CorEvitas Statistical Analysis Plan (SAP): Treatment Patterns and 6-Month Effectiveness of Tofacitinib in CorEvitas' Rheumatoid Arthritis Registry

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NOTE: Final SAP revised to include descriptive data on history of biologics presented by MOA and clarification regarding study population for looking at outcomes.

1. Table of Contents

Section **Page**

2. Research Protocol

2.1. Background and Rationale

Previous work in the Corrona registry described the early experience of tofacitinib (tofa) initiators. As tofa has been on the market since 2012, it is possible that there has been a shift to use of tofa as an earlier line of therapy. Therefore, there is a need to update the analyses of treatment patterns and effectiveness. This query will inform the design of future comparative effectiveness analyses.

2.2. Objectives

To describe treatment patterns and effectiveness of tofa initiators in the Corrona RA registry.

2.2.1. Objective 1

To describe the demographics, clinical characteristics, and treatment patterns of tofa initiators at time of initiation.

2.2.2. Objective 2

To estimate 6-month effectiveness in tofa initiators.

2.2.3. Objective 3

To estimate 12-month effectiveness in tofa initiators.

2.3. Hypothesis

This is a descriptive query, thus there are no a priori hypotheses.

2.4. Research Design

2.4.1. Study Type

This study is a retrospective observational study using registry data for RA patients.

2.4.2. Data Source

Corrona[1] was founded in 2000 and is an independent registry without any ownership links to the pharmaceutical industry. This registry contains clinical data (e.g. disease activity scores, laboratory results, comorbidities, imaging results, patient-reported outcomes data, etc.) that is not available in claims databases such as the Truven MarketScan database. The Corrona RA

registry is the largest longitudinal registry studying chronic diseases in the world. The current Corrona dataset includes 189 private and academic active clinical sites with over 800 physicians throughout 42 states in the U.S. The Corrona Rheumatoid Arthritis study is an ongoing longitudinal clinical registry that was established in 2001. This registry collects data from both the physicians and the patients at the time of a regular office visit. Corrona has enrolled over 54,000 patients with RA. The collection of data from Corrona represents over 195,000 patient years of data.

To be enrolled in the registry, patients must meet the following criteria:

- Have RA diagnosed by a rheumatologist
- Be at least 18 years of age
- Must be able and willing to provide informed consent

2.4.3. Study Populations

Inclusion Criteria

For this analysis patients must:

1. Initiate tofa (defined as first ever use of tofa) at the Corrona enrollment visit or at a Corrona follow up visit from November 2012 onward.
2. Have CDAI measured at baseline.
3. Have a 6-month or 12-month follow-up visit and CDAI measured at 6-month or 12-month follow-up visit

Note: Additionally, the specified populations will be used to calculate each of the following variables.

- Achievement of LDA (CDAI≤10).
    - Among patients with moderate or high disease activity (CDAI>10) at baseline.
- Rate of response at follow up visit-achievement of remission (CDAI≤2.8).
    - Among patients with LDA, moderate, or high disease activity (CDAI>2.8) at baseline.
- Achievement of LDA or remission defined by DAS28(ESR) (<= 3.2)
    - Among patients who have DAS28>3.2 at the initiation visit.
- Achievement of “mild pain”, defined as ≤ 20mm on 100 VAS scale
    - Among patients who have pain >20 mm on 100 VAS at the initiation visit

2.4.4. Sample Size and Power Considerations

Sample size

As of the end of August 31, 2020, there are 2744 RA patients who initiated tofa in the Corrona RA registry. Of these, 1650 have a visit at 6 months (3-9 months) and 1223 have a visit at 12

months (10-15 months) have CDAI measured at the initiation visit (baseline) and at 6- or 12-month follow-up visit.

Number of initiators with tofa initiation and had a 6-month or 12-month follow up visit in 4 milestones

	With 6 month Follow up	With 12 month Follow up
Milestone 1		
Monotherapy	730	536
Combotherapy	920	687
Total	1650	1223
Milestone 2		
2nd line	236	168
3rd line	333	234
4+ line	1027	781
Total	1596	1183
Milestone 3		
5 mg/ BID	732	579
11 mg/QD	663	463
Total	1395	1042
Milestone 4		
2012-2014	451	349
2015-2017	725	597
2018-2020	474	277
Total	1650	1223

Definition of line of therapy:

1st line: no prior use of any DMARD at time of initiation
2nd line: prior use of at least one csDMARD and no prior use of any biologic
3rd line: prior use of at least one csDMARD and prior use of 1 biologic
4th line+: prior use of at last one csDMARD and prior use of 2+ biologics

2.4.5. Time Periods

Study visits

The Corrona RA registry is an observational registry collecting patient and physician data at regular patient clinical visits with the rheumatologist. Unlike in clinical trials, visits are not timed at exact uniform time periods. We will define the 6-month visit as a Corrona visit that occurs between 3-9 months post- index visit. We will define the 12 month visit as a Corrona visit that occurs between 10-15 months post index visit. If the patient had more than one visit in the

window between 3 and 9 months (or 10-15 months), the visit closest to 6 (or 12) months will be selected.

2.4.6. Variables

For Objective 1 (Demographics, clinical characteristics, treatment patterns):

Demographic/socioeconomic characteristics

- Age, sex, race, education, work status, insurance

Lifestyle

- Weight, body mass index(BMI), smoking status

History of comorbidities

- History of CV disease (include the following: MI, stroke, acute coronary syndrome, coronary artery disease, CHF, revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, peripheral ischemia, peripheral arterial disease, hypertension, other CV, DVT, and TIA.)
- History of malignancy (breast cancer, lung cancer, lymphoma, skin cancer, other cancer)
- History of hypertension, diabetes, osteoporosis, fibromyalgia, and depression

Clinical Characteristics and Assessments

- Duration of disease
- Age of onset
- CDAI (continuous, categorical)
- Tender joint count (28)
- Swollen Joint count (28)
- Physician global assessment (0-100)
- DAS28(ESR)
- Patient global assessment (0-100)
- Patient reported pain (0-100)
- Patient reported fatigue (0-100)
- HAQ (0-3)
- mHAQ
- Morning stiffness (yes/no)
- Morning stiffness duration (hours)

Treatment Characteristics and Medication history

- Concomitant therapies (Monotherapy, Combo with: MTX alone, other CDMARD, MTX + other CDMARD)

- Number of prior biologics/JAKis (TNFi: Enbrel, Humira, Remicade, Cimzia, Simponi; non-TNFi: Orencia, Actemra, Rituxan, Kineret, Kevzara; JAKis: Olumiant, Rinvoq)
- Number of prior csDMARDs (MTX, Arava, Azulfidine, Plaquenil, Cyclosporine, Imuran, Minocin, Cuprimine, Ridaura)
- Steroid use
    - History of prednisone use (yes/no)
    - Current prednisone use (yes/no)
    - Prednisone dose (in users)
- Mode of Action (MOA) History
    - TNF inhibitor
    - Non-TNF inhibitor
    - csDMARDs
    - tsDMARDs
- History of treatment of MOA (Ever)
    - TNF inhibitor
    - Non-TNF inhibitor
    - csDMARDs
    - tsDMARDs

Reason for initiation of Tofa:

- Number of patients with at least 1 initiation reason reported
- Total number of reasons
- % Safety, % Efficacy, % Cost/Insurance, %Other reasons

Reason for Discontinuation of tofa (Among those who discontinue at or before 6-months):

- Total number (%) of discontinuations
- Number of patients with at least 1 reason reported
- Total number of reasons
- % Safety, % Efficacy, % Cost/Insurance, %Other reasons

For objective 2 (6-months effectiveness) and objective 3 (12-months effectiveness)

Primary outcomes:

- Achievement of LDA (CDAI ≤ 10)

Secondary outcomes:

- Achievement of remission (CDAI ≤ 2.8)
- Δ CDAI
- Δ HAQ

- Δ patient pain
- Δ patient fatigue
- Achievement of mACR20/50/70
- Achievement of LDA or remission defined by DAS28(ESR) (<= 3.2)
- Achievement of "mild pain", defined as ≤ 20mm on 100 VAS scale

2.5. Plan of Analysis

Definitions:

Index visit (Baseline): The Corrona visit with the first reported use of tofa.

Disease activity measures and patient-reported outcomes (PROs) from the index (baseline) visit will be used if the initiation date is the same as the visit date. If tofa is initiated between visits, and the prior visit is within 4 months of the initiation date, disease activity measures and PROs from the prior visit will be used as the baseline value.

Line of therapy:

1st line: no prior use of any DMARD at time of initiation
2nd line: prior use of at least one csDMARD and no prior use of any biologic
3rd line: prior use of at least one csDMARD and prior use of 1 biologic
4th line+: prior use of at last one csDMARD and prior use of 2+ biologics

Study Cohorts:

- Overall tofa initiators who meet inclusion criteria
- Tofa monotherapy at initiation visit (tofa only)
- Tofa combo therapy at initiation visit (tofa+MTX, Arava, Azulfidine, Plaquenil, or cyclosporine)
- Tofa initiators by line of therapy in 2nd line, 3rd line and 4th line
- Tofa dose of 5mg, twice a day at initiation visit
- Tofa dose of 11mg, once a day at initiation visit
- Tofa initiators by year of initiation (2012-2014, 2015-2017, 2018-2020)

This project will be separated into 4 milestones:

1. Analysis in overall tofa initiators, and monotherapy v. combination therapy
2. Analysis by line of therapy in 2nd line, 3rd line and 4th line
3. Analysis by tofa dose (5mg v. 11mg)
4. Analysis by three time periods of initiation (2012-2014, 2015-2017, 2018-2020)

2.5.1. Descriptive analysis

Baseline patient demographics and clinical characteristics of (listed in section 2.4.4) will be presented. For categorical variables, n(%) will be presented, and for continuous variables, means, standard deviation (SD), median, 25th and 75ths quartile values will be presented in overall tofa initiators, and by group (for each milestone). P-values will be estimated using student-t test for continuous variables between two comparison groups, one-way Anova for continuous variables among three comparison groups and chi-square test for categorical variables. Two sets of baseline tables will be reported – one for patients with 6 months follow-up and one for patients with 12 months follow-up.

2.5.2. Effectiveness Analysis

Primary outcome analyses

We will estimate the rate of response at 6 and 12 months. Response is defined as the achievement of LDA (CDAI≤10) in patients with moderate or high disease activity (CDAI>10) at baseline. Patients who discontinue tofa within 6 (or 12) months and switch to another biologic or JAK will be considered "non-responders". Effectiveness outcomes at the 6- and 12- month visits will be estimated in overall tofa initiators and by groups for each milestone. We will report the rate of response and 95% CI for the proportion of response, for patients overall and for each group in table 5.

Secondary outcomes analysis

The following secondary outcomes will be considered:

- Rate of response at follow up visit-achievement of remission (CDAI≤2.8) in patients with LDA, moderate, or high disease activity (CDAI>2.8) at baseline. Patients who discontinue tofa within 6 months and switch to another biologic or JAK will be considered "non-responders".

- Mean of change in CDAI from baseline to follow up visit (6/12). Change in CDAI will be calculated by subtracting baseline CDAI from CDAI measured at 6 months. If a patient discontinues tofa but does not switch to another biologic, the CDAI value at follow up visit (6/12) will be used. If a patient discontinues tofa and switches to another biologic or JAK, the CDAI value at the switch visit will be used for change in CDAI calculation.

- HAQ (HAQ):
  Mean change of HAQ from index date to follow-up visit

- Patient pain (0-100 VAS scale):
  Mean change in pain from index date to follow-up visit

- Patient fatigue (0-100 VAS scale):
  Mean change in fatigue from index date to follow-up visit

- Achievement of modified ACR (mACR)20, mACR50, mACR70

- Achievement of LDA or remission defined by DAS28(ESR) (<= 3.2) in those patients who have DAS28>3.2 at the initiation visit

- Achievement of “mild pain”, defined as ≤ 20mm on 100 VAS scale in those patients who have pain >20 mm on 100 VAS at the initiation visit

Mean changes, rates of response, and corresponding 95% confidence intervals will be reported in total and in each group [Table 5].

Two sets of analyses will be report based on patient with 6 month follow up and patients with 12 months follow up.

All statistical analyses will be performed using STATA Version 15.1 (StataCorp, LLC, College Station, TX).

3. Shell Tables

Milestone 1: Results for tofa monotherapy and combination therapy

Milestone 2: Results for line of therapy (2nd, 3rd, 4th line)

Milestone 3: Results for tofa dose (5mg and 11mg)

Milestone 4: Results for tofa initiation time periods (2012-2014, 2015-2017, and 2018-2020)

Table 1. Demographic and clinical characteristics at tofa initiation visit, overall and for monotherapy and combination therapy in patients with 6 months follow up.

	All Patients	**Tofa monotherapy**	**Tofa combination therapy‡**	***P*-value***
	N=	**N=**	**N=**	
Demographic/socioeconomic characteristics				
Age: Mean±SD Median (IQR)				
Female: n(%)				
Race/Ethnicity: n(%)				
White				
Hispanic				
Black				
Asian				
Other				
Type of Insurance:				
None: n (%)				
Private: n (%)				
Medicare: n (%)				
Medicaid: n (%)				
Final education: n(%)				
Primary				
High school				
College/Univ.				
Unknown				
Work Status: n(%)				
Full Time				
Part Time				
Disabled				

Retired				
Other				
Lifestyle				
Smoking status: n(%)				
Never				
Previous				
Current				
Weight (lb): Mean±SD Median (IQR)				
BMI: Mean±SD Median (IQR)				
History of comorbidities: n(%)				
Cardiovascular disease**				
Malignancy***				
Hypertension				
Diabetes				
Osteoporosis				
Fibromyalgia				
Depression				

* T-tests will be used to evaluate mean differences between groups for continuous variables, and Chi-square tests will be used to evaluate differences between treatment groups for categorical variables

** included: MI, stroke, TIA acute coronary syndrome, coronary artery disease, CHF, revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, other CVs, carotid artery disease.

*** History of lung cancer, breast cancer, lymphoma, skin cancer (melanoma and squamous), and other cancer

‡ Combination therapy refers to tofa+MTX, arava, azulfidine, plaquenil, or cyclosporine

Table 2. RA disease characteristics, disease activity measures and PROs at tofa initiation visit, overall and for monotherapy and combination therapy in patients with 6 months follow up.

	All Patients	Tofa Monotherapy	Tofa Combination Therapy‡	*P* value*
	N=	N=	N=	
RA disease characteristics				
Duration of RA: Mean±SD Median (IQR)				
Age onset RA: Mean±SD Median (IQR)				
Disease Activities				
CDAI: Mean±SD Median (IQR)				
Category of disease activity: n(%)				
Remission				
LDA				
MDA				
HAD				
Tender Joint Count (28): Mean±SD Median (IQR)				
Swollen Joint Count (28): Mean±SD Median (IQR)				
Physician Global Assessment(0-100): Mean±SD Median (IQR)				
DAS28(ESR): Mean±SD Median (IQR)				
Patient reported outcomes				
Patient Global Assessment: Mean±SD Median (IQR)				
Patient Pain Assessment: Mean±SD Median (IQR)				
Patient Fatigue Assessment: Mean±SD Median (IQR)				
HAQ (0-3): Mean±SD Median (IQR)				
mHAQ: Mean±SD Median (IQR)				
Morning Stiffness: n(%)				

Stiffness(mins): Mean±SD** Median (IQR)				
Treatment				
Concomitant therapies: n(%)				
None				
MTX only				
nonMTX csDMARD only				
MTX & nonMTX csDMARD				
History of csDMARD: n(%)				
None				
1				
2+				
History of biologics: n(%)				
None				
1				
2+				
Prednisone				
History of prednisone use: n(%)				
Current prednisone use: n(%)				
Dose in users: Mean±SD Median (IQR)				
Mode of Action (MOA) History				
Immediately previous treatment				
TNF inhibitor				
Non-TNF inhibitor				
csDMARDs				
tsDMARDs				
History of treatment of MOA (Ever)				
TNF inhibitor				
Non-TNF inhibitor				
csDMARDs				
tsDMARDs				

* T-tests will be used to evaluate mean differences between groups for continuous variables, and Chi-square tests will be used to evaluate differences between categorical variables

** in patients reported morning stiffness

‡ Combination therapy refers to tofa+MTX, arava, azulfidine, plaquenil, or cyclosporine

Table 3. Reasons for initiation of tofacitinib in patients with 6 month follow up

n(%)	All Tofa	Tofa mono	Tofa combo
	N=	N=	N=
# of initiations			
# of patients reporting at least one reason			
Total # of reasons			
Safety			
Efficacy			
Cost/Insurance			
Other reason			

Table 4. Reasons for discontinuation of tofacitinib in 6 months

n(%)	All	Tofa mono	Tofa combo
	N=	N=	N=
# of discontinuations			
# of patients reporting at least one reason			
Total # of reasons			
Safety			
Efficacy			
Cost/Insurance			
Other reason			

Notes:

- Side effect: includes infection, lymphoma/malignancy, toxicity, serious and minor side effect;
- Efficacy: includes lack of efficacy, disease flare, active disease, primary loss of efficacy, and secondary loss of efficacy, inadequate initial response, failure to maintain initial response;
- Cost/Insurance: includes lack of insurance
- Other reason: includes no longer needed, formulary restriction, patient preference, recent journal report, recent meeting report, withdrawn by FDA, physician preference, peer suggestion, fear of future side effect, patient doing well, and frequency of administration, temporary interruption, to improve compliance, to improve tolerability, route of administration.

Table 5. Outcome measures at 6 months after tofa initiation, overall and for monotherapy and combination therapy groups

Binary outcomes n(%) 95% CI	**All Tofa Initiators** **N=**	**Tofa Monotherapy** **N=**	**Tofa Combo therapy** **N=**
	n=	n=	n=
LDA (CDAI≤10)[a]			
	n=	n=	n=
Remission (CDAI≤2.8)[b]			
mACR20			
mACR50			
mACR70			
	n=	n=	n=
DAS28(ESR)≤3.2[c]			
	n=	n=	n=
Achievement of “mild pain” (≤ 20mm on 100 VAS)[d]			
Continue outcomes: Mean (SD) 95% CI			
Δ CDAI:			
Δ patient global			
Δ HAQ			
Δ patient pain			
Δ patient fatigue			

[a] Calculated among those patients with moderate or high disease activity (CDAI>10) at baseline.
[b] Calculated among those patients with LDA, moderate or high disease activity (CDAI>2.8) at baseline.
[C] Calculated among those patients who have DAS28>3.2 at the initiation visit
[d] Calculated among those patients who have pain >20 mm on 100 VAS at the initiation visit

Tables 6-10 will repeat tables 1-5, by line of therapy (2nd line, 3rd line, and 4th line) for Milestone 2.

Table 11-15 will repeat table 1-5, by tofa dose (5mg/bid and 11mg/qd) for Milestone 3.

Table 16-20 will repeat table 1-5 for the three time periods of initiation (2012-2014, 2015-2017, 2018-2020) for milestone 4.

Table 21-40 will repeat tables 1-20 for patients with 12 months follow up by 4 milestone.

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