Cover Page for ClinicalTrials.gov

Document:
STATISTICAL ANALYSIS PLAN (SAP)

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

Document Date:
November 11, 2022

STATISTICAL ANALYSIS PLAN (SAP)

PROJECT TITLE	A Clinical Utility Study of PrismRA Testing Therapeutic Response for Rheumatoid Arthritis (DRIVE)
SAP/STUDY NO.	SCIPHER-RA-005
VERSION & DATE	1.0 November-11-2022
AUTHORS	Jason Nelson, MPH, OM1 Kazuki Yoshida, MD, MPH, ScD, OM1 Sam Asgarian, MD, MBA, Scipher Chief Medical Officer Viatcheslav Akmaev, PhD, Scipher Chief Technology Officer
SPONSOR	Scipher Medicine Corporation
CONDUCTED BY	OM1 Inc. 31 St. James Ave, Suite 1125 Boston, MA 02116

Sponsor Signature Page

Reviewed and Approved by:

Sponsor

<Sponsor> Signature	Job Title	Date

OM1 Author

<SAP Author> Signature	Job Title	Date

OM1 Reviewer

<SAP Reviewer> Signature	Job Title	Date

Document History

Version	Author(s)	Date	Changes
0.1	Jason Nelson	08-SEP-2022	Initial Release
0.2	Jason Nelson, Kazuki Yoshida	16-SEP-2022	Revisions after Scipher team review
0.3	Jason Nelson, Kazuki Yoshida	22-SEP-2022	Revisions after Scipher team review
0.4	Jason Nelson, Kazuki Yoshida	07-OCT-2022	Revisions after Scipher team review
0.5	Jason Nelson, Kazuki Yoshida	12-OCT-2022	Revisions after Scipher team review
1.0	Jason Nelson, Kazuki Yoshida, Sam Asgarian, Viatcheslav Akmaev	11-NOV-2022	Revisions after Scipher team review

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ACR	American College of Rheumatology
AE	Adverse Event
ATT	Average Treatment Effect on the Treated
bDMARD	Biologic Disease Modifying Anti-Rheumatic Drug
CAP	College of American Pathologists
CBC	Complete Blood Count
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
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
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
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
IPCW	Inverse Probability of Censoring Weight
IPTW	Inverse Probability of Treatment Weight
IPTCW	Inverse Probability of Treatment and Censoring Weight
IQR	Interquartile Range
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
JAKi	Janus Kinase inhibitor
LDA	Low Disease Activity
MAR	Missing at Random
MCID	Minimal Clinically Important Difference
MI	Multiple Imputation
MID	Minimal Important Difference
MNAR	Missing Not at Random
MOA	Mechanism of Action
MTX	Methotrexate
NPI	National Provider Identifier
NSAIDs	Non-Steroidal Anti-Inflammatory Drug
PRO	Patient Reported Outcomes
PS	Propensity Score
PtGA	Patient Global Assessment
RA	Rheumatoid Arthritis
RAPID3	Routine Assessment of Patient Index Data 3
RDCI	Rheumatic Disease Comorbidity Index
RNA	Ribonucleic Acid
RWDC	Real-World Data Cloud
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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

1.0 OVERVIEW OF STUDY DESIGN

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 rheumatoid arthritis (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). The study will be conducted using a modified intention-to-treat (ITT) principle.[1] All eligible participants meeting inclusion and exclusion criteria *and* initiating the study treatment will be included.

PrismRA arm:

In this arm, all patients will be enrolled into the PrismRA informed treatment selection arm. 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 biologic and targeted small molecule synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs) do not terminate follow-up following protocol. 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 tumor necrosis factor inhibitor (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 following protocol. Controls may be sampled from time intervals contemporaneous with the trial (March 2022 and onward) as well as historical periods.

2.0 OBJECTIVES

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

3.0 STUDY OUTCOMES

In main analyses, binary outcomes measures specified at 12 weeks and 24 weeks below under the Composite Strategy in the ICH E9's estimand framework will be assessed.[2 3]. In the Composite Strategy, a successful outcome will be defined as success achieved at 12 or 24 weeks

and study completed without post-baseline treatment switch during 12 or 24 weeks. In the additional analyses, outcome measures specified at 12 weeks and 24 weeks below will be assessed under the Treatment Policy Strategy. In the Treatment Policy Strategy, any post-baseline treatment switch in the study medication is disregarded.

3.1 Primary Outcome Measure

The proportion of patients with moderate or high disease activity at baseline who achieve a minimal important difference (MID)[4] in CDAI of ≥ 6 (baseline moderate) or ≥12 (baseline high) at 24 weeks after study treatment initiation.

The main Composite Strategy analysis examines the proportion of patients with moderate or high disease activity at baseline who achieve a MID[4] in CDAI of ≥ 6 (baseline moderate) or ≥12 (baseline high) at 24 weeks after study treatment initiation AND complete study without post-baseline treatment switch. In the additional Treatment Policy Strategy, continuing the study treatment at 24 weeks is not required.

3.2 Secondary Outcome Measures

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)[5] 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[6] (≥ 1.1 on the scale of 0–10) compared to the baseline pain at 12 and 24 weeks after study treatment initiation.
g) The proportion of treatment decisions that were guided by PrismRA test results (in the PrismRA arm only).

Proportions for all the binary endpoints assessed at 12 and/or 24 weeks (a, c–f) will be assessed in the Composite Strategy, which will require no post-baseline treatment switch during 12 and 24 weeks, respectively. The additional Treatment Policy Strategy will disregard post-baseline

treatment switch during 12 and 24 weeks for the binary endpoints assessed at 12 and/or 24 weeks (a, c–f).

3.3 Exploratory Outcome Measures

a) The proportion of moderate to high disease activity patients that achieve American College of Rheumatology 50% improvement (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).
b) The proportion of patients receiving TNFi therapy and non-TNFi b/tsDMARDs as the study treatment at the index date.
c) 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 will only be a description of any discontinuation or change in the study treatment).

Exploratory Outcome (a) will be assessed in the Composite Strategy, which will require no post-baseline treatment switch during 12 and 24 weeks. In the additional Treatment Policy Strategy, post-baseline treatment switch during 12 and 24 weeks will be disregarded.

4.0 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.

Terms	Definition of Terms
Study Treatment	The b/tsDMARDs (FDA approved for RA) that is initiated at Visit 2 (See Protocol 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 defined as Visit 2
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.[7] CDAI scores from all data sources will be used.
TNFi-naïve subgroup	Patients who have never taken a TNFi prior to visit 2.
TNFi-exposed subgroup	Patients who had received at least one TNFi prior to visit 2.

5.0 GENERAL STATISTICAL CONSIDERATIONS

5.1 Sample Size and Power Calculations

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 the MID as defined in Section 3.1 between the PrismRA arm and the external control arm. Results are shown in **Table 1**. 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 PrismRA 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 1. 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 PrismRA arm before attrition	Sample size 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	PrismRA arm, attrition			
				30%	35%	40%	45%
				Study power			
600	1,000	0.45	0.35	86%	84%	82%	80%
600	1,000	0.40	0.30	87%	86%	84%	82%
600	1,000	0.35	0.25	90%	89%	87%	85%
600	1,500	0.45	0.35	91%	90%	88%	86%
600	1,500	0.40	0.30	92%	91%	89%	88%
600	1,500	0.35	0.25	94%	93%	92%	90%
600	2,000	0.45	0.35	93%	92%	90%	88%
600	2,000	0.40	0.30	95%	93%	92%	90%
600	2,000	0.35	0.25	96%	95%	94%	92%

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

5.2 Analysis Populations

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 Section 6.1.1 and 6.1.2 for patient inclusion and exclusion criteria for details.

This study will perform analyses for two sets of populations from the PrismRA arm. The first one is the modified ITT analysis population, which consists of patients that initiate the study

treatment at Visit 2. A sub-population of patients who are adherent to the PrismRA test results will also be analyzed. This sub-population will exclude patients who initiated TNFis despite having a PrismRA result indicating a molecular signature of non-response to TNFi therapies.

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 (PS) 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, with no less than 750 patients having CDAI scores at both baseline and Week 24. Data from patients who initiated b/tsDMARDs in the contemporaneous period (March 2022 and onward) will be used 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 PS model building process will aim to retain the inclusion of as many PrismRA arm participants as possible. If less than 95% of the PrismRA arm is included due to the lack of a matched control or non-overlapping PS, the historical period will be used for identifying external control patients. The smallest historical time window that can retain inclusion of greater than 95% of PS matched PrismRA patients will be used. The overlap in PS distributions between the external control and PrismRA arms will inform the ultimate sample size.

The data source for the analysis is the OM1 PremiOM RA Dataset within the OM1 Real-World Data Cloud (RWDC [OM1, Inc, Boston, MA, US]). The OM1 RWDC 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 RWDC 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.

5.3 Data Summarization and Analysis

Summary statistics for continuous variables to be reported will include mean, median, standard deviation (SD), 25th and 75th percentile. Categorical variables will be reported using counts and proportions. Hypothesis testing will be two-sided with an alpha level of 5%. For all outcome measures, point estimates as well as two-sided 95% confidence intervals (CIs) will be provided. P-values will be reported where appropriate to four decimal points unless all p-values in a table are greater than 0.01 in which case p-values will be reported to three decimal points in that table as the fourth decimal point is not needed. Details of the specific analytic methods are described below (Section 6).

5.4 Handling Missing Data

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 study design.

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

External control arm: At least one observed CDAI measurement in the 3-month period prior to the index date (b/tsDMARD initiation) and at least three observed CDAI measurements in the 12-month period prior to the index date (including the measurements in the aforementioned 3-month period) 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.

The rigorous design of the study aims to reduce the amount of missing data in baseline variables. If needed, single imputation [8] of missing baseline characteristics will be used to ensure that all eligible patients are included in the PS model to estimate the probability of treatment [9] for confounding control. Further details of the treatment PS methods are described below in Section 6.3.

Longitudinal outcomes may be unobserved due to patients that are lost-to-follow up ("drop-out"), missed scheduled visits (PrismRA arm), encounters that fall outside of the specified follow up window (external control arm) or not measured during a completed visit. It is anticipated that at 24-weeks roughly 45% of the PrismRA arm and 50% of the external control arm will be missing outcome data. Within each study arm the number and proportion of missing outcomes at

12 and 24-week visits will be described and baseline characteristics of patients with complete versus incomplete outcome data will be compared.

For the primary efficacy analysis multiple imputation (MI) will be used with the assumption that patients with unreported outcome measures at 12 and 24 weeks have outcome events that are non-informative under the missing at random (MAR) assumption. This assumes that missingness occurs independent of the unobserved outcome: that is, the possibly unknown true outcome for a patient is the same regardless of whether it is actually observed. This assumption underlies the ITT principle, which analyses all eligible patients according to the treatment group to which they were assigned regardless of subsequent missingness.

For all approaches using MI, fully conditional specification (FCS) methods will be used, which assume the existence of a joint distribution for all variables. [10] All eligible patients meeting inclusion and exclusion criteria and initiating the study treatment will be used to impute missing observations. Imputation models will include all relevant available observations at baseline and 12 and 24 week follow up visits. Separate MI models will be used to create *m* imputed datasets for each study arm and combined into *m* analysis datasets with complete data. The choice of *m* will be determined by the fraction of missing information in the variables to be imputed. [11] MI performed separately within each study arm maintains the structure of the missing data patterns and the relationship between covariates specific to each database and ensures that no outcome information is used in PS matching. [12] Each imputation model will include all covariates listed in Table 4 of Section 6.2 along with the dependent variables and continuous scores for each study outcome as specified in Section 3.0. Dichotomous endpoints will be derived based on continuous scores within each imputed dataset. Analyses will proceed as described in Sections 6.3 and 6.4 using each of the imputed datasets. Finally, treatment effect estimates will be averaged using Rubin's rule [13] to obtain a pooled estimate with standard errors.

5.5 Statistical Bias Reduction

Studies using observational data are prone to multiple biases. These potential biases in this study are addressed as described below.

Selection Bias. To minimize selection bias for identifying an external control arm for a clinical trial, the study was designed using the target trial emulation framework. [14] The external control arm inclusion/exclusion criteria are carefully defined and matched to the PrismRA arm to reduce potential selection bias. All available patients in the external control arm meeting the criteria for selection will be used in the analyses.

The design of the study is aimed to emulate a randomized clinical trial as closely as possible. In a randomized clinical trial, on average, treated and control groups are balanced with respect to pre-treatment characteristics. The analysis of the entire randomized sample will give the unbiased estimate of the causal effect in the entire trial eligible population. Any "selection" of individuals after randomization could lead to covariate imbalance, change in the population for whom the result may apply, and biased treatment effect estimates. PS methods attempt to emulate the process of randomization by using only pre-treatment covariates (blinded to outcomes and other follow-up observations) to control for potential confounding. We propose a PS model building

process that will estimate a PS for each patient in the entire eligible cohort to be used in analyses of all study objectives.

Information bias. Observational studies relying on retrospective data collection are at risk of information bias, as the accurate assessment of exposures, outcomes and key covariates may be challenged by issues such as the timing of clinical assessments, criteria for treatment response, and documentation in the EMR that vary between and within sites. Objective measures of outcomes and other variables at predefined time points will be used where possible. All data for eligible patients will be extracted and data from multiple sources will be deterministically linked to create a more complete capture of the patient journey. For the external control arm, information on confounders will be limited to data as it is documented in the patient's record.

Confounding. Within randomized controlled trials, an appropriate control group for comparison to treated patients for causal inference is constructed through randomization. [15] On average, due to randomization, treated and control groups are balanced with respect to pre-treatment characteristics and confounding bias in estimated treatment effects is largely avoided. Confounding bias in observational studies arises because risk factors that are associated with the outcome of interest may also influence treatment decisions. Thus, a major assumption for the estimation of unbiased treatment effects is that after adjusting for pre-treatment covariates, potential outcomes are independent of the actual treatment received. PS methods are a way to estimate causal treatment effects conditional on pre-treatment characteristics. [9 16] Using logistic regression we can estimate the individual probability of being treated. This approach allows analyses with observational data to emulate randomization such that conditioning on the PS provides unconfounded treatment effects.

5.6 Interim Analysis

A single interim analysis will be conducted at the time of 50% PrismRA arm completion (first 300 enrolled have reached treatment initiation visit or have dropped out of the PrismRA arm). All data available in the PrismRA arm at the time of the interim analysis will be included, but clinical utility of the PrismRA will not be evaluated to protect the integrity of the study. The interim analysis will be restricted to baseline characteristics, data completeness, treatment decision impact, and physician questionnaire survey analyses. All interim analyses will be conducted by the Scipher Medicine team.

5.7 Programming Environment

Data will be queried and prepared using SQL. Analytic procedures and generation of tables for the final analysis will be performed using SAS (version 9.4 or higher; Cary, NC). Interim analysis will be performed using R version 4.2.1.

6.0 STATISTICAL ANALYSES

6.1 Patient Cohort

A detailed description of study procedures can be found in Section 8 of the protocol.

6.1.1 Inclusion Criteria

Table 2 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 2. 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/tsDMARDs 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 5.2 Study Population of the Protocol).
3	Patient has active, moderate to high RA with a CDAI of >10 at Visit 1.	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.	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	External control arm will enroll b/tsDMARD initiators 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) Interleukin-6 inhibitor (IL-6i) (tocilizumab, sarilumab) IL-1i (anakinra) T-cell co-stimulation inhibitor (abatacept) B-cell depletion agent (rituximab) Janus Kinase inhibitor (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: • Conventional synthetic DMARD (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.	It requires ≥ 1 CDAI in the 3-month period prior to the b/tsDMARD initiation to ensure patients from practices where CDAI is routinely used and baseline CDAI is well defined in this 3-month window. Furthermore, ≥ 3 CDAI measurements in the 12-month period prior to the b/tsDMARD initiation will also be required. If we can retain enough patients to fully match the PrismRA arm, then ≥ 4 CDAI measurements in the 12-month period prior to the b/tsDMARD initiation will be required. To ensure sufficient medical history information and past b/tsDMARDs usage history, it requires at least 12 months of enrollment in the database prior to the study treatment initiation. All history information prior to 12 months will also be utilized.

6.1.2 Exclusion Criteria

Table 3. describes the exclusion criteria that will be used prospectively in the PrismRA arm and their best approximation for the selection of comparable patients in the observational external control arm.

In addition to the exclusion criteria outlined below, this study will exclude patients in the external control arm that are managed by physicians participating in the PrismRA arm to avoid potential for contamination bias (e.g., erroneous inclusion of patients who received PrismRA). Patients whose study treatment initiation is managed by PrismRA physicians identified by National Provider Identifier (NPI) will be excluded from eligibility.

Table 3. 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).	It assumes 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 will be excluded. 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. This study assumes 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 cared for by rheumatologists who have participated in the PrismRA arm any time in the past will be excluded to avoid including patients using PrismRA.

6.2 Demographics and Baseline Characteristics

The OM1 team will identify an eligible pool of patients for an external control arm in the OM1 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 based on propensity score matching will be selected.

Baseline covariates including the following listed in **Table 4** will be considered (defined in a 6-month window prior to the index date unless otherwise specified elsewhere).

Table 4. Baseline covariates

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 PrismRA arm and external control arm, respectively) and is considered a mediator of the potential benefit of PrismRA.

In addition to the adjustment covariates, the following socioeconomic variables will be used for descriptive purposes among those who have non-missing values: household income, housing status, education, reduced employment status (e.g. employed, unemployed/disabled, student, retired, other/unknown), insurance, usual place of care (PrismRA arm).

The baseline characteristics of patients will be compared across the PrismRA arm and the external control arm both before and after the PS 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.

6.3 Analyses Addressing Primary Study Endpoint

The following statistical approaches apply to all study endpoints outlined in Section 3.

Baseline data analyses. Baseline characteristics and proportion of missing data will be summarized for each study arm. If necessary, single imputation will be used to impute values for missing observations as described in Section 5.4. Covariate balance will be assessed using standardized differences (mean or proportion differences for continuous and binary outcomes, respectively). [17] Balance between study arms will be assessed before and after PS matching.

Propensity score model for the arm assignment. A stratified PS model procedure will be used. Strata will be defined by baseline prior exposure to TNFi treatment (e.g. TNFi-naive and TNFi-exposed). Within unique combinations of subgroup strata logistic regression models will be used to estimate the probability of being assigned to the PrismRA arm using pre-treatment covariates and/or missing data indicator variables. All covariates used to estimate the PS will be measured before initiation of study treatment and are listed in Table 4 of Section 6.2. Inclusion of non-linear terms (e.g., transformations, restricted cubic splines) and variable interactions will be considered on the basis of balance diagnostics and subject matter expertise. The PS model will be fit without using outcome information to avoid selection of a model that leads to a favorable treatment effect estimate. [18] If model convergence issues (e.g. model non-convergence warnings or failures) arise, the PS will be re-estimated using the full eligible cohort. Evaluation of the PS model will rely on the ability of the PS to achieve covariate balance between the PrismRA arm and the external control arm. [19] Covariate balance will be described using standardized differences. Standardized differences greater than 0.1 indicate “meaningful” residual imbalance in the corresponding covariate and indicate the need for further refinement of the PS model. [20] In matched analyses, F tests for equality of variances for continuous variables will be used. [17] Graphical summaries of balance will include boxplots, Love plots [21], and empirical density functions of the distribution of covariates in the PrismRA arm and the external control arm. The distribution and overlap of propensity scores among individuals in the PrismRA arm and the external control arm will be examined graphically.

Propensity score matching. Patients in the external control arm will be PS matched with participants in the PrismRA trial arm within strata.[22] Individuals will be matched on the logit-transformed PS using an optimal nearest-neighbor without replacement method within calipers.[23] Optimal matching will be used to minimize the total absolute difference in the logit PS across all matches. [24] Caliper widths will be determined based on the SD of the logit of PS (e.g., 0.2×SD). [25 26] In order to avoid excluding unmatched PrismRA patients an upper limit

of the caliper width (e.g. 0.3×SD of the logit PS) will be specified before expanding the historical control period (as described in Section 5.2). Each PrismRA arm subject will be matched with between one and three external control arm subjects using a variable matching ratio, and the targeted total number of matched external control arm subjects will be approximately twice the size of PrismRA arm. [27] Matched external control arm patients will be further weighted based on the following principle: if a PrismRA arm patient is matched to x controls, then these matched controls will be assigned $w = \frac{N_c}{xN_t}$, where N_t is the total number of matched PrismRA patients and N_c is the total number of matched control patients. Propensity score matching is used to estimate the average treatment effect for the treated (ATT), which provides an estimate of the treatment effect among patients who ultimately received treatment. [16]

Imputation of missing outcome data. All eligible patients meeting inclusion and exclusion criteria and initiating the study treatment will be included in MI models for handling missing outcome data as specified in Section 5.4.

6.3.1 Main Analysis

Main analyses will proceed according to the following order of procedures:

1) Perform single imputation for all missing pre-treatment covariates.
2) Estimate the probability of treatment with PrismRA for matching. Only pre-treatment covariates will be included as predictors of treatment (e.g., blinded to outcomes).
3) Perform stratified PS matching and describe patient characteristics of this single matched cohort. Matched external control arm should be weighted following the principle in Section 6.3 before describing patient characteristics.
4) Impute missing outcome data using MI as described in Section 5.4.
5) Within each imputed dataset, fit treatment effect outcome model with arm assignment as the independent variable with covariates adjustment.
6) Pool treatment effect estimates using Rubin's rule.

Steps 1-4 will be performed once at the start of analyses for each analysis population. Steps 5 and 6 will be repeated for each study endpoint and for the Treatment Policy Strategy and Composite Strategy.

Outcome regression models may also include direct adjustment for important patient covariates (e.g. age, sex, race/ethnicity, RDCI, baseline scores). In general, these methods improve confounding control in cases of imperfect matching and stratification. [30] The proportion of patients within each study arm with moderate or high disease activity at baseline who achieve an MID in CDAI of ≥ 6 (baseline moderate) or ≥12 (baseline high) at 24 weeks after study treatment initiation will be reported. Odds ratio and 95% CI will be estimated using weighted logistic regression.

6.3.2 Sensitivity Analysis

Sensitivity analyses will assess the robustness of treatment effect estimates to limiting primary endpoint to patients who have the complete CDAI scores.

6.4 Analyses Addressing Secondary Study Endpoints

Secondary endpoints are outlined in Section 3.2.

6.4.1 Secondary Analysis

Statistical approaches for secondary study endpoints follow all methods described in Section 6.3.

For binary endpoints, the proportion of patients within each study arm meeting the outcome of interest will be calculated. Odds ratio and 95% CI will be estimated using weighted logistic regression.

For the continuous endpoint (change in CDAI scores), the average change in CDAI scores along with the average difference and 95% CI estimated using weighted least squares will be reported.

6.4.2 Sensitivity Analysis

Sensitivity analyses will assess the robustness of treatment effect estimates to limiting primary endpoints to patients who have the complete CDAI scores.

6.5 Analyses Addressing Exploratory Study Endpoints

The exploratory endpoints in Section 3.3 will be assessed and results will be described.

7.0 SUBGROUP ANALYSES

For the primary outcome measure in Section 3.1 and secondary outcome measures (a-f) in Section 3.2, subgroup analyses by prior TNFi exposure (TNFi-naïve and TNFi-exposed prior to Visit 2) will be performed for the eligible patients who meet inclusion and exclusion criteria and initiated the study treatment.

8.0 CONSIDERATIONS FOR FUTURE ANALYSES

MI for missing data is performed under the assumption that data are MAR. This assumption is sensitive to (1) differential rate of discontinuation between study arms that is also related to prognostic factors (e.g., informative drop-out) and (2) the possibility of unmeasured confounders. To assess the robustness of the MAR assumption sensitivity analyses may be performed. To analyze the sensitivity of treatment effect estimates to informative drop-out, missing outcomes are first imputed for completed visits and missed or out-of-window visits that occur prior to study drop-out. Any remaining missing outcomes occurring due to drop-out will

be accounted for using inverse probability of censoring weights (IPCW). [33-35] The IPCW method is a regression approach that assigns weights to each individual based on the inverse of the estimated probability of having complete follow-up data. A logistic regression model is used to predict the probability of having missing outcome data conditional on baseline and time-varying covariates at available follow-up visits. The IPCW are subsequently applied to individuals with complete (observed and imputed) data in outcome models creating a pseudo-population such that the inference is with respect to the original full cohort. [31] For outcome models using inverse probability of treatment weights (IPTW) and IPCW methods simultaneously, the individual weights are multiplied, and the resulting weighted treatment effect estimate is referred to as an inverse-probability-of-treatment-and-censoring weighted estimate (IPTCW). [25] To assess robustness of the modeling assumptions to different missing data mechanisms (e.g., not MAR), a "tipping-point" analysis [36] may be conducted that test a series of pre-determined alternative assumptions for reasons outcome data are missing during follow-up.

9.0 REFERENCES

1. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. Int J Epidemiol. 1992.21(5):837-41.
2. Mallinckrodt CH, Molenberghs G, Lipkovich I, Ratitch B. *Estimands, estimators and sensitivity analysis in clinical trials*. Boca Raton: CRC Press, 2020.
3. ICH. ICH E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. ICH E9 statistical principles for clinical trials. Secondary ICH E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. ICH E9 statistical principles for clinical trials 2020. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials.
4. Curtis JR, Yang S, Chen L, et al. Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients. Arthritis Care Res (Hoboken). 2015.67(10):1345-53.
5. 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. 2019.46(1):27-30.
6. 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. 2007.34(8):1674-83.
7. Spencer AK, Bandaria J, Leavy MB, et al. Validation of a machine learning approach to estimate Clinical Disease Activity Index Scores for rheumatoid arthritis. RMD Open. 2021.7(3).
8. Little RJA, Rubin DB. *Statistical analysis with missing data*. New York: Wiley, 1987.
9. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983.70:41-55.
10. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007.16(3):219-42.
11. White I, Royston P, Wood A. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011.30(4):377-99.

12. Rippin G, Ballarini N, Sanz H, Largent J, Quinten C, Pignatti F. A Review of Causal Inference for External Comparator Arm Studies. Drug Saf. 2022.45(8):815-37.
13. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York ;: Wiley, 1987.
14. Hernán M, Robins J. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016.183:758-64.
15. Holland P. Statistics and causal inference. Journal of the American statistical Association. 1986.81(396):945-60.
16. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011.46(3):399-424.
17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009.28(25):3083-107.
18. Rubin DB. On principles for modeling propensity scores in medical research. Pharmacoepidemiol Drug Saf. 2004.13(12):855-7.
19. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Med Decis Making. 2009.29(6):661-77.
20. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol. 2001.54(4):387-98.
21. Ahmed A, Husain A, Love T, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: An observational study using propensity score methods. European Heart Journal. 2006.27(12):1431-39.
22. Wang SV, Jin Y, Fireman B, et al. Relative Performance of Propensity Score Matching Strategies for Subgroup Analyses. Am J Epidemiol. 2018.187(8):1799-807.
23. Williamson E, Morley R, Lucas A, Carpenter J. Propensity scores: from naive enthusiasm to intuitive understanding. Stat Methods Med Res. 2012.21(3):273-93.
24. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010.25(1):1-21.
25. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011.10(2):150-61.
26. Rosenbaum P, Rubin D. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. The American Statistician. 1985.39(1):33-38.
27. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol. 2010.172(9):1092-7.
28. Imbens G. Nonparametric estimation of average treatment effects under exogeneity: A review. The Review of Economics and Statistics. 2004.86:4-29.
29. Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. Stat Med. 1998.17(11):1261-91.
30. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol. 2006.163(3):262-70.

31. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000.11(5):550-60.
32. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics. 1988.44(4):1049-60.
33. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004.15(5):615-25.
34. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res. 2013.22(3):278-95.
35. Norvang V, Haavardsholm EA, Tedeschi SK, et al. Using observational study data as an external control group for a clinical trial: an empirical comparison of methods to account for longitudinal missing data. BMC Med Res Methodol. 2022.22(1):152.
36. Liublinska V, Rubin DB. Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial. Stat Med. 2014.33(24):4170-85.

10.0 SHELLS FOR TABLES, FIGURES, AND LISTINGS

Figure 1 Patient flow and attrition diagram by study arm

Table 1.1 Baseline characteristics of modified ITT cohort by study arms before PSM

Characteristic		PrismRA N = xxx	Control N = xxx	SMD
Age in years	n	xxx	xxx	x.xx
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
Sex				x.xx
	Female	xxx (xx%)	xxx (xx%)	
	Male	xxx (xx%)	xxx (xx%)	
Race				x.xx
	Black	xxx (xx%)	xxx (xx%)	
	White	xxx (xx%)	xxx (xx%)	
	Other	xxx (xx%)	xxx (xx%)	
	Unknown	xxx	xxx	
Ethnicity				x.xx
	Hispanic	xxx (xx%)	xxx (xx%)	
	Non-Hispanic	xxx (xx%)	xxx (xx%)	
	Unknown	xxx	xxx	
Census region				x.xx
	Midwest	xxx (xx%)	xxx (xx%)	
	Northeast	xxx (xx%)	xxx (xx%)	
	South	xxx (xx%)	xxx (xx%)	
	West	xxx (xx%)	xxx (xx%)	
	Unknown	xxx	xxx	
BMI, kg/m^2	n	xxx	xxx	x.xx
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
Smoking status				x.xx
	Current	xxx (xx%)	xxx (xx%)	
	Former	xxx (xx%)	xxx (xx%)	
	Never	xxx (xx%)	xxx (xx%)	
	Unknown	xxx	xxx	
Comorbidities[1]				
Lung disease	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Myocardial infarction	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	

Other cardiovascular	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Stroke	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Hypertension	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Fractures (spine, hip, or leg)	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Depression	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Diabetes mellitus	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Ulcer or stomach problem	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Fibromyalgia	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
RDCI	n	xxx	xxx	x.xx
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
RA Characteristics				
Duration of RA (years)	n	xxx	xxx	x.xx
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
Seropositivity[2]	Positive	xxx (xx%)	xxx (xx%)	x.xx
	Negative	xxx (xx%)	xxx (xx%)	
CDAI at baseline	n	xxx	xxx	x.xx
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
Previous use of TNFi	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Concurrent RA Medications				
Methotrexate	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Folic acid	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	
Non-methotrexate major csDMARDs	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	

Glucocorticoids	Yes	xxx (xx%)	xxx (xx%)	x.xx
	No	xxx (xx%)	xxx (xx%)	

Footnotes
[1] Using all available data before the index date comorbidities are based on the presence of at least two diagnostic codes at least 30 days apart in the external control arm; based on an additional questionnaire in the PrismRA arm.
[2] Rheumatoid factor or anti-citrullinated peptide antibody.

The following tables will be created using the same layout as Table 1.1.

Table 1.2 Baseline characteristics of modified ITT cohort by study arms after PSM

Table 1.1.1 Baseline characteristics of modified ITT cohort by study arms for TNFi-naïve group before PSM

Table 1.1.2 Baseline characteristics of modified ITT cohort by study arms for TNFi-exposed group before PSM

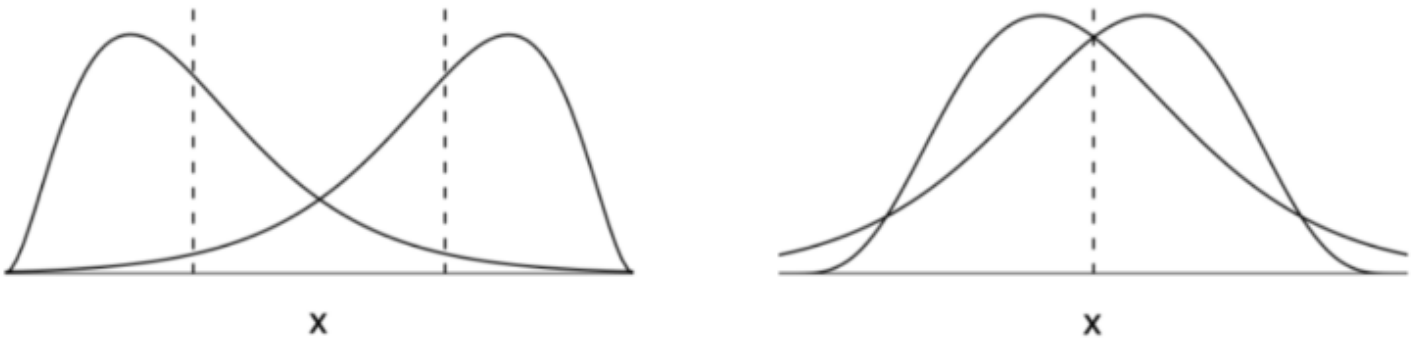
Table 1.2.1 Baseline characteristics of modified ITT cohort by study arms for TNFi-naïve group after PSM

Table 1.2.2 Baseline characteristics of modified ITT cohort by study arms for TNFi-exposed group after PSM

Table 1.3 Baseline characteristics of PrismRA-adherent cohort by study arms before PSM

Table 1.4 Baseline characteristics of PrismRA-adherent cohort by study arms after PSM

Figure 2.1 PS overlap for modified ITT cohort before and after PSM



Programmer note: The figure above is an example figure showing propensity score distributions by study arm before (left panel) and after (right panel) matching.

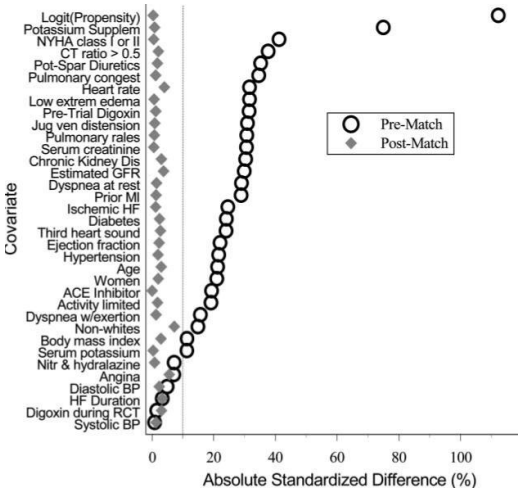
The following figures will be created using the same layout as Figure 2.1.

Figure 2.1.1 PS overlap for modified ITT cohort for TNFi-naïve group before and after PSM

Figure 2.1.2 PS overlap for modified ITT cohort for TNFi-exposed group before and after PSM

Figure 2.2 PS overlap for PrismRA-adherent cohort before and after PSM

Figure 3.1 Baseline covariate balance plots for modified ITT cohort before and after PSM



Programmer note: The figure above is an example figure showing absolute standardized differences before (diamond) and after (circle) matching.

The following figures will be created using the same layout as Figure 3.1.

Figure 3.1.1 Baseline covariate balance plots for modified ITT cohort for TNFi-naïve group before and after PSM

Figure 3.1.2 Baseline covariate balance plots for modified ITT cohort for TNFi-exposed group before and after PSM

Figure 3.2 Baseline covariate balance plots for PrismRA-adherent cohort before and after PSM

Table 2.1 Primary and secondary composite strategy study endpoints for modified ITT cohort by study arm

Study endpoint	PrismRA	Control	Odds ratio (95% CI)
CDAI MID at 24 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
CDAI MID at 12 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
CDAI LDA or Remission at 24 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
CDAI LDA or Remission at 12 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
PtGA MCID at 24 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
PtGA MCID at 12 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
RAPID3 MCID at 24 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
RAPID3 MCID at 12 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
Pain VAS MCID at 24 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
Pain VAS MCID at 12 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
ACR50 at 24 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)
ACR50 at 12 weeks	n/N (%)	n/N (%)	x.xx (x.xx-x.xx)

Programmer note: N= number of patients with moderate or high disease activity; n= number of patients achieving endpoint criteria

The following Tables will be created using the same layout as Table 2.1.

Table 2.1.1 Primary and secondary composite strategy study endpoints for modified ITT cohort by study arm for TNFi-naïve group

Table 2.1.2 Primary and secondary composite strategy study endpoints for modified ITT cohort by study arm for TNFi-exposed group

Table 2.2 Primary and secondary treatment policy strategy study endpoints for modified ITT cohort by study arm

Table 2.2.1 Primary and secondary treatment policy strategy study endpoints for modified ITT cohort by study arm for TNFi-naïve group

Table 2.2.2 Primary and secondary treatment policy strategy study endpoints for modified ITT cohort by study arm for TNFi-exposed group

Table 2.3 Primary and secondary composite strategy study endpoints for PrismRA-adherent cohort by study arm

Table 2.4 Primary and secondary treatment policy strategy study endpoints for PrismRA-adherent cohort by study arm

Table 3.1 CDAI change from baseline at 12 and 24 weeks for modified ITT cohort by study arm

Characteristic		PrismRA N = xxx	Control N = xxx	Average difference (95% CI)
CDAI at baseline	n	xxx	xxx	
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	xxx (xxx-xxx)
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
CDAI at 12 weeks	n	xxx	xxx	
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	xxx (xxx-xxx)
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
Change in CDAI at 12 weeks	n	xxx	xxx	
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	xxx (xxx-xxx)
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
CDAI at 24 weeks	n	xxx	xxx	
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	xxx (xxx-xxx)
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	
Change in CDAI at 24 weeks	n	xxx	xxx	
	Mean (s.d.)	xxx (xx.x)	xxx (xx.x)	xxx (xxx-xxx)
	Median (Q1-Q3)	xxx (xxx-xxx)	xxx (xxx-xxx)	

The following Tables will be created using the same layout as Table 3.1.

Table 3.1.1 CDAI change from baseline at 12 and 24 weeks for modified ITT cohort by study arm for TNFi-naïve group

Table 3.1.2 CDAI change from baseline at 12 and 24 weeks for modified ITT cohort by study arm for TNFi- exposed group

Table 3.2 CDAI change from baseline at 12 and 24 weeks for PrismRA-adherent cohort by study arm

The following Table will be created using the same layout as Table 2.1.

Table 4 Sensitivity analyses of primary and secondary composite strategy study endpoints for modified ITT cohort by study arm