 doi: 10.1089/nsm.2020.0007. Accepted June 2020.
10. Cohen s, Wells AF, Curtis JR, Dhar R, Mellors T, Zhang L, Withers JB, Jones A, Ghiassian SD, Wang M, Connolloy-Strong E, Rapisardo S, Gatalica Z, Pappas DA, Kremer JM, Saleh A, Akmaev VR. A Molecular Signature Response Classifer to Predict Inadequate Response to Tumor Necrosis Factor-α Inhibitors: The NETWORK-004 Prospective Observational Study. Rheumatol Ther. 2021 Jun 19:1-18. doi:10.1007/s40744-021-00330-y.
11. Curtis JR, Yang S, Chen L, Pope JE, Keystone EC, Haraoui B, Boire G, Thorne JC, Tin D, Hitchon CA, Bingham CO 3rd, Bykerk VP. Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients. Arthritis Care Res (Hoboken). 2015 Oct;67(10):1345-53. doi: 10.1002/acr.22606. PMID: 25988705; PMCID: PMC4580563.
12. Ward MM, Castrejon I, Bergman MJ, Alba MI, Guthrie LC, Pincus T. Minimal Clinically Important Improvement of Routine Assessment of Patient Index Data 3 in Rheumatoid Arthritis. J Rheumatol. 2019 Jan;46(1):27-30. doi: 10.3899/jrheum.180153. Epub 2018 Oct 15. PMID: 30323010; PMCID: PMC6314888.
13. Wolfe F, Michaud K. Assessment of pain in rheumatoid arthritis: minimal clinically significant difference, predictors, and the effect of anti-tumor necrosis factor therapy. J Rheumatol. 2007 Aug;34(8):1674-83. Epub 2007 Jul 1. PMID: 17611989.
14. Burcu M, Dreyer NA, Franklin JM, Blum MD, Critchlow CW, Perfetto EM, Zhou W. Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms. Pharmacoepidemiol Drug Saf. 2020 Oct;29(10):1228-1235. doi: 10.1002/pds.4975. Epub 2020 Mar 11. PMID: 32162381; PMCID: PMC7687199.

15. Desai RJ, Solomon DH, Jin Y, Liu J, Kim SC. Temporal Trends in Use of Biologic DMARDs for Rheumatoid Arthritis in the United States: A Cohort Study of Publicly and Privately Insured Patients. J Manag Care Spec Pharm. 2017 Aug;23(8):809-814. doi: 10.18553/jmcp.2017.23.8.809. PMID: 28737992.
16. Kim SY, Servi A, Polinski JM, Mogun H, Weinblatt ME, Katz JN, Solomon DH. Validation of rheumatoid arthritis diagnoses in health care utilization data. Arthritis Res Ther. 2011 Feb 23;13(1):R32. doi: 10.1186/ar3260. PMID: 21345216; PMCID: PMC3241376.