CLINICAL STUDY PROTOCOL

COMPOUND: Leflunomide

STUDY TITLE

A Phase IV, Multi-Centric, Prospective, Observational Study to Assess the **C**linical Efficacy and Safety of **L**eflunomide in **E**gyptian Patients with **A**ctive **R**heumatoid Arthritis

STUDY CODE: EVA_CLEAR_11022017

Study Name: CLEAR

Phase: IV

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2. List of Abbreviations

Abbreviation	Term
ACR/EULAR	The American College of Rheumatology/European League Against Rheumatism
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANOVA	Analysis of Variance
Anti-CCP	Anti-Cyclic Citrullinated Peptide
AST	Aspartate Transaminase
BMI	Body Mass Index
CBC	Complete Blood Count
CDAI	Clinical Disease Activity Index
Child C-class	Child–Pugh score, Class C
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-Reactive Protein
DAS28	Disease Activity Score 28
DBP	Diastolic Blood Pressure
DMARDs	Disease-Modifying Antirheumatic Drugs
ESR	Erythrocyte Sedimentation Rate
FBG	Fasting Blood Glucose
HAQ Disability Index	Health Assessment Questionnaire, Disability Index
HBsAg	Hepatitis B Surface Antigen
HCV-Ab	Hepatitis C Virus Antibody
ID	Identification number
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LPI	Last Patient In
LPO	Last Patient Out
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
ml	Milliliter
NA	Not Applicable
QC	Quality Control
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation

SDAI	Simple Disease Activity Index
SOP	Standard Operating Procedure
Sr ACPA	Serum Anti-Citrullinated Peptide Antibody
Sr RF	Serum Rheumatoid Factor
Sr Cr	Serum Creatinine
WHO	World Health Organization

3. Synopsis

STUDY TITLE	A Phase IV, Multi-Centric, Prospective, Observational Study to Assess the **C**linical Efficacy and Safety of **L**eflunomide in **E**gyptian Patients with **A**ctive **R**heumatoid Arthritis. (**CLEAR**)
STUDY CODE	EVA_CLEAR_11022017
STUDY SPONSOR	EVAPHARMA Egypt
PRODUCT NAME	Arthfree
ACTIVE INGREDIENT	Leflunomide
INDICATION	Active Rheumatoid Arthritis
STUDY LOCATION (S)	Egypt
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CENTRAL LABORATORY	NA
MEDICAL AND/OR TECHNICAL DEPARTMENTS	NA
STUDY QUESTIONS	1. What is the clinical efficacy of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, and Sulfasalazine) with or without Steroids use in Egyptian patients with Active Rheumatoid Arthritis? 2. What are the pattern of management and characteristics of Egyptian patients with Active Rheumatoid Arthritis receiving Leflunomide treatment? 3. What is the clinical safety of Leflunomide as first line therapy and

	as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, and Sulfasalazine) with or without Steroids use in Egyptian patients with Active Rheumatoid Arthritis?
STUDY OBJECTIVES	**Primary Objective:** 1. Assessing the clinical efficacy of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids in Egyptian patients with Active Rheumatoid Arthritis. **Secondary Objectives:** 1. Describing pattern of management and characteristics of Egyptian patients with Active Rheumatoid Arthritis receiving Leflunomide treatment. 2. Identifying the safety profile of Leflunomide whether used as first line therapy and/or as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids in Egyptian patients with Active Rheumatoid Arthritis.
SUMMARY OF STUDY DESIGN	**Study Design Description:** This is a phase IV, multi-centric, prospective, observational study to assess the clinical efficacy and safety of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids use in Egyptian patients with Active Rheumatoid Arthritis. **Study Duration:** 3 months for recruitment and 9 months for treatment. **Sample Size:** It is estimated to recruit 400 patients (around 17 patients per site). Patients will be between 18 and 60 years of age, with Active Rheumatoid Arthritis selected according to the ACR/EULAR classification criteria with score ≥ 6 points. Patients will be Leflunomide naïve or after previous Leflunomide administration (after at least 6 month wash out period from date of baseline visit). Patients will be with or without other DMARDs including Methotrexate, Sulfasalazine and/or Hydroxychloroquine with or without steroids use who experienced therapy resistance, inadequate response or intolerance.

RECRUITMENT MODALITIES	**Selection of Patients:** **Inclusion Criteria:** Patient must meet ALL of the following criteria to be eligible for enrolment into the study 1. Active Rheumatoid Arthritis patients selected according to the ACR/EULAR classification 2010 criteria with score ≥ 6 points. 2. Male or female patients aged 18-60 years old. 3. Leflunomide naïve patients or patients with previous Leflunomide administration (after at least 6 month wash out period from date of baseline visit) who will be prescribed Leflunomide at the sole decision of the treating physician. 4. Patients with or without another DMARDs including Methotrexate, Sulfasalazine and/or Hydroxychloroquine with or without steroids use who experienced therapy resistance, inadequate response or intolerance. 5. Patients read, understand and signed informed consent prior to inclusion. 6. Patients willing to complete and literate in the language of the available Health Assessment Questionnaire (HAQ Disability Index) either alone or with minimal assistance from caregivers and/or trained site personnel. **Exclusion Criteria:** Patient meeting the following criteria is not eligible for enrolment into the study 1. Female patients who are pregnant or lactating at the time of inclusion or those who are planning for pregnancy within the coming year from the time of inclusion to the study. 2. Patients with contraindications to active constituent of Leflunomide. 3. Patients with severe concurrent infection (necessitating IV antibiotics or hospitalization). 4. Patients with history of non-treated hepatitis B &/or C infection. 5. Patients with history of severe liver disease (child C class). 6. Patients with history of severe renal insufficiency (creatinine clearance ≤30 ml/min.). **Selection of Investigators:** The study will be conducted by rheumatologists. In order to ensure the representativeness of investigators, the participating investigators will be randomly selected among an extended list of sites (private clinics; rheumatologist) provided by the

<table>
<tr><td></td><td>study sponsor.</td></tr>
<tr><td>TOTAL EXPECTED NUMBER OF PATIENTS</td><td>It is estimated to recruit around 17 patients per site (Total 400 patients).</td></tr>
<tr><td>EXPECTED NUMBER OF SITES</td><td>24 sites (Private clinics)</td></tr>
<tr><td>MEDICINAL PRODUCT</td><td>Arthfree (Leflunomide 20mg)
Dose: 1 tablet once daily, should be swallowed whole with sufficient amounts of liquids. The extent of Leflunomide absorption is not affected if taken with meals. Doses higher than 20 mg/day are not recommended. Improvement in the rheumatoid condition usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.
Loading dose: a tablet of Leflunomide 100 mg for three days. should be swallowed whole with sufficient amounts of liquids. The extent of Leflunomide absorption is not affected if taken with meals.
Due to the long half-life in patients with rheumatoid arthritis and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly.
Patients will be prescribed Arthfree (Leflunomide) at the sole decision of the treating physician.</td></tr>
<tr><td>DATA COLLECTION SCHEDULE</td><td>This phase IV study will last for 9 months in addition to recruitment period of 3 months. A total of 6 visits will be performed as shown in the table below;
<table>
<tr><th>Visit 1</th><th>Visit 2</th><th>Visit 3</th><th>Visit 4</th><th>Visit 5</th><th>Visit 6</th></tr>
<tr><td>Baseline & ICF signing</td><td>Week 6 (± 2 weeks)</td><td>Week 12 (± 2 weeks)</td><td>Week 20 (± 2 weeks)</td><td>Week 28 (± 2 weeks)</td><td>Week 36 (± 2 weeks) EOS</td></tr>
<tr><td>Clinical Assessment</td><td>Clinical Assessment</td><td colspan="3">Clinical Assessment if applicable</td><td>Clinical Assessment</td></tr>
<tr><td>Lab Data</td><td>Lab Data</td><td colspan="3">Lab Data if applicable</td><td>Lab Data</td></tr>
<tr><td></td><td colspan="5">Safety Data</td></tr>
</table></td></tr>
<tr><td>DATA TO BE COLLECTED (FOR PRIMARY AND SECONDARY OBJECTIVES)**</td><td><u>At Baseline Visit:</u>
Data on Informed consent, Inclusion and exclusion criteria, Demographics, Smoking status, Alcohol consumption, Medical history, Gynecological History for female patients only, Concomitant medications, Laboratory tests and Poor prognostic factors will be</td></tr>
</table>

	collected along with RA history. Disease assessment (CDAI) and Physical examination will be done and also Vital signs will be recorded. Patients will fill Health Assessment Questionnaire (HAQ Disability Index) and related data will be recorded. **<u>At Visit 2 (Week 6 ± 2 weeks) & Visit 3 (Week 12 ± 2 weeks) & Visit 4 (Week 20 ± 2 weeks) & Visit 5 (Week 28 ± 2 weeks):</u>** Data on Concomitant medications and Laboratory tests will be collected. Disease assessment (CDAI) and Physical examination will be done and also Vital signs will be recorded. Patients will fill Health Assessment Questionnaire (HAQ Disability Index) and related data will be recorded. Data on Adverse events/Serious adverse events experienced by patient since the previous visit will be documented. **<u>At Visit 6 (Week 36 ± 2 weeks):</u>** Data on Concomitant medications and Laboratory tests will be collected. Disease assessment (CDAI) and Physical examination will be done and also Vital signs will be recorded. Patients will fill Health Assessment Questionnaire (HAQ Disability Index) and related data will be recorded. Data on Adverse events/Serious adverse events experienced by patient since the previous visit will be documented. Study Completion Form will be also filled.
STUDY ENDPOINTS	**<u>Primary Endpoints:</u>** - To assess **disease severity** (Remission, Low activity, Moderate activity and High activity) and the **mean relative change of in Clinical Disease Activity Index (CDAI)** among patients with active rheumatoid arthritis treated with Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids between baseline and week 36. - To assess the **mean relative change** in **Health Assessment Questionnaire score (HAQ Disability Index)** among patients

	with active rheumatoid arthritis treated with Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids between baseline and week 36. **Secondary Endpoints:** - To describe pattern of management and patients' characteristics (including demographics, medical history, RA severity, RA Duration, line of therapy, daily dose, treatment duration, reasons for treatment adjustment and Previous therapies) of active RA patients receiving Leflunomide treatment. - To assess the frequency of AEs/SAEs among patients using Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids and its relation to study medication.
STATISTICAL CONSIDERATIONS	• **Statistical Power and Sample Size Justification** The primary objective of CLEAR study is to assess the clinical efficacy of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids as measured by the mean relative change in Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ Disability Index) among patients with active rheumatoid arthritis. Considering an alpha error of **5%** using two-sided 95% CI of Wilcoxon signed-rank test and a study power of **80%**, a sample of **332 patients** will be required to detect an effect size of **0.158** between baseline and study endpoint, plus an expected **drop-out rate of 20%** during the 9 months observational study duration. Thus, a sample of **398 patients** will be appropriate that rounded to **400 patients**. • **Randomization method** Not applicable. • **Statistical methodologies:** - **Descriptive analysis:** o Percent (%) distribution for all categorical variables and

	mean with (SD) and median (Minimum: Maximum) for continuous variables according their distribution. - **Comparative analysis:** o Student t-test and One Way ANOVA to estimate the comparison between the treatment arms for the numerical variables (according to their distribution; non-parametric substitution tests could be used). o Paired t-test and repeated measure ANOVA test to estimate the change in numerical variables throughout the study visits (according to their distribution; non-parametric substitution tests could be used). o Chi2 test (or Fisher's Exact test) for unpaired and McNemar's test for paired categorical variables. ▪ All tests will be performed on the 5% level of significance. ▪ Any deviation(s) from the original statistical plan will be described in the final report). ▪ Procedure for accounting for missing, unused, and spurious data will be explained in the statistical analysis plan (SAP). • **Interim analysis** When approximately the enrolled patients completed 50% of their visits (after Visit 3), an interim analysis for safety and efficacy will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
ESTIMATED DURATION	- **Protocol planned date:** June 2017 - **First patient In (FPI):** September 2017 - **Last patient In (LPI):** December 2017 - **Last patient Out (LPO):** September 2018 - **Estimated enrollment duration:** 3 months - **Estimate treatment duration:** 9 months - **Database lock planned date:** September 2018 - **Estimated Report date:** November 2018

Data to be collected	**Data Collection Schedule					
	Visit 1 (Baseline)	Visit 2 (Week 6)	Visit 3 (Week 12)	Visit 4 (Week 20)	Visit 5 (Week 28)	Visit 6 (Week 36)
Informed consent	x					
Inclusion/ Exclusion	x					
Physical Examination/ Vital Signs[1]	x	x	x	x	x	x
Demographics	x					
Smoking Status	x					
Alcohol Consumption	x					
Medical history	x					
Gynecological History (FEMALES ONLY)	x					
Concomitant Medications	x	x	x	x	x	x
RA History[2]	x					
Disease Assessment[3]	x	x	x	x	x	x
Laboratory Tests[4]	x	x	x	x	x	x
Health Assessment Questionnaire (HAQ Disability Index)[5]	x	x	x	x	x	x
Poor Prognostic Factors[6]	x					
Adverse Events & Serious Adverse Events		x	x	x	x	x
Study Completion Form						x

***1**: Physical Examination/Vitals Signs: Height will be collected in V1 only.*

***2**: Rheumatoid Arthritis History will include RA Duration, Previous/Current therapies including duration, dose, adverse events/serious adverse events experienced during previous treatment and Reason for starting Leflunomide* (previous DMARDs failure, insufficient response, allergy, intolerance, side effects) *dose (if the patient received loading dose or not) and Previous X-RAY reports.*

***3**: Disease Assessment will be done by Clinical Disease Activity Index (CDAI).*

***4**: Laboratory Tests include CBC, ESR assessed by Westergren method (First hour), C-reactive protein (titer), AST, ALT, Sr Cr, Sr ACPA, Sr RF titer, FBG, HBsAg and HCV-Ab.*

***5**: Stanford University-Health Assessment Questionnaire (HAQ Disability Index).*

***6**: Poor prognostic factors: Presence of 1 or more of; Bony erosions by radiograph, High swollen joint count, Extra-articular disease (nodules, vasculitis, Felty's syndrome), Functional limitation (HAQ), High disease activity as measured by composite indices (DAS28, SDAI and/or CDAI), High acute phase reactants (CRP and ESR) or High RF and/or anti-CCP.*

4. Study and Disease Information

4.1. Background

Rheumatoid Arthritis (RA) is a systemic, chronic, autoimmune and inflammatory disease that affects joints, muscles, tendons, connective tissues and fibrous tissues[1,2]. RA is considered to be the most common autoimmune disease in adults that affects approximately 1% of the global population[3,4].

In The Global Burden of Disease 2010 study "GBD 2010 Study" which was conducted in 187 countries, it was found that Disability-Adjusted Life Year (DALY "per 100000") for RA in 1990 was 63 which was increased in 2010 to be 70[5].

Data from a systematic literature review of Medline, Embase and Global Health Library which reclaimed a total of 335 publications showed that in 1990, the estimated crude prevalence of RA in Africa based on the available studies was 0.36% (2.3 million affected individuals) which was thought to be increased in 2010 to 0.42% with burden of 4.3 million affected individuals[6].

During the past 30 years, the management of RA has changed drastically as few therapeutic agents were extant[7]. At the present time, numerous therapeutic agents are used in managing RA along with relieving signs and symptoms such as DMARDs, Glucocorticoids and NSAIDs[7,8].

In 2016, Despite the fact that The European League Against Rheumatism (EULAR) recommended that Methotrexate (MTX) should be part of the first line treatment strategy, Leflunomide or Sulfasalazine were recommended as part of the first treatment strategy in patients with a contraindication to Methotrexate or with early intolerance[8].

Leflunomide is one of the most used DMARDs around the world, it can be used as a monotherapy or in combination with other DMARDs to inhibit the production of inflammatory cells and accordingly to reduce inflammation[9].

In a number of studies which were conducted to investigate the efficacy and safety of Leflunomide n RA management, it was found that Leflunomide was equivalent to Methotrexate and its safety profile was acceptable compared to other DMARDs[9,10,11]. It was also found that Leflunomide was superior to Methotrexate in terms of Quality of Life measurements[9,10,11].

4.2. Rationale

The aim of this study is to assess the clinical efficacy and safety of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids in Egyptian patients with Active Rheumatoid Arthritis.

4.3. Incidence and Prevalence

RA is considered to be the most common autoimmune disease in adults that affects approximately 1% of the global population[3,4].

In The Global Burden of Disease 2010 study "GBD 2010 Study" which was conducted in 187 countries, it was found that Disability-Adjusted Life Year (DALY "per 100000) for RA in 1990 was 63 which was increased in 2010 to be 70[5].

Data from a systematic literature review of Medline, Embase and Global Health Library which reclaimed a total of 335 publications showed that in 1990, the estimated crude prevalence of RA in Africa based on the available studies was 0.36% (2.3 million affected individuals) which was thought to be increased in 2010 to 0.42% with burden of 4.3 million affected individuals[6].

In 2004, A study was conducted to assess the prevalence of rheumatic diseases in rural Egypt and the results showed that in 857 individuals, The prevalence of RA in rural Egypt was 0.29% in the population, which was similar to other oriental rural populations but lower than Western populations[12].

5. Study Questions and Objectives

5.1. Study Questions

1. What is the clinical efficacy of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, and Sulfasalazine) with or without Steroids use in Egyptian patients with Active Rheumatoid Arthritis ?
2. What are the pattern of management and characteristics of Egyptian patients with Active Rheumatoid Arthritis receiving Leflunomide treatment?
3. What is the clinical safety of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, and Sulfasalazine) with or without Steroids use in Egyptian patients with Active Rheumatoid Arthritis?

5.2. Primary Objectives

1. Assessing the clinical efficacy of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids in Egyptian patients with Active Rheumatoid Arthritis.

5.3. Secondary Objectives

1. Describing pattern of management and characteristics of Egyptian patients with Active Rheumatoid Arthritis receiving Leflunomide treatment.

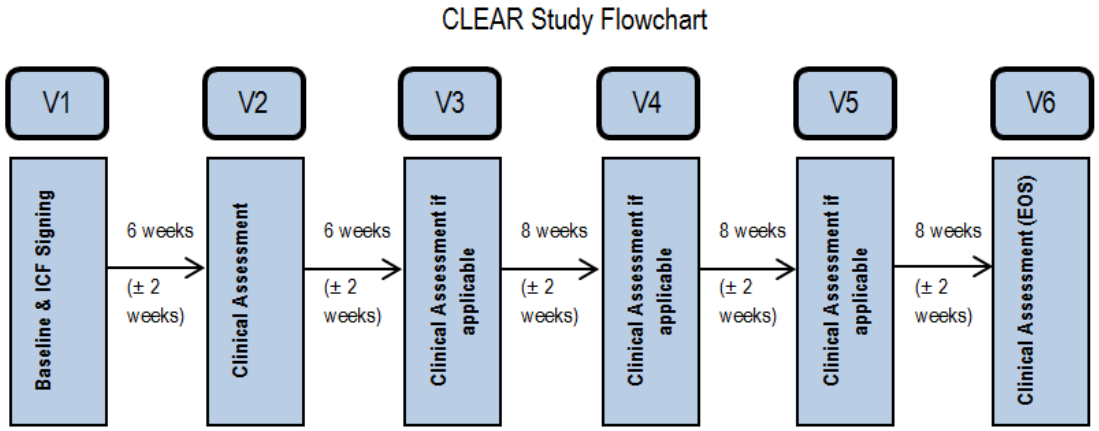
2. Identifying the safety profile of Leflunomide whether used as first line therapy and/or as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids in Egyptian patients with Active Rheumatoid Arthritis.

6. Study Methods

6.1. Study Design

This is a phase IV, multi-centric, prospective, observational study to assess the clinical efficacy and safety of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids use in Egyptian patients with Active Rheumatoid Arthritis.

6.2. Study Flowchart and Graphical Study Design



6.3. Recruitment Modalities

6.3.1. Selection of Subjects

6.3.1.1. Inclusion Criteria

Patient must meet ALL of the following criteria to be eligible for enrolment into the study

1. Active Rheumatoid Arthritis patients selected according to the ACR/EULAR classification 2010 criteria with score ≥ 6 points.
2. Male or female patients aged 18-60 years old.
3. Leflunomide naïve patients or patients with previous Leflunomide administration (after at least 6 month wash out period from date of baseline visit) who will be prescribed Leflunomide at the sole decision of the treating physician.

4. Patients with or without another DMARDs including Methotrexate, Sulfasalazine and/or Hydroxychloroquine with or without steroids use who experienced therapy resistance, inadequate response or intolerance.
5. Patients read, understand and signed informed consent prior to inclusion.
6. Patients willing to complete and literate in the language of the available Health Assessment Questionnaire (HAQ Disability Index) either alone or with minimal assistance from caregivers and/or trained site personnel.

6.3.1.2. Exclusion Criteria

Patient meeting the following criteria is not eligible for enrolment into the study

1. Female patients who are pregnant or lactating at the time of inclusion or those who are planning for pregnancy within the coming year from the time of inclusion to the study.
2. Patients with contraindications to active constituent of Leflunomide.
3. Patients with severe concurrent infection (necessitating IV antibiotics or hospitalization).
4. Patients with history of non-treated hepatitis B &/or C infection.
5. Patients with history of severe liver disease (child C class).
6. Patients with history of severe renal insufficiency (creatinine clearance ≤30 ml/min.).

6.3.2. Selection of Investigators

The study will be conducted by rheumatologists.

In order to ensure the representativeness of investigators, the participating investigators will be randomly selected among an extended list of sites (private clinics; rheumatologist) provided by the study sponsor.

6.4. Duration of Study Participation

3 months for recruitment and 9 months for treatment.

7. Management of Data

7.1. Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the CRF), clinical and office charts, laboratory and pharmacy records…etc.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g.: there is no other written or electronic record of data)

All documents will be stored safely in confidential conditions. On all study-specific documents,

other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Direct access to source documents will be granted to DATACLin CRO monitoring team as authorized representatives from the sponsor and to regulatory authorities to permit trial-related monitoring, audits and inspections.

7.2. Data Collection

7.2.1. Data Collection Schedule

Data to be collected	Data Collection Schedule					
	Visit 1 (Baseline)	Visit 2 (Week 6)	Visit 3 (Week 12)	Visit 4 (Week 20)	Visit 5 (Week 28)	Visit 6 (Week 36)
Informed consent	x					
Inclusion/ Exclusion	x					
Physical Examination/ Vital Signs[1]	x	x	x	x	x	x
Demographics	x					
Smoking Status	x					
Alcohol Consumption	x					
Medical history	x					
Gynecological History (FEMALES ONLY)	x					
Concomitant Medications	x	x	x	x	x	x
RA History[2]	x					
Disease Assessment[3]	x	x	x	x	x	x
Laboratory Tests[4]	x	x	x	x	x	x
Health Assessment Questionnaire (HAQ Disability Index)[5]	x	x	x	x	x	x
Poor Prognostic Factors[6]	x					
Adverse Events & Serious Adverse Events		x	x	x	x	x
Study Completion Form						x

***1**: Physical Examination/Vitals Signs: Height will be collected in V1 only.*

***2**: Rheumatoid Arthritis History will include RA Duration, Previous/Current therapies including duration, dose, adverse events/serious adverse events experienced during previous treatment and Reason for starting Leflunomide* (previous DMARDs failure, insufficient response, allergy, intolerance, side effects) *dose (if the patient received loading dose or not) and Previous X-RAY reports.*

***3**: Disease Assessment will be done by Clinical Disease Activity Index (CDAI).*

***4**: Laboratory Tests include CBC, ESR assessed by Westergren method (First hour), C-reactive protein (titer), AST, ALT, Sr Cr, Sr ACPA, Sr RF titer, FBG, HBsAg and HCV-Ab.*

***5**: Stanford University-Health Assessment Questionnaire (HAQ Disability Index).*
***6**: Poor prognostic factors: Presence of 1 or more of; Bony erosions by radiograph, High swollen joint count, Extra-articular disease (nodules, vasculitis, Felty's syndrome), Functional limitation (HAQ), High disease activity as measured by composite indices (DAS28, SDAI and/or CDAI), High acute phase reactants (CRP and ESR) or High RF and/or anti-CCP.*

7.2.2. Data Collection Process

Data will be collected using NCR CRF according to the below manner;

At Baseline Visit:

Data on Informed consent, Inclusion and exclusion criteria, Demographics, Smoking status, Alcohol consumption, Medical history, Gynecological History for female patients only, Concomitant medications, Laboratory tests and Poor prognostic factors will be collected along with RA history.

Disease assessment (CDAI) and Physical examination will be done and also Vital signs will be recorded.

Patients will fill Health Assessment Questionnaire (HAQ Disability Index) and related data will be recorded.

At Visit 2 (Week 6 ± 2 weeks) & Visit 3 (Week 12 ± 2 weeks) & Visit 4 (Week 20 ± 2 weeks) & Visit 5 (Week 28 ± 2 weeks):

Data on Concomitant medications and Laboratory tests will be collected.

Disease assessment (CDAI) and Physical examination will be done and also Vital signs will be recorded.

Patients will fill Health Assessment Questionnaire (HAQ Disability Index) and related data will be recorded.

Data on Adverse events/Serious adverse events experienced by patient since the previous visit will be documented.

At Visit 6 (Week 36 ± 2 weeks):

Data on Concomitant medications and Laboratory tests will be collected.

Disease assessment (CDAI) and Physical examination will be done and also Vital signs will be recorded.

Patients will fill Health Assessment Questionnaire (HAQ Disability Index) and related data will be recorded.

Data on Adverse events/Serious adverse events experienced by patient since the previous visit will be documented.

Study Completion Form will be also filled.

Data on Adverse events/Serious adverse events experienced by patient since the previous visit will be documented.

Study Completion Form will be also filled.

7.3. Conventions (Data Entry)

Double data entry (interactive verification):Two people independently enter the same data and the second entry operator resolves discrepancies between first and second entry while being aware of the values entered by the first entry operator.

Data entry will be done using ClinCapture version 2.1.15.9.

7.4. Data Validation and Discrepancy Management by the CRO

The computerized handling of data by DATACLin CRO may generate additional queries automatically through pre-programmed and tested validation rules. Validation rules will be detailed in the Data validation Plan (DVP).

In addition to automatic validation rules, manual/ medical review of data may generate further queries that will be raised on the system as well. Site staff will be responsible for resolving automatic and manual queries by confirming or modifying the data questioned.

7.5. Clinical Data Coding

DATACLin CRO will be responsible for coding of safety data using the latest available version of MedDRA (Medical Dictionary for Regulatory Activities).

Collected trade names of drugs (e.g. concomitant medications) will be also coded to the relevant generic names.

8. Statistical Considerations

8.1. Determination of Sample Size

The primary objective of CLEAR study is to assess the clinical efficacy of Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids as measured by the mean relative change in Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ Disability Index) among patients with active rheumatoid arthritis.

Considering an alpha error of **5%** using two-sided 95% CI of Wilcoxon signed-rank test and a study power of **80%**, a sample of **332 patients** will be required to detect an effect size of **0.158** between baseline and study endpoint, plus an expected **drop-out rate of 20%** during the 9 months observational study duration. Thus, a sample of **398 patients** will be appropriate that rounded to **400 patients**.

8.2. Randomization

Not Applicable.

8.3. Analysis Population

The obtained clinical data will be analyzed on an intention-to-treat basis. Primary analysis will be done by intention-to-treat including all eligible enrolled patients with at least one treatment dose and post first assessment score (CDAI and HAQ) attending any post treatment visit and efficacy variables will be analyzed using the last-observation-carried-forward convention (LOCF).

8.4. Study Endpoints

8.4.1. Primary Endpoints

- To assess **disease severity** (Remission, Low Activity, Moderate Activity and High activity) and the **mean relative change** in **Clinical Disease Activity Index (CDAI)** among patients with active rheumatoid arthritis treated with Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids between baseline and week 36.
- To assess the **mean relative change** in **Health Assessment Questionnaire Score (HAQ Disability Index)** among patients with active rheumatoid arthritis treated with Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids between baseline and week 36.

8.4.2. Secondary Endpoints

- **Qualitative and quantitative descriptive analysis with (95% confidence intervals)** for the below variable :
    - Demographics
    - Medical History
    - RA severity
    - RA duration
    - Line of therapy
    - Daily dose
    - Treatment duration
    - Reason for treatment adjustment

- Previous therapies

8.4.3. Safety Endpoints

- To assess the frequency of AEs/SAEs among patients using Leflunomide as first line therapy and as add-on therapy to other DMARDs (such as Methotrexate, Hydroxychloroquine, Sulfasalazine) with or without Steroids and its relation to study medication.

8.5. Endpoints Variables

8.5.1. Efficacy Variables

- **Clinical Disease Activity index (CDAI)** in **baseline and at week 36** to measure disease severity **and relative mean change** between study endpoints.
- **Health assessment questionnaire** (HAQ Disability Index) in **baseline and at week 36** to measure relative mean change between study endpoints.

8.5.2. Safety Variables

- **AE/SAE form** to assess frequency of AEs/SAEs among patients.

8.6. Other Covariate/Control Variables

- **Management patterns** and **patients characteristics** as described parameters below:
  - **Demographics**
  - **Medical History**
  - **RA severity**
  - **RA duration**
  - **Line of therapy**
  - **Daily dose**
  - **Treatment duration**
  - **Reason for treatment adjustment**
  - **Previous therapies**

8.7. Statistical Analysis Methods

8.7.1. Descriptive Analysis

- Percent (%) distribution for all categorical variables and mean with (SD) and median (Minimum: Maximum) for continuous variables according their distribution.

8.7.2. Comparative Analysis

- Student t-test and One Way ANOVA to estimate the comparison between the treatment

arms for the numerical variables (according to their distribution; non-parametric substitution tests could be used).

- Paired t-test and repeated measure ANOVA test to estimate the change in numerical variables throughout the study visits (according to their distribution; non-parametric substitution tests could be used).
- Chi2 test (or Fisher's Exact test) for unpaired and McNemar's test for paired categorical variables.

- All tests will be performed on the 5% level of significance.
- Any deviation(s) from the original statistical plan will be described in the final report.

8.7.3. Interim Analysis

- When approximately the enrolled patients completed 50% of their visits (after Visit 3), an interim analysis for safety and efficacy will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

8.8. Handling of Missing Values

- Procedure for accounting for missing, unused, and spurious data will be explained in the statistical analysis plan (SAP).

9. Treatment

9.1. Product

Each Arthfree 20 mg contains:

Active ingredient: Leflunomide 20 mg

Inactive ingredients: Microcrystalline cellulose, Lactose monohydrate, Maize starch, Anhydrous colloidal silica, Polyvinylpyrrolidone, Croscarmellose sodium, Magnesium stearate.

Each Arthfree 100 mg contains:

Active ingredient: Leflunomide 100 mg

Inactive ingredients: Microcrystalline cellulose, Lactose monohydrate, Maize starch, Anhydrous colloidal silica, Polyvinylpyrrolidone, Croscarmellose sodium, Magnesium stearate.

Patients will be prescribed Arthfree (Leflunomide) at the sole decision of the treating physician.

9.2. Mode of Administration

Arthfree (Leflunomide 20mg)

Dose: 1 tablet once daily, should be swallowed whole with sufficient amounts of liquids. The extent of Leflunomide absorption is not affected if taken with meals. Doses higher than 20 mg/day are not recommended. Improvement in the rheumatoid condition usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

Loading dose: a tablet of Leflunomide 100 mg for three days. should be swallowed whole with sufficient amounts of liquids. The extent of Leflunomide absorption is not affected if taken with meals.

Due to the long half-life in patients with rheumatoid arthritis and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly.

10. Pharmacovigilance

For Safety Reference; this study will be conducted consistent with The International Conference on Harmonization Guideline E2A and 21 CFR Part 312 and WHO Guidelines.

Safety assessments will consist of monitoring and recording adverse events; including serious and non-serious adverse events, measurement of protocol-specified safety laboratory assessments, measurement of Protocol-Specified Vital Signs and other Protocol-Specified Measures that are deemed critical to the safety evaluation of the study.

10.1. Definitions

10.1.1. Adverse Events

An adverse event is any untoward medical occurrence in a clinical investigation subject associated with the use of a product or a medical device; the event does not necessarily need to have a causal relationship with the treatment or usage.

Examples of Adverse Events include but are not limited to:

- Abnormal lab test findings of clinical concerns
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease
- Additionally, they may include the signs or symptoms resulting from:
- Drug Overdose
- Drug Withdrawal
- Drug Abuse
- Drug Misuse
- Drug Interactions
- Drug Dependency

- Exposure During Pregnancy
- Drug Quality Defect That Has Impact On The Patient Safety

10.1.2. Adverse Event of Special Interest

An Adverse Event of Special Interest (AESI) is an AE (Serious or Non-Serious) of scientific and medical concern specific to the Sponsor's Product Or Program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by Protocol Amendment.

In this study, No Adverse Event of Special Interest will be collected.

10.1.3. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results In Death
- Is Life-Threatening (Immediate Risk Of Death)
- Requires Inpatient Hospitalization or Prolongation of Existing Hospitalization
- Results In Persistent Or Significant Disability/Incapacity
- Results In Congenital Anomaly/Birth Defect
- Important Medical Event

Medical and Scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.1.4. Adverse Reaction (Adverse Drug Reaction)

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. This would include all noxious and unintended responses to the MP related to any dose.

10.1.5. Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a judgment by the clinical investigator or study sponsor that there is a reasonable possibility that the AE has a causal relationship with the Investigational Product, though with a lesser degree of certainty about causality, compared to the use of the term “adverse reaction” (or “adverse drug reaction”) as defined above

For the purposes of U.S. IND safety reporting, the meaning of ‘Reasonable Possibility’ is clarified in FDA’s recent changes to CFR 312 by the following examples of types of evidence that would suggest a causal relationship between the drug and the AE, such as:

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

10.1.6. Unexpected Adverse Drug Reaction

An AE or suspected adverse reaction is considered “Unexpected” if it is not listed in the Approved Product Label (for regulatory-approved, commercially available products) or in the investigator brochure, or is not listed at the specificity or severity that has been observed in a serious adverse event at hand; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the available information about the MP. "Unexpected," as used in this context, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with the given class of drugs or may be anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular MP under investigation.

10.1.7. Abnormal Test Findings

Treatment-emergent laboratory test abnormalities considered to be of clinical concern should be recorded as AEs in the CRF

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or

3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
4. Test result is considered to be an adverse event by the investigator or sponsor.

   Merely repeating an abnormal test, in the absence of any of the above conditions, **does not** constitute an adverse event.

   Any abnormal test result that is determined to be **an error** does not require reporting as an adverse event.

10.1.8. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

10.2. Adverse Events Monitoring

All AEs regardless of seriousness or relationship to Medicinal Product (MP), spanning from the signature of the informed consent form, until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) included in the CRF and reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Sponsor or its designated representative.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the MP, Follow-Up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Sponsor concurs with that assessment. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Monitoring Team up to as noticed by the sponsor

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to MP, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the MP.

10.3. Reporting Period

For serious adverse events, the reporting period to Sponsor or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e. prior to undergoing any study-related procedures and/or receiving MP, through and till the end of the Follow-Up Period as specified in the study protocol.

Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to MP is SUSPECTED.

10.4. Severity Assessment

The severity of each AE and laboratory abnormality is to be assessed by the investigator according to following criteria

- Mild (Grade 1): AE or laboratory abnormality that is transient or is easily tolerated on continuation of study drug.
- Moderate (Grade 2): AE or laboratory abnormality that causes the patient discomfort and causes interference with the patient's usual activities.
- Severe (Grade 3): AE or laboratory abnormality that is incapacitating and causes considerable interference with the patient's usual daily activities, and/or may be life-threatening if it worsens.
- Life-Threatening (Grade 4): The AE or laboratory abnormality is life threatening as it exists (i.e., no worsening is required for the abnormality to be life-threatening).
- Death Related AE (Grade 5)

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met at ease one of the 6 seriousness criteria.

10.5. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (Serious and Non-Serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that MP caused or contributed to an adverse event. If the investigator's causality assessment is "unknown but not related to MP", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

10.5.1. WHO-UMC Causality Categories

Causality Term	Assessment Criteria

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassified	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

10.6. Exposure During Pregnancy

For Investigational Products and for Marketed Products, an exposure during pregnancy (also referred to as Exposure In-Utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to the Investigational Product(e.g., environmental exposure), or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the Investigational Product (maternal exposure).

2. A male has been exposed, either due to treatment or environmental, to the Investigational Products prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

   If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the Medicinal Product, the investigator must submit this information to the Sponsor.

   This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy.

   The information submitted should include the anticipated date of delivery.

   Follow-up is conducted to obtain pregnancy outcome information on all Exposure during pregnancy reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Pregnant Form. The reason(s) for an induced abortion should be specified.

   An EIU report is NOT created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

   If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [Including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

   In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Pregnant Form can be completed).

   The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

   Additional information about pregnancy outcomes that are classified as serious adverse events follows:

1. Spontaneous abortion; includes miscarriage and missed abortion.
2. All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the exposure during pregnancy to the investigational medication should be reported.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g. follow-up on preterm infants to identify developmental delays).

10.7. Withdrawal Due to Adverse Events

Withdrawal due to adverse event should be distinguished from withdrawal due to Insufficient Response, according to the definition of adverse event noted earlier, and recorded on the appropriate Adverse Event CRF Page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

10.8. Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points.

Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

10.9. Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event CRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event Form.

10.10. Reporting Requirements

10.10.1. General Instructions

Investigators will seek information on adverse events at each patient contact.

All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event Form in CRF.

After prescription of MP, all adverse events, regardless of relationship to study drug, will be reported.

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

10.10.2. Reporting of Serious Adverse Event

If a serious adverse event occurs, Sponsor or its representative is to be notified within 24 HOURS OF AWARENESS OF THE EVENT by the investigator or delegate on behalf. In particular, if the serious adverse event is fatal or life-threatening, notification to Sponsor or its representative must be made IMMEDIATELY, irrespective of the extent of available adverse event information.

This timeframe also applies to additional new information (Follow-Up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure during pregnancy cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after being aware of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Sponsor or its representative in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Sponsor or its representative to obtain specific additional follow-up information in an expedited fashion.

In general, this information will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its representative or its designated representative.

10.10.3. Reporting of Non-Serious Adverse Event

All Non-Serious Adverse Events will be documented on the Adverse Event Page(s) of the CRF and reported properly to the local regulatory authority.

10.11. Instructions for Reporting SAEs for Study Team

In the case of occurrence of a SAE, the Investigator must immediately:

1. **SEND** the Signed and Dated Corresponding Page(s) from the CRF to the Representative Of The Monitoring Team whose Name, Fax Number and E-mail Address appear on the Study Protocol
2. **ATTACH** a Photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any

copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges;

3. All further documentation should be sent to the Monitoring Team within 1 working day of knowledge. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.

If the CRA is Not Available, Please Contact:

Name	Mina Saeed
Title	Pharmacovigilance Manager
Mobile	(+2) 01022242873
E-mail	mina.saeed@dataclin.com
Tel	(+202) 3761-7301/2
Fax	(+202) 3345 0061

And Sponsor's Representative:

Name	Mina Maxy
Title	Medical advisor/Deputy QPPV
Mobile	(+2) 01110014883
E-mail	mina.maxy@evapharma.com
Tel	Tel: (+202) 239 92700
Fax	Fax: (+202) 239 92782

10.12. Sponsor Reporting Requirements to Regulatory Authorities

During the course of the study, the Sponsor will report All Adverse Events to the Local Health Authorities, in accordance with the Local Timeframes for Reporting.

10.13. Breaking Randomization Code

Not Applicable.

11. Ethical and Regulatory Standards

11.1. Ethical principles

This study will be conducted in accordance with the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments and ICH guidelines for Good Clinical Practice (ICH-E6). Study team will ensure all necessary regulatory submissions (e.g.: IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

11.2. Laws and Regulations

This Clinical Trial will be conducted in compliance with all applicable international laws and regulations, and national laws and regulations of Egypt in which the Clinical Trial is performed, as well as any applicable guidelines.

11.3. Data Informed Consent

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the Clinical Trial, the written Informed Consent Form must be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

11.4. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC).Written dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition must be obtained.

Investigational Product will not be released at the study site and the Clinical Trial will not start until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety.

If requested, a summary of the Clinical Trial's outcome at the end of the Clinical Trial is sent to the Ethics Committee (IRB/IEC).

11.5. Discontinuation / Withdrawal of participants from study

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

1. Ineligibility (either arising during the study or retrospective having been overlooked at screening)
2. Significant protocol deviation
3. Significant non-compliance with treatment regimen or study requirements
4. Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures.
5. Consent withdrawn.
6. Lost to follow up

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilized. Patients who withdraw from the study will not be replaced.

12. Quality Control and Quality Assurance

12.1. Quality Control

12.1.1. In Process Quality Control of Biometrics

As per DataClin CRO SOPs, quality control by an independent qualified reviewer is performed on all biometrics related documents developed internally. This includes study protocol, case report form, informed consent form and study plans. In addition to these documents, database QC is performed automatically (programmed edit checks) and manually (manual review of line listings) to ensure that data is complete and consistent.

12.1.2. Monitoring and Site Data Quality Control

Study monitors will perform ongoing source data verification to confirm that critical protocol data collected into the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

100 % Source Data Verification (SDV) will be performed only for All Signed Informed Consents and Critical Variables which will be described in a “Critical Variables List” that will be ready before sites monitoring

If specific issues are identified in a certain site, the percentage of Quality Control in the concerned site and/or in all sites must be appropriately increased and corrective actions must be set up.

12.2. Quality Assurance

All study procedures will be subject to pre-planned internal audit(s) by DataClin CRO quality assurance team. This covers biometrics phases, clinical operations and overall project management.

13. Responsible Parties

13.1. Responsibilities of Investigators

The Investigator is responsible to strictly follow the study protocol and all applicable regulations and guidelines.

Investigator’s responsibilities include recording precise and accurate data pertinent to the study in the CRF in addition to obtaining written informed consents from patients prior to inclusion in the study.

The investigator will be responsible for taking all appropriate measures to ensure patient’s safety all over the study duration.

Study documents will be appropriately retained until the end of the study. In addition the Investigator should comply with local regulations with regards to record retention.

It is recommended that the Investigator retains the study documents at least five years after the completion or discontinuation of the study.

The Investigator agrees to allow and help with the performance of sponsor auditors/ regulatory authorities’ inspectors to have direct access to study records, all necessary data, documents and facilities. Once the investigator is notified of an inspection, he shall inform the sponsor and authorize sponsor to participate in this inspection. The confidentiality of the data verified and the protection of the patients should be respected during these inspections. The investigator will make sure that any results and information resulting from the inspections will be immediately communicated to sponsor. It will be the

investigator's responsibility to take corrective actions for any issues raised during the audits or inspections.

Names and responsibilities of coordinating investigator(s) and the other participating investigators will be documented prior to the start of the trial. All investigators will be given instructions on following the protocol, complying with a uniform set of standards for the assessment of clinical and laboratory findings, and completing the CRFs. Communication between investigators should be facilitated.

13.2. Responsibilities of Sponsor

The sponsor will be responsible for providing adequate resources to ensure the proper conduct of the study according to study protocol and all applicable laws and regulations.

The sponsor will delegate a CRO to conduct the study.

Sponsor/ delegated CRO is responsible for all regulatory submission(s). In addition, sponsor/ delegated CRO will contract insurance for all participating patients during study participation.

Delegated CRO will be responsible for ongoing reporting of adverse events and serious adverse events to local regulatory authorities.

14. Administrative Expectations

14.1. Record Retention and Archiving of Study Documents

The Investigator shall arrange for the retention of study documentation until the end of the study. In addition the Investigator will comply with specific local regulations/ recommendations with regards to patient record retention

It is recommended that the Investigator retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the Investigator Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

14.2. Confidentiality and Protection of Study Data

All study related material, information and unpublished documents provided to the investigator are the exclusive property of sponsor.

These materials or information cannot be disclosed by any person to unauthorized persons without the prior formal written approval from sponsor.

The Investigator will consider all received information or resulted data as confidential and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

Patient's personal data (name, phone number, address …etc) shall be kept confidential all over the study participation period and after study completion as well.

Upon archiving or processing patients' personal data, sponsor shall take all appropriate measures to prevent access to this data by any unauthorized third party.

14.3. Insurance

The Sponsor may contract Insurance according to Local Regulatory Requirements.

14.4. Sponsor Audits and Inspections by Regulatory Agencies

The Investigator agrees to allow sponsor auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the sponsor and authorize sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be immediately communicated by the Investigator to sponsor.

The Investigator shall take appropriate measures required by sponsor to take corrective actions for all problems found during the audit or inspections.

14.5. Premature Discontinuation of The Study/Premature Close-out of a Site

Sponsor can decide at any time and for any reason to prematurely stop or to interrupt the study; the decision will be communicated in writing to the Investigator.

Similarly, should the Investigator decide to withdraw from the study, she/he will have to immediately inform sponsor in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

14.6. Ownership and Use of Study Data

No use of the data will be possible without the authorization of sponsor conducting the study.

15. Amendments and Updates

Any change to the protocol will be recorded in a written amendment, which will be signed by the Investigator.

Amendment to the protocol may require regulatory submissions (e.g.: IRB/IEC) in accordance with local regulations.

In some cases, an amendment may require a change to the written subject information/informed consent form.

16. Milestones

- **Protocol planned date:** June 2017
- **First patient In (FPI):** September 2017
- **Last patient In (LPI):** December 2017
- **Last patient Out (LPO):** September 2018
- **Estimated enrollment duration:** 3 months
- **Estimate treatment duration:** 9 months
- **Database lock planned date:** September 2018
- **Estimated Report date:** November 2018

17. Appendices


Stanford HAQ 20-Item Disability Scal


2015 American College of Rheumatolc


EULAR recommendations for

18. Publications

All study investigators give full authority to the sponsor for primary publication of results. No other publication is allowed before the primary publication. Any subsequent publications by a study participant must be approved by the sponsor and make reference to the study and the primary

publication. Sponsor may request that his name and/or names of one or several of its employees appear or do not appear in such publications.

19. References

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