CLINICAL TRIAL PROTOCOL

CLINICAL TRIAL PHASE- III

A prospective, multicenter, randomized, double blind, Phase III study to compare the efficacy and safety of Biosimilar Adalimumab injection of Enzene Biosciences Ltd. with HUMIRA® (adalimumab) injection in subjects with active Ankylosing spondylitis (AS).

Protocol Number –ALK20/ENZ129-ADA1

Version2.0, Dated 27/Jan/2020

SPONSOR

Enzene Biosciences Ltd.
165/1/26, Block – T,
Bhosari MIDC,
PCMC,Pune-411026
Phone 020-30674622

CO-SPONSOR

Alkem Laboratories Ltd.
ALKEM HOUSE, "Devashish",
Adjacent to Matulya centre,
Senapati Bapat Marg,
Lower Parel, Mumbai – 400 013
Telephone: +91- 22- 39829999

1. STUDY INFORMATION

1.1. STUDY CONTACT INFORMATION DETAILS

Sponsor	**Enzene Biosciences Ltd.** 165/1/26, Block – T, Bhosari MIDC, PCMC, Pune-411026 Phone 020-30674622
Co-Sponsor	**Alkem Laboratories Ltd** ALKEM HOUSE, "Devashish", Adjacent to Matulya centre, Senapati Bapat Marg, Lower Parle, Mumbai – 400 013 Telephone: +91- 22- 39829999
Sponsor's Representative	**Dr. Akhilesh Sharma** President &Chief Medical Officer, Alkem Laboratories Ltd . ALKEM HOUSE, "Devashish", Adjacent to Matulya centre, Senapati Bapat Marg, Lower Parle, Mumbai – 400 013 Telephone: +91- 22- 39829999

1.2. SPONSOR'S DECLARATION

Study Title: A prospective, multicenter, randomized, double blind, Phase III study to compare the efficacy and safety of Biosimilar Adalimumab injection of Enzene Biosciences Ltd. with HUMIRA® (adalimumab) injection in subjects with active Ankylosing spondylitis (AS).

Protocol Number: ALK20/ENZ129-ADA1

Version: 2.0, Dated 27/Jan/2020

I, on behalf of Enzene Biosciences Ltd. have read and understood this protocol and hereby approve the same. I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013), which are consistent with the ICH-GCP E6(R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules, 2019 and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017). I agree to provide compensation in the case of clinical trial related injury or death for which subjects are entitled to as per CDSCO and other applicable regulatory guidelines. I also agree to comply with cGMP requirements for the study drug for human consumption.

Akhilesh Sharma

Signature:

28/01/2020

Date:

Dr. Akhilesh Sharma
President &Chief Medical Officer,
Alkem Laboratories Ltd.
ALKEM HOUSE, "Devashish",
Adjacent to Matulya centre, Senapati Bapat Marg,
Lower Parle, Mumbai – 400 013
Telephone: +91- 22- 39829999

1.3. INVESTIGATOR'S AGREEMENT

Study Title: A prospective, multicenter, randomized, double blind, Phase III study to compare the efficacy and safety of Biosimilar Adalimumab injection of Enzene Biosciences Ltd. with HUMIRA® (adalimumab) injection in subjects with active Ankylosing spondylitis (AS).

Protocol Number: ALK20/ENZ129-ADA1

Version: 2.0, Dated 27/Jan/2020

I, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with the approved protocol complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013),which are consistent with the ICH-GCP E6(R2) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), New Drugs and Clinical Trial Rules, 2019 and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than evaluation or conduct of the clinical investigation without the prior consent of Sponsor. I understand that the Sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial, I will communicate my intention immediately in writing to the Sponsor.

I further agree to ensure that all associates assisting in the conduct of this study are well informed regarding their obligations and confirm to conduct this study under my direction.

_____ Date: _____

Investigator

Name:

Site Address:

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

AE	:	Adverse Event
ALT	:	Alanine aminotransferase
ANC	:	Absolute Neutrophil Count
AS	:	Ankylosing spondylitis
ASAS	:	Assessment in Ankylosing spondylitis response criteria
AST	:	Aspartate aminotransferase
BASDAI	:	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	:	Bath Ankylosing Spondylitis Functional Index
BSA	:	Body Surface Area
BUN	:	Blood Urea Nitrogen
ºC	:	Degree celsius
CDSCO	:	Central Drugs Standard Control Organization
CDMS	:	Clinical Data Management System
CLA	:	Central Licensing Authority
CRA	:	Clinical Research Associate
CrCl	:	Creatinine Clearance
CRO	:	Contract Research Organization
CRP	:	C-reactive protein
CTCAE	:	Common Terminology Criteria for Adverse Events
CTRI	:	Clinical Trials Registry India
dL	:	Deciliter
DMARDs	:	Disease-Modifying Anti-Rheumatic Drugs
DRF	:	Discrepancy Resolution Form
ECG	:	Electrocardiogram
eCRF	:	Electronic Case Record Form
EDC	:	Electronic Data Capture
ELAM-1	:	Endothelial cell leukocyte adhesion molecule-1
EOS	:	End of Study
ESR	:	Erythrocyte sedimentation rate
ºF	:	Degree Fahrenheit
GCP	:	Good Clinical Practice
GMP	:	Good Manufacturing Practice
Hb	:	Hemoglobin
HBV	:	Hepatitis B Virus
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
ICAM	:	Intercellular Adhesion Molecule 1
ICF	:	Informed Consent Form

ICH	:	International Council for Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Independent Ethics Committee
IGRA	:	Interferon gamma release assay
IP	:	Investigational Product
IRB	:	Institutional Review Board
IUD	:	Intrauterine Device
IUS	:	Intrauterine System
IWRS	:	Interactive Web Response System
mITT	:	Modified Intention To Treat
MRI	:	Magnetic Resonance Imaging
mL	:	Milliliter
NMSC	:	Non-Melanoma Skin Cancer
NSAIDs	:	Non-steroidal anti-inflammatory drugs
PCS	:	Physical Component Summary
PCV	:	Packed Cell Volume
PK	:	Pharmacokinetics
QM	:	Query Management
RBC	:	Red Blood Cell
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SC	:	Subcutaneous
SOP	:	Standard Operating Procedure
TB	:	Tuberculosis
TEAE	:	Treatment Emergent Adverse Event
TNF	:	Tumor Necrosis Factor
ULN	:	Upper Limit of Normal
UPT	:	Urine Pregnancy test
VAS	:	Visual Analog Score
VCAM-1	:	Vascular cell adhesion protein 1
WBC	:	White Blood Cell
WMA	:	World Medical Association

4. GLOSSARY

Concomitant medication	:	A concomitant medication (con-med) is a drug or biological product, other than the investigational product, taken by a subject during a clinical trial participation
Eligible subjects	:	The subjects who fulfills all the inclusion criteria and none of the exclusion criteria are considered as eligible for the study
Enrolled subject	:	The subjects who sign the informed consent form will be enrolled in the study
Evaluable subjects	:	Subjects who complete the study as per the approved protocol
Modified Intention-to-Treat (mITT) Population	:	All randomized subjects who receive at least one dose of study treatment and have at least one efficacy assessment
Per Protocol Population	:	All randomized subjects who complete the study visits as per protocol without any major protocol deviations
Pharmacokinetic Population	:	Subjects who have all PK samples collected
Randomization	:	A method based on chance alone by which the subjects are assigned to a treatment group
Randomization number	:	A unique number assigned to the eligible subjects which describes the assigned sequence of administration of the investigational product as per approved randomization schedule
Safety population	:	All randomized subjects who receive at least one dose of study treatment will be included in the safety population
Screening	:	The process to determine that the subject is eligible to participate in the study
Study duration	:	The duration from the screening visit till the last safety follow up visit
Treatment period	:	The period during which investigational product is being administered

5. PROTOCOL SYNOPSIS

Title	A prospective, multicenter, randomized, double blind, Phase III study to compare the efficacy and safety of Biosimilar Adalimumab injection of Enzene Biosciences Ltd. with HUMIRA® (adalimumab) injection in subjects with active Ankylosing spondylitis (AS).
Protocol Number	ALK20/ENZ129-ADA1
Trial Location	India
Development Phase	Phase III
Indication	Active Ankylosing spondylitis (AS)
No. of centers	Multicenter; approximately 30 centers in India
Study Objective(s)	**Primary Objective:** • To compare the efficacy of Biosimilar Adalimumab injection with HUMIRA® (adalimumab) injection, in subjects with active Ankylosing spondylitis (AS) by assessment of ASAS20 response criteria **Secondary Objective(s):** • To evaluate the following: ✓ Pharmacokinetics (PK) of Biosimilar versus HUMIRA® (adalimumab) injection ✓ Immunogenicity of Biosimilar and HUMIRA® (adalimumab) injection by assessment of anti-Adalimumab antibody ✓ Safety and tolerability of the investigational product
Study Endpoints	**Primary Efficacy Endpoint:** • Number of achievers in Assessment in Ankylosing spondylitis (ASAS20) response criteria at week 6 and week 12, where the achievers are defined as subjects experiencing at least 20 % improvement and an absolute improvement of at least one unit as compared to baseline in at least 3 out of four domains, with no deterioration (defined as a worsening of at least 20 % or an absolute increase of at least one unit from baseline) in the

	remaining domain. The four domains of response criteria are: 1. Subjects global assessment of disease activity during the previous week (assessed by 0-10-cm VAS), 2. Subject's assessment of pain during the previous week, represented by total back pain score (assessed by 0-10-cm VAS), 3. Function, represented by Bath Ankylosing Spondylitis Functional Index (BASFI) score, (assessed by 0-10-cm VAS), 4. Inflammation, represented by the mean of the severity and duration of morning stiffness (i.e., questions 5 & 6 of the BASDAI assessed by 0-10-cm VAS) **Secondary Efficacy Endpoint:** • Number of subjects achieving ASAS40 response criteria at week 6 and week 12 • Number of subjects achieving ASAS70 response criteria at week 6 and week 12 • Number of subjects achieving ASAS5/6 response criteria at week 6 and week 12 • Number of subjects achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response criteria at week 6 and week 12 • Physician's global assessment of disease activity using 0-10 VAS at week 6 and week 12 **Safety Endpoints:** • Treatment emergent serious and non-serious adverse events (AEs) • Alteration in clinical laboratory parameters • Assessment of Anti-Adalimumab antibody **PK Endpoint:** • To assess the PK profile of Biosimilar Adalimumab and HUMIRA® (adalimumab) injection in a subset of subjects with AS.
Study design	A prospective, multicenter, randomized, double blind Phase III study in Subjects with active Ankylosing spondylitis (AS)
Sample Size	192 subjects Of these 192 subjects, a total of 24-evaluable subjects will be considered for PK assessments in the study. A total of 192 subjects who meet the eligibility criteria will be randomized in a ratio of 2:1 to either of the treatment groups:

	• Group A (N =128): Biosimilar Adalimumab • Group B (N =64): Innovator Adalimumab
Test Product, Dose, Route of Administration and Regimen	Biosimilar Adalimumab injection, 40 mg/0.4 mL, single-use glass vial, for subcutaneous use of Enzene Biosciences Ltd. 40 mg every other week, administered subcutaneously for a total of 12 weeks
Reference Product, Dose, Route of Administration and Regimen	Innovator Adalimumab (HUMIRA®) 40 mg/0.4 mL, single-use glass vial, for subcutaneous use of AbbVie Inc. 40 mg every other week, administered subcutaneously for a total of 12 weeks
Prior and Concomitant Drug/Therapy	**Prior therapy/ies:** • The details of the previous anti-AS medication/s (name, dose, and route of administration, date of initiation and stoppage) must be documented. **Concomitant Medications** • Subjects requiring concomitant use of other medications would be treated at the discretion of the Investigator. The details of the medication (name, dose, and route of administration, date/time of administration, and indication for use) must be documented during all the visits. **Permitted Medications** Subjects will be allowed to continue NSAIDs if the dosage had remained stable for at least 2 weeks prior to randomization. Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last dose of study drug. Acceptable methods of contraception are: a. Oral or parenteral (injection, patch or implant) hormonal contraception which has been used continuously for at least one month prior to the first dose of study medication b. Intrauterine device (IUD) or intrauterine system (IUD/IUS) c. Double barrier method of contraception (Condom and occlusive cap or condom and spermicidal agent) d. Male sterilization (at least 6 months prior to the screening and should

	be the sole male partner for that subject) e. Female sterilization (surgical bilateral oophorectomy) or tubal ligation within at least 6 weeks prior to study participation f. Total abstinence, partial abstinence is not acceptable. **Prohibited Medications** • Any other anti-TNF therapy • All DMARDs • Anakinra • Abatacept • Live vaccines
Study duration	The study duration will be approximately 13 months, considering 09 months of recruitment phase, 3 weeks of screening phase and 12 weeks of treatment • **Screening Period:** It will last up to 21 days during which the subject will be assessed for eligibility in the study; • **Treatment Period:** It will be of 12 weeks duration.
Key Inclusion Criteria	The subjects will be included in the study based on the following criteria: 1. Willing to provide voluntary written informed consent. 2. Male or Female subjects between 18 to 65 years of age (both inclusive) 3. Subjects with diagnosis of Axial Ankylosing spondylitis (AS) based on the 1984 modified New York classification criteria, has active AS, as defined by fulfillment of at least 2 of the following 3 conditions at both Screening and Baseline visits: a. BASDAI score ≥ 4 b. Total back pain on a visual analog scale (VAS; 0-10 cm) ≥ 4 c. Morning stiffness ≥ 1 hour 4. Has inadequate response to or intolerance to one or more non-steroidal anti-inflammatory drugs (NSAIDs) as assessed by the Investigator 5. Willing and able to comply with the protocol. Willing and able to comply with the protocol.
Key Exclusion Criteria	The subjects will be excluded from the study based on the following criteria: 1. Has total spinal ankylosis (bamboo spine) 2. Has undergone spinal surgery or joint surgery involving joints assessed within 2 months prior to screening 3. Has received intra-articular joint injection(s), spinal or paraspinal corticosteroid injection(s) within 28 days prior to Baseline 4. Has prior exposure to any anti-TNF (tumor necrosis factor) therapy at

	any time 5. Subjects with clinically active TB (Note: In case of subjects with latent TB, the treatment for latent TB should be initiated before the first dose of the investigational product.) 6. Subjects with underlying conditions that may predispose them to infection 7. Subjects with history or presence of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease which in the opinion of the investigator does not allow participation of the subject in this study 8. Known hypersensitivity to any component of the investigational product and other medications used in this study 9. Subjects with a non-healed fracture 10. Subject's having the following laboratory results at screening a. Absolute neutrophil count (ANC) < 1,500/mm^3 b. Hemoglobin (Hb) <10 g/dL c. Platelet count < 100,000/mm^3 d. Total bilirubin level > 1.5 times the upper limit of the normal laboratory range (ULN) e. AST and ALT $\geq$3 x ULN f. Alkaline phosphatase $\geq$3 x ULN g. Serum Creatinine level > 1.25 xULN 11. Subjects suffering from acute or chronic infection(s) 12. Subjects with congestive heart failure 13. Positive serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) at screening 14. Subjects of child bearing potential, who are not willing to use adequate contraception during the study period. 15. Female subjects who are pregnant or nursing 16. Has any concurrent disease or condition, which in the opinion of the investigator does not allow participation of the subject in this study 17. Has participated in any other clinical trial and received experimental medications within 4 weeks prior to screening
Study specific Discontinuation/Withdrawal criteria	The subject may be withdrawn/discontinued from the study due to the following reasons: 1. Subject whose condition worsens and require alternate or supplemental therapy for the treatment of AS, as per investigator's discretion 2. Subject's voluntary withdrawal of consent 3. Subject fails to comply with the protocol requirements 4. Subject is found to have entered the study in violation of this protocol 5. Any AE or SAE which requires discontinuation of subject in opinion of

	investigator 6. Requirement of prohibited medication 7. Subject develops a serious infection or sepsis 8. Subject develops an anaphylactic or other serious allergic reaction 9. Subject develops symptoms suggestive of a lupus-like syndrome 10. Subject with confirmed significant hematologic abnormalities 11. Subject develops congestive heart failure 12. If it is felt in investigator's opinion that it is not in the subject's best interest to continue 13. Study termination by the sponsor 14. Any other justifiable reason, which should be adequately documented
Study Procedure/ **Methodology**	This is a prospective, multicenter, randomized, double blind, Phase III study. The study is planned to be conducted in 192 subjects with active Ankylosing spondylitis (AS) (in a ratio of 2:1 i.e.128 subjects in Biosimilar Adalimumab and 64 subjects in Innovator Adalimumab arm) at approximately 30 sites in India. After signing the informed consent form, the subjects will be screened for confirming the eligibility for study participation. Subjects will be screened on the basis of Demographics, Physical examination including vital signs, past medical history, medication history, ECG, active and latent TB test (Mantoux test and IGRA assessment), hematology, biochemistry, serology and Urine analysis. **Note:** In case of subjects with latent TB, the treatment for latent TB should be initiated before the first dose of the investigational product. Eligible subjects will be randomized in a ratio of 2:1 i.e. Biosimilar Adalimumab or Innovator Adalimumab arm respectively to enter into the treatment period of 12 weeks (a total of 6 doses of the investigational product). During the treatment period, subjects will report to the clinical site (visit) on Day 1, 15, 29, 43, 57, 71 and 85. A window period of ± 1 day is allowed from Visit 3 to Visit 9. For subjects participating in PK sub-study, PK samples will be collected as mentioned in PK sample collection section. Subjects will be monitored closely for TB during the course of study. Subjects will be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Adalimumab.

<table>
<tr><td></td><td>An interim analysis will be conducted after all subjects complete 6 weeks of treatment.</td></tr>
<tr><td>Investigational Product Administration procedure</td><td>Based on the randomization schedule, investigational product will be administered at the dose of 40 mg subcutaneously every other week for a total of 6 doses.

Injections should occur at separate sites in the thigh or abdomen. The injection sites should be rotated and the injections should not be given into the areas where skin is tender, bruised, red or hard.

The time of investigational product administration will be noted. The investigational product will be administered preferably at the same time.</td></tr>
<tr><td>PK Sample Collection</td><td>The following are the pre-and post-infusion time-points for collection of blood samples for PK assessments.
<table>
<tr><th>Sr. No.</th><th>Day</th><th>Time point (hour)</th><th>Window period</th></tr>
<tr><td>1</td><td rowspan="4">1</td><td>00.00 (Before dosing)</td><td>Within 10 minutes prior to dosing</td></tr>
<tr><td>2</td><td>4.00</td><td rowspan="2">± 5 minutes</td></tr>
<tr><td>3</td><td>8.00</td></tr>
<tr><td>4</td><td>12.00</td><td rowspan="2">± 10 minutes</td></tr>
<tr><td>5</td><td>2</td><td>24.00</td></tr>
<tr><td>6</td><td>3</td><td>48.00</td><td>± 10 minutes</td></tr>
<tr><td>7</td><td>4</td><td>72.00</td><td rowspan="2">± 1 hour</td></tr>
<tr><td>8</td><td>5</td><td>96.00</td></tr>
<tr><td>9</td><td>6</td><td>120.00</td><td rowspan="4">± 2 hour</td></tr>
<tr><td>10</td><td>7</td><td>144.00</td></tr>
<tr><td>11</td><td>8</td><td>168.00</td></tr>
<tr><td>12</td><td>11</td><td>240.00</td></tr>
<tr><td>13</td><td>15</td><td>336.00*</td><td>Will be collected prior to next dosing of the study drug</td></tr>
</table>
*The blood sample for PK assessment will be collected prior to next dosing of the study drug

Any blood sample drawn before or after the window period to the scheduled time point will be noted as “late blood draw”. Actual blood sampling time points will be recorded in source documents and (e)CRF. Blood samples collected before or later to scheduled time point will be appropriately corrected for time point value during the calculation of PK.</td></tr>
<tr><td>Bioanalysis</td><td>PK and anti-Adalimumab antibody assessment will be done at central laboratory. The procedure for sample handling, storage and analysis will be provided in the central lab manual.</td></tr>
</table>

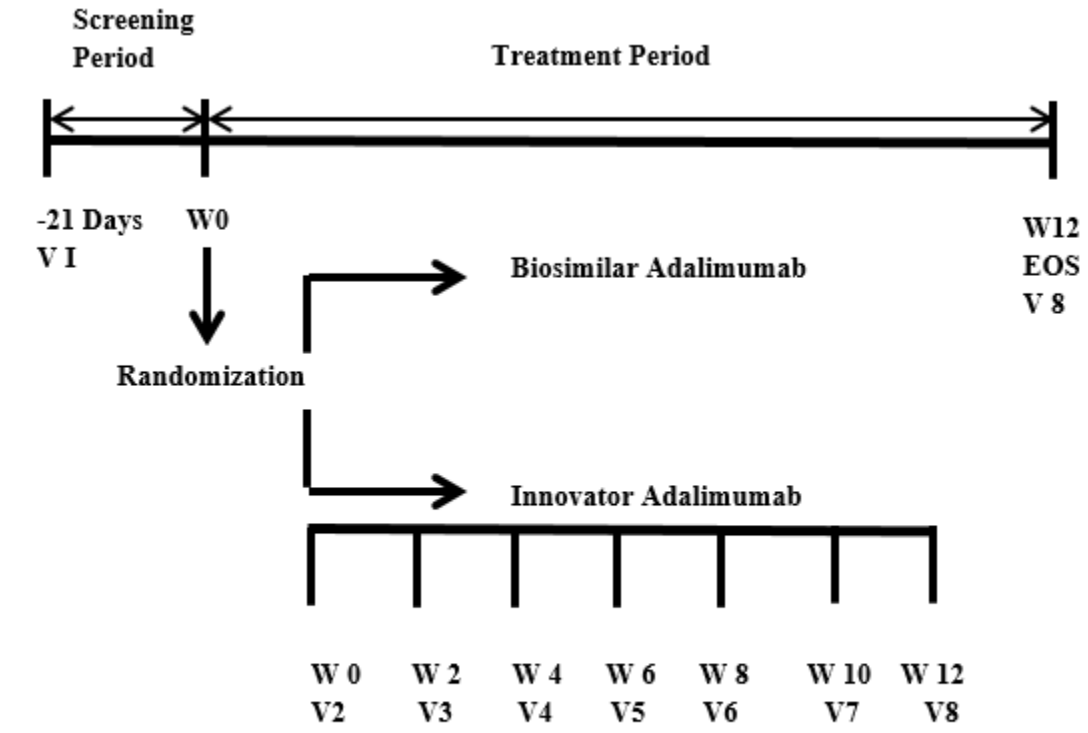
Efficacy Assessment	➢ **ASAS20:** An ASAS20 responder is defined as a subject experiencing improvement of at least 20% and absolute improvement of at least 1 unit (on a scale of 0–10) as compared with baseline in at least 3 of the following 4 domains: 1. Subject's global assessment of disease activity during the previous week (assessed by a 0–10-cm VAS); 2. Subject's assessment of pain during the previous week, represented by the total back pain score (assessed by a 0–10-cm VAS); 3. Function, represented by the Bath Ankylosing Spondylitis Functional Index (BASFI) score (assessed by a 0–10-cm VAS); and 4. Inflammation, represented by the mean of the severity and duration of morning stiffness (i.e., questions 5 and 6 of the BASDAI) (assessed by a 0–10-cm VAS) **5.** Additionally, absence of deterioration (defined as a worsening of at least 20% and an absolute increase of at least 1 unit) in the remaining domain will be documented ➢ **ASAS40:** Improvement of at least 40% and absolute improvement of at least 2 units (on a scale of 0–10) compared with baseline in at least 3 of the 4 domains of the ASAS20 criteria, with no worsening in the remaining domain. ➢ **ASAS70:** Improvement of at least 70% and absolute improvement of at least 2 units (on a scale of 0–10) compared with baseline in at least 3 of the 4 domains of the ASAS20 criteria, with no worsening in the remaining domain. ➢ **ASAS5/6:** At least 20% improvement in 5 of 6 domains: 1. spinal mobility (according to the Bath Ankylosing Spondylitis Metrology Index [BASMI]) and 2. acute-phase reactants (the CRP concentration) 3. 4 domains included in the ASAS20 response criteria. ➢ **BASDAI50:** Measures the severity of fatigue, spinal and peripheral joint pain, localized tenderness, and morning stiffness (both qualitative and quantitative) as assessed on a 0–10-cm VAS. A 50% improvement in the BASDAI score is considered clinically meaningful ➢ **Subject's Global Assessment of Disease Activity:** Subject's assessment of disease activity during the previous week using a 0–10-cm VAS ➢ **Total back pain score:** Subject's assessment of his/her back pain during the previous week using a 0–10-cm VAS ➢ **BASFI:** It consists of 10 questions regarding ability to perform specific tasks assessed on a 0–10-cm VAS

Safety Assessment	Safety assessment will be carried out as outlined in section 11 of this protocol and adverse event (AE) or Serious Adverse Event (SAE) information will be collected and reported as discussed in Section 13 of the protocol. Adverse event and Serious adverse events as and when occur, will be properly recorded, evaluated, managed and reported from signing informed consent till EOS visit. Safety will be evaluated throughout the study based on complete physical examination, including signs and symptoms, adverse event monitoring, vital signs (Blood pressure, Pulse rate, respiratory rate and oral temperature), ECG, anti-Adalimumab antibody assessment and laboratory tests. Any clinically significant abnormalities including those present prior to the start of study medication will be recorded as medical history. Adverse events persisting at the end of the study will be followed up by the investigator until resolution or until a clinically stable endpoint is reached. All AEs will be summarized according to appropriate medical dictionary.
Pharmacokinetic Assessment	A comparative PK assessment will be performed to evaluate PK parameters of Biosimilar Adalimumab versus Innovator Adalimumab in a total of 24 evaluable subjects (i.e. 12 subjects in each treatment group). The following PK parameters will be evaluated in the study: C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $t_{1/2}$
Sample size estimation	The sample size is based on the number of achievers in assessment in Ankylosing spondylitis (ASAS20) response criteria at week 12of 58% with Innovator Adalimumab and Biosimilar Adalimumab in subjects with active Ankylosing spondylitis (AS). Fifty-seven (57) patients in Biosimilar Adalimumab group and one hundred fourteen (114) patients in innovator Adalimumab group will provide 80 % power to detect non-inferiority of Biosimilar Adalimumab versus innovator Adalimumab, using a non-inferiority margin off 20 % and a 1-sided confidence interval of 5 %. Considering a drop-out rate of around 10 %, a total of 192 patients (128 patients in test group and 64 patients in comparator group) will be recruited.
Statistical analysis	A detailed description of the analysis will be provided in the statistical analysis plan (SAP). This plan will include a description of handling of missing and, if applicable, unused and spurious data. The descriptive statistics for continuous variables will be presented with number (n) of non-missing observations, mean, standard deviation, median, and minimum and maximum (range). For categorical data, the descriptive statistics will be presented with number of exposed subjects and number (n) with percentage of observations in various categories of the endpoint, where percentage will be based on the

	exposed subjects. Descriptive analyses will also include graphical presentations of data wherever appropriate. Individual data listings will be also provided. An interim analysis will be conducted after all subjects complete 6 weeks of treatment. The purpose of this interim analysis is to assess initial treatment effects and plan for regulatory submission. No change will be made to the conduct of the study based on the outcome of the interim results, hence no multiplicity adjustment is needed.
Ethical Considerations	The study will commence only after obtaining written approval from the Indian Regulatory (Central Drugs Standard Control Organization) and site Institutional Ethics Committee. The trial will be conducted as per [New Drugs and Clinical Trial Rules, 2019 of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India], [National Ethical guidelines for Biomedical and Health Research involving Human Participants, ICMR (Indian Council of Medical Research (2017)], [ICH (International Council on Harmonization) E6(R2) 'Guideline for Good Clinical Practice'] and the Declaration of Helsinki (Brazil) 2013. The Study will be registered on The Clinical Trials Registry– India.

5.1. STUDY FLOW CHART

Figure 5.1: Flow Chart



Where, W=Week
V= Visit

5.2. STUDY VISIT SCHEDULE (Table 5.1)

Evaluation	Screening	Treatment Period						
Visit	1	2	3	4	5	6	7	8[a]
Week	-3	0	2	4	6	8	10	12
Day	-	1	15	29	43	57	71	85
Window period (day)	NA	NA	±1	±1	±1	±1	±1	±1
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Medical/surgical history	X							
Prior medication history	X							
Demographics (Age, sex, race, ethnicity)	X							
Subject characteristics (Height, weight, BSA)	X							
Physical examination	X	X	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X	X	X	X
ECG	X				X			X
Chest- X-ray(PA view)	X							
X-ray spine (Lateral view and AP)	X[g]							
2D-ECHO	X				X			X
Latent TB (IGRA assessment and Mantoux test)	X							
ESR and CRP	X	X	X	X	X	X	X	X
Serology: HIV, HBV, HCV	X							
Hematology: total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, HCT (PCV), lymphocytes, monocytes, granulocytes (neutrophils, basophils, eosinophils), platelet count, ANC	X				X			X
Biochemistry: ALT, AST, ALP, total bilirubin, Creatinine, CrCl, Serum proteins,	X				X			X
Urinalysis: color, transparency, pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leucocyte esterase, Microscopy: RBC, leucocytes, epithelial cells, bacteria, crystals	X				X			X
Urine pregnancy test [c]	X				X			X
ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50	X	X	X	X	X	X	X	X

Subject's Global Assessment of Disease Activity	X	X	X	X	X	X	X	X
Total Back Pain, BASFI assessment	X	X	X	X	X	X	X	X
Anti-Adalimumab Antibody		X			X			X
Randomization		X						
IP administration		X	X	X	X	X	X	
Subject diary dispensing		X						
Subject diary review			X	X	X	X	X	X [d]
PK blood sample collection [e]		X						
Concomitant Medication(s) [f]	X	X	X	X	X	X	X	X
AE(s)/SAE(s) Recording [f]	X	X	X	X	X	X	X	X

Note: All the investigations will be performed and evaluated prior to IP administration

a. In case of subjects prematurely discontinued from the study/study withdrawal, all assessment will be performed on that visit
b. Vital signs will be recorded in supine position after 5 min of rest: PR (beats/minute), BP measurement (mm/Hg); RR (breaths/minute), and body temperature (°F)
c. Only for females of childbearing potential or who are ≤ 1 year postmenopausal at the time of screening
d. Collection of subject diary
e. Blood sample collection for PK assessment: Refer section blood sample collection
f. Recording of AE/ SAE and concomitant medications will start after signing of informed consent up to EOS
g. MRI will be performed if necessary as per investigator's discretion

6. BACKGROUND AND INTRODUCTION[1]

6.1. Overview of Biosimilar Adalimumab:

Biosimilar Adalimumab has been developed as a similar biological medicinal product to HUMIRA® (adalimumab). Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of subjects with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10} M).

6.2. Potential Risk and Benefits of Innovator Adalimumab

Adverse Reactions:

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections
- Malignancies

Other:

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, lichenoid skin reaction

Vascular disorders: Systemic vasculitis, deep vein thrombosis

6.3. Non-clinical Data of Innovator Adalimumab

- **Nonclinical Toxicology**

  Carcinogenesis, Mutagenesis, Impairment of Fertility

  Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

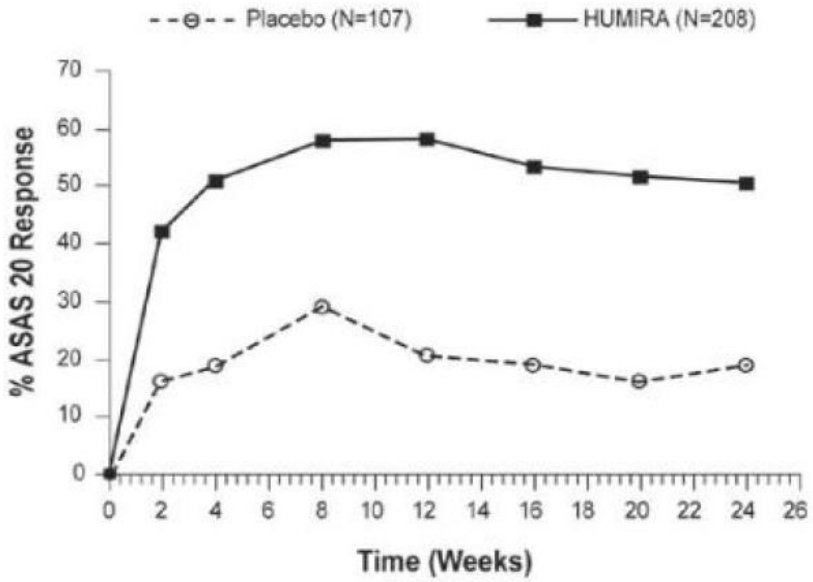
- **Animal Toxicology and/or Pharmacology**

  In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received Adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week).Adalimumab did not elicit harm to the fetuses or malformations.

6.4. Clinical Data of Innovator Adalimumab

The safety and efficacy of HUMIRA 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active ankylosing spondylitis (AS) who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Active AS was defined as patients who fulfilled at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness ≥ 1 hour. The blinded period was followed by an open-label period during which patients received HUMIRA 40 mg every other week subcutaneously for up to an additional 28 weeks. Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown below. Responses of patients with total spinal ankylosis (n=11) were similar to those without total ankylosis.

ASAS 20 response by visit, study AS-I



At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo ($p < 0.001$). Similar responses were seen at Week 24 and were sustained in patients receiving open-label HUMIRA for up to 52 weeks.

A greater proportion of patients treated with HUMIRA (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

Table: Components of Ankylosing Spondylitis Disease Activity

	Placebo N=10		**HUMIRA N=20 8**	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease	65	60	63	38
Total back pain*	67	58	65	37
Inflammation[b]*	6.7	5.6	6.7	3.6
BASFI[c]*	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48 .4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94 .0	93.5	100 .8
CRP[f]*	2.2	2.0	1.8	0 .6

a Percent of subjects with at least a 20 % and 10 -unit improvement measured on a Visual Analog Scale
(VAS) with 0 = "no ne" and 10 0 = "severe"
b mean of questions 5 and 6 of BASDAI (defined in 'd')
c Bath Ankylosing Spondylitis Functional Index
d Bath Ankylosing Spondylitis Disease Activity Index
e Bath Ankylosing Spondylitis Metrology Index
f C-Reactive Protein (mg /dL)
* statistically significant for comparisons between HUMIRA and placebo at Week 24

A second randomized, multicenter, double-blind, placebo -controlled study of 82 patients with ankylosing spondylitis showed similar results.

Patients treated with HUMIRA achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 vs. -1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 vs. 1.9) compared to placebo -treated patients at Week 24.

6.5. Rationale for the Study:

Sponsor has developed Biosimilar Adalimumab. This study will investigate the similarity of Biosimilar Adalimumab of Enzene Biosciences Ltd. and HUMIRA® in subjects with active Ankylosing spondylitis (AS). Thus, the primary objective of the study is the safety and efficacy of Biosimilar Adalimumab in in subjects with active Ankylosing spondylitis (AS) by assessment of ASAS20 response criteria.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1. STUDY OBJECTIVES

Primary Objective:

To compare the efficacy of Biosimilar Adalimumab injection with HUMIRA® (adalimumab) injection, in subjects with active Ankylosing spondylitis (AS) by assessment of ASAS20 response criteria

Secondary Objectives:

- To evaluate the following:
  - ✓ Pharmacokinetics (PK) of Biosimilar versus HUMIRA® (adalimumab) injection
  - ✓ Immunogenicity of Biosimilar and HUMIRA® (adalimumab) injection by assessment of anti-Adalimumab antibody
  - ✓ Safety and tolerability of the investigational product

7.2. STUDY ENDPOINTS

Primary Efficacy Endpoint:

- Number of achievers in Assessment in Ankylosing spondylitis (ASAS20) response criteria at week 6 and week 12, where the achievers are defined as subjects experiencing at least 20 % improvement and an absolute improvement of at least one unit as compared to baseline in at least 3 out of four domains, with no deterioration (defined as a worsening of at least 20 % or an absolute increase of at least one unit from baseline) in the remaining domain.
  The four domains of response criteria are:
  1. Subjects global assessment of disease activity during the previous week (assessed by 0-10-cm VAS),
  2. Subject's assessment of pain during the previous week, represented by total back pain score (assessed by 0-10-cm VAS),
  3. Function, represented by Bath Ankylosing Spondylitis Functional Index (BASFI) score, (assessed by 0-10-cm VAS),
  4. Inflammation, represented by the mean of the severity and duration of morning stiffness (i.e., questions 5 & 6 of the BASDAI assessed by 0-10-cm VAS)

Secondary Efficacy Endpoint:

- Number of subjects achieving ASAS40 response criteria at week 6 and week 12
- Number of subjects achieving ASAS70 response criteria at week 6 and week 12
- Number of subjects achieving ASAS5/6 response criteria at week 6 and week 12
- Number of subjects achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response criteria at week 6 and week 12

- Physician's global assessment of disease activity using 0-10 VAS at week 6 and week 12

Safety Endpoints:

- Treatment emergent serious and non-serious adverse events (AEs)
- Alteration in clinical laboratory parameters
- Assessment of Anti-Adalimumab antibody

PK Endpoint:

- To assess the PK profile of Biosimilar Adalimumab and HUMIRA® (adalimumab) injection in a subset of subjects with AS.

8. INVESTIGATIONAL PLAN

8.1. STUDY DURATION AND DESIGN

This is a prospective, multicenter, randomized, double blind, Phase III study to compare the efficacy and safety of Biosimilar Adalimumab and HUMIRA® (adalimumab) injection in a subset of subjects with active Ankylosing spondylitis (AS).

A total of 192 subjects are planned to be enrolled and the study will be conducted at approximately 30 sites across India. Eligible subjects will be assigned to one of the two groups in 2:1 ratio i.e. Biosimilar Adalimumab or Innovator Adalimumab arm respectively to enter into the treatment period of 12 weeks (a total of 6 doses of the investigational product).

During the treatment period, subjects will be randomized to receive either Biosimilar Adalimumab (Enzene Biosciences Ltd.) or Innovator Adalimumab arm (HUMIRA®). During the treatment period, subjects will report to the clinical site (visit) on Day 1, 15, 29, 43, 57, 71 and 85. A window period of ± 1 day is allowed from Visit 3 to Visit 9.There will be additional visits for those subjects who provide consent for participation in pharmacokinetic (PK) sampling. Details of the study visit schedule and PK schedule are provided in sections 5.1and 5.2 of the protocol respectively**.**

During the study, blood and urine samples will be collected for eligibility, safety (hematology and routine biochemistry and Anti-Adalimumab antibody) assessments.

8.2. RANDOMIZATION AND BLINDING

RANDOMIZATION

Randomization will be performed using Interactive Web Response System (IWRS) in a 2:1 ratio of treatment allotment for test and reference product, respectively. The randomization schedule will be generated using SAS® (SAS Institute Inc., USA) by the statistician.

A total of 192 subjects will be randomized to either of the two treatment groups:

- Group A (N =128): Biosimilar Adalimumab
- Group B (N =64): Innovator Adalimumab

Subjects who fulfill the eligibility criteria will be assigned a randomization code.

BLINDING

This study is a randomized, double blind study. The subjects, the study team (investigators or their designee, sponsor or their designee, contract research organization (CRO) or their designee, local radiologist/designee, the central radiological evaluation committee), or any other relevant personnel involved in conduct and interpretation of the study results will be blinded to the administration of investigational product.

EMERGENCY UNBLINDING

Emergency unblinding is not likely to be necessary in this study, as the active ingredient of both the test and comparator is Adalimumab. However, in the case of medical emergency investigator may request unblinding of study treatment for any individual subject to ensure subjects' safety. The date and reason for unblinding will be documented in the source document (subject's medical record) appropriately. In such cases, the subject will be withdrawn from the study and EOS visit procedures will be conducted. Every attempt must be made to contact the medical monitor/sponsors' designee before the code is unblinded. If the investigator is unable to contact the medical monitor/sponsors' designee prior to unblinding procedure, the investigator must notify the same as soon as possible without revealing the subjects assigned study treatment. Any accidental unblinding will be recorded as a protocol deviation and the subject's continuation or discontinuation from the study will be decided after discussion with sponsor's representative.

9. POPULATION

Approximately 192 subjects with active Ankylosing spondylitis (AS) (128 in Biosimilar Adalimumab and 64 in Innovator Adalimumab study arm), aged between 18 to 65 years (both inclusive) and fulfilling the study selection criteria will be enrolled from approximately 30 sites in India.

9.1. ENTRY CRITERIA

The investigator must ensure that all subjects being considered for the study meet the following (All the inclusion and none of the exclusion) criteria. A subjects' selection will be established by reviewing all inclusion/ exclusion criteria at screening and at baseline.

9.1.1. INCLUSION CRITERIA

The subjects will be included in the study based on the following criteria:

1. Willing to provide voluntary written informed consent.
2. Male or Female subjects between 18 to 65 years of age (both inclusive)
3. Subjects with diagnosis of Axial Ankylosing spondylitis (AS) based on the 1984 modified New York classification criteria, has active AS, as defined by fulfillment of at least 2 of the following 3 conditions at both Screening and Baseline visits:
   a. BASDAI score ≥ 4
   b. Total back pain on a visual analog scale (VAS; 0-10 cm) ≥ 4
   c. Morning stiffness ≥ 1 hour
4. Has inadequate response to or intolerance to one or more non-steroidal anti-inflammatory drugs (NSAIDs) as assessed by the Investigator
5. Willing and able to comply with the protocol.

9.1.2. EXCLUSION CRITERIA

The subjects will be excluded from the study based on the following criteria:

1. Has total spinal ankylosis (bamboo spine)
2. Has undergone spinal surgery or joint surgery involving joints assessed within 2 months prior to screening
3. Has received intra-articular joint injection(s), spinal or paraspinal corticosteroid injection(s) within 28 days prior to Baseline
4. Has prior exposure to any anti-TNF (tumor necrosis factor) therapy at any time
5. Subjects with clinically active TB (Note: In case of subjects with latent TB, the treatment for latent TB should be initiated before the first dose of the investigational product.

6. Subjects with underlying conditions that may predispose them to infection
7. Subjects with history or presence of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease which in the opinion of the investigator does not allow participation of the subject in this study
8. Known hypersensitivity to any component of the investigational product and other medications used in this study
9. Subjects with a non-healed fracture
10. Subject's having the following laboratory results at screening
    a. Absolute neutrophil count (ANC) < 1,500/mm^3
    b. Hemoglobin (Hb) < 10 g/dL
    c. Platelet count < 100,000/mm^3
    d. Total bilirubin level > 1.5 times the upper limit of the normal laboratory range (ULN)
    e. AST and ALT $\geq$ 3 x ULN
    f. Alkaline phosphatase $\geq$ 3 x ULN
    g. Serum Creatinine level > 1.25 x ULN
11. Subjects suffering from acute or chronic infection(s)
12. Subjects with congestive heart failure
13. Positive serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) at screening
14. Subjects of child bearing potential, who are not willing to use adequate contraception during the study period.
15. Female subjects who are pregnant or nursing
16. Has any concurrent disease or condition, which in the opinion of the investigator does not allow participation of the subject in this study
17. Has participated in any other clinical trial and received experimental medications within 4 weeks prior to screening

9.2. DISCONTINUATIONCRITERIA

The subject may be withdrawn/discontinued from the study due to the following reasons:

1. Subject whose condition worsens and require alternate or supplemental therapy for the treatment of AS, as per investigator's discretion
2. Subject's voluntary withdrawal of consent
3. Subject fails to comply with the protocol requirements
4. Subject is found to have entered the study in violation of this protocol
5. Any AE or SAE which requires discontinuation of subject in opinion of investigator
6. Requirement of prohibited medication
7. Subject develops a serious infection or sepsis
8. Subject develops an anaphylactic or other serious allergic reaction
9. Subject develops symptoms suggestive of a lupus-like syndrome

10. Subject with confirmed significant hematologic abnormalities
11. Subject develops congestive heart failure
12. If it is felt in investigator's opinion that it is not in the subject's best interest to continue
13. Study termination by the sponsor
14. Any other justifiable reason, which should be adequately documented

9.3. DATA COLLECTION AND FOLLOW-UP FOR DISCONTINUED SUBJECTS

Investigator should try to obtain the reason from subject withdrawing consent. Reason for withdrawal from the study shall be documented, whenever possible.

EOS Assessment (As per Section 11.5) shall be performed for all prematurely discontinued and withdrawn subjects. For all discontinued subjects, data collected till the time of discontinuation shall be reported in (e)CRF.

Safety data shall be collected for all discontinued subjects, who are discontinued due to an adverse event (AE) or serious adverse event (SAE). In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If the subject is discontinued due to an event subject should be given an appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

9.4. REPLACEMENT OF SUBJECTS

10 % drop out rate has been considered while estimating the sample size, hence subjects who withdraw or are withdrawn from the study will not be replaced. However, a minimum of 171 subjects (in a ratio of 2:1 i.e. 114 subjects in Biosimilar Adalimumab and 57 subjects in Innovator Adalimumab arm) will be enrolled so as to provide relevant data necessary to evaluate the efficacy & safety of the investigational product.

10. STUDY TREATMENTS

A Separate IP management plan may be prepared to describe procedure for handling of IPs

10.1. DESCRIPTION OF INVESTIGATIONAL PRODUCTS

Clinical supplies (both test and reference drug) will be packed, labeled, handled and stored in accordance with current Good Manufacturing Practice of investigational products. Each single use vial will contain 40 mg Adalimumab in 0.4 ml as the active ingredient.

Table: Details of Test Product and Reference Product

IP Details	Test (T)	Reference (R)
Brand Name	Biosimilar Adalimumab	HUMIRA®
Active Ingredient	Adalimumab	Adalimumab
Pharmaceutical Dosage Form and Strength	Injection; single dose vial 40 mg Adalimumab in 0.4 ml solution (40 mg/0.4 ml)	Injection, single dose vial 40 mg Adalimumab in 0.4 ml solution (40 mg/0.4 ml)
Storage Condition	2 to 8 °C	2 to 8 °C
Dose	40 mg every other week	40 mg every other week
Route	Subcutaneous	Subcutaneous

10.2. PRIOR AND CONCOMITANT DRUG/THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject receives during his/her participation in the study should be reported in the (e)CRF. In addition, any diagnostic, therapeutic or surgical procedure performed during the study period (from Screening to EOS), should be recorded. The study-designated physician/investigator should be contacted if there are any questions regarding concomitant or prior therapy (ies).

Prior ther

apy/ies:

The details of the previous anti-AS medication/s (name, dose, and route of administration, date of initiation and stoppage) must be documented.

Concomitant Medications

- Subjects requiring concomitant use of other medications would be treated at the discretion of the Investigator. The details of the medication (name, dose, and route of administration, date/time of administration, and indication for use) must be documented during all the visits.

Permitted Medications

Subjects will be allowed to continue NSAIDs if the dosage had remained stable for at least 2 weeks prior to randomization

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last dose of study drug.

Acceptable methods of contraception are:

a. Oral or parenteral (injection, patch or implant) hormonal contraception which has been used continuously for at least one month prior to the first dose of study medication
b. Intrauterine device (IUD) or intrauterine system (IUD/IUS)
c. Double barrier method of contraception (Condom and occlusive cap or condom and spermicidal agent)
d. Male sterilization (at least 6 months prior to the screening and should be the sole male partner for that subject)
e. Female sterilization (surgical bilateral oophorectomy) or tubal ligation within at least 6 weeks prior to study participation
f. Total abstinence, partial abstinence is not acceptable.

Prohibited Medications

- Any other anti-TNF therapy
- All DMARDs
- Anakinra
- Abatacept
- Live vaccines

10.3. INVESTIGATIONAL PRODUCT ADMINISTRATION

Based on the randomization schedule, investigational product will be administered at the dose of 40mg/0.4 mL subcutaneously (SC) every other week for 12 weeks. Adalimumab is administered by subcutaneous injection. The injection will be administered either in front of subject's thighs or lower abdomen. In case of lower abdomen, do not use the area 2 inches around your belly button (navel).

The investigational product will be administered preferably at the same time throughout the study.

10.4. INVESTIGATIONAL PRODUCT RECEIPT AND STORAGE

Both investigational products (test and reference) will be supplied by the sponsors. in quantities as required by the study. Individual subject containers as required for each study period will be shipped to the sites. The received investigational products will be verified for the sealed condition of packs and adequacy of the label, including product name, strength, number of dosage units, lot number or batch number, expiry date/retest date and storage condition mentioned clearly.

It is the investigator's responsibility to perform the accountability check and verify that the shipment contains all the items noted in the shipment inventory including a check for any damages or unusable investigational product. A record of the inventory received should be documented in the drug accountability form. The investigator or the investigator's designated personnel, should verify the investigational product, and sign and date the drug receipt and maintain a copy of the receipt at the site.

Investigational product labels will be prepared in compliance to the applicable regulatory requirements and will have the following information:

- Name and address of sponsor
- Study number
- Randomization ID
- Week/Day
- Investigator and site details
- Subject details
- Lot number
- Dosing instructions
- Storage conditions
- Manufacturing date
- Expiry /Retest date
- Statement: 'For clinical trial use only"

Temperature will be monitored on a daily basis by the site personnel during conduct of the study. The investigational products will be stored as per the product requirements.

The investigator, site pharmacist or other investigator's assigned personnel allowed to receive, store, issue and dispense the investigational product will be responsible for ensuring that the investigational product to be used in the clinical trial is securely maintained as specified by the sponsor and in accordance with the current Good Clinical Practice.

Investigational products shall be issued and used in accordance with the protocol and it is the investigator's responsibility to ensure that an accurate record of the investigational products issued and returned is maintained.

Under no circumstances will the investigator supply the investigational product to a third party, allow the investigational product to be used other than as directed by this clinical trial protocol, or dispose of the investigational product in any other manner.

10.5. ACCOUNTABILITY OF INVESTIGATIONAL PRODUCTS

The investigator or investigator's designated personnel will maintain a careful record of the inventory and disposition of all agents received for study using a drug accountability form or log. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received
- Amount currently in place
- Label ID number or batch number and use by date or expiry date
- Dates and initials of person responsible for each investigational product inventory
- Amount dispensed, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (e.g., lost, wasted, broken)
- Amount returned to sponsor
- Amount destroyed at study site, if applicable

10.6. RETRIEVAL OFINVESTIGATIONAL PRODUCTS

As the investigational product is an injectable, IP (test or reference) will be administered to the subject at the site during the applicable visit. Any discrepancies between amounts of IP administered, ancillary medications dispensed and returned will be recorded appropriately.

At the completion of the study, there will be a final reconciliation of investigational product shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form. Any discrepancies noted will be investigated, resolved, and documented prior to return unused investigational product.

10.7. UNUSED INVESTIGATIONAL PRODUCTS

Units of investigational products that have not been dispensed will be retained in their original containers. Any product that had been dispensed but not used will be labeled as '**UNUSED'** and returned, along with other unused products to the sponsor at the end of the study.

Note: *If investigational products are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and written authorization has been granted by the sponsor, and the procedures for proper disposal have been established according to applicable regulations, guidelines, Sponsor's instructions and institutional procedures.*

Appropriate records of the disposal must be maintained. The unused study products can only be destroyed after being inspected and reconciled by the responsible study monitor.

11. STUDY PROCEDURES

The study procedures described below will be carried out at the study visits.

11.1. Visit 1 / Screening (Day -21 to -01)

The screening procedures are to be completed within 21 days from the signing of the informed consent form (ICF).

- Written informed consent will be taken from the subject. No trial related procedure will be conducted prior to obtaining written informed consent. As per New Drugs and Clinical Trial Rules 2019, audio-video recording of the informed consent process is not applicable for this study.
- Assessment of subject eligibility as per Inclusion and Exclusion criteria
- Demographic parameters and subject characteristics (age, sex, race, ethnicity, weight [in kg], height, BSA etc) will be noted
- Medical/Surgical history- Relevant medical history will be collected including prior and ongoing medical illnesses, conditions, and surgical procedures.
- Prior Medication history
- Physical examination
- Vital signs measurement (pulse rate [beats/minute], respiratory rate [breaths per minute], systolic & diastolic blood pressure, [mmHg] body temperature [°F]) will be recorded. Vitals will be recorded in supine position after 5 minutes of rest.
- ECG
- Chest X-Ray (PA view)
- X-ray spine (Lateral and AP view) or MRI will be performed if necessary as per investigator's discretion
- 2D-ECHO
- Blood sample collection for the following
  - Hematology- total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, HCT (PCV), lymphocytes, monocytes, granulocytes (neutrophils, basophils, eosinophils), platelet count, ANC
  - Biochemistry- ALT, AST, ALP, total bilirubin, Creatinine, Serum proteins,
  - ESR and CRP
  - Serology- HIV, HBV, HCV
- Urine Pregnancy test- for females of childbearing potential or who are ≤ 1 year postmenopausal
- Urine sample collection for routine urine analysis: color, transparency, pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leucocyte esterase and microscopic examination: RBC, Leucocytes, epithelial cells, bacteria, crystals.
- ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 assessments
- Latent TB test (IGRA assessment and Mantoux test)

Note: In case of subjects with latent TB, the treatment for latent TB should be initiated before the first dose of the investigational product.

- Subject's Global Assessment of Disease Activity
- Total Back Pain, BASFI assessment
- Concomitant medication details
- AE/SAE recording

11.2. Visit 2 (Week 0-Day 1)

- Review of subject eligibility as per Inclusion and Exclusion Criteria on day 1.
- Physical examination
- Vital signs assessment (pulse rate [beats/minute], respiratory rate [breaths per minute], systolic and diastolic blood pressure [mmHg] and body temperature [°F]) will be recorded. Vitals will be recorded in supine position after 5 minutes of rest.
- Subjects fulfilling all inclusion criteria will be randomized by IWRS to one of the two study arms and given a randomization number.
- ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 assessments
- Subject's Global Assessment of Disease Activity
- Total Back Pain, BASFI assessment
- ESR and CRP
- Blood sample collection for Anti-Adalimumab Antibody
- Investigational product (Biosimilar or Innovator Adalimumab) will be administered and subject compliance will be monitored.
- Subject diary dispensing
- Documentation of AEs/SAEs: All the subjects will be instructed to contact their physician in case they have any symptom or complaint.
- Note any changes in concomitant medication.

Note: In case of subjects participating in PK sub-study, the details pertaining to sampling time points during first IP administration is provided in section 11.6of the protocol.

11.3. Visit 3 (Week 2-Day 15)/ Visit 7 (Week 10-Day 71)

- Physical examination
- Vital signs assessment (pulse rate [beats/minute], respiratory rate [breaths per minute], systolic and diastolic blood pressure [mmHg] and body temperature [°F]) will be recorded. Vitals will be recorded in supine position after 5 minutes of rest
- Subject diary check
- ESR and CRP
- ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 assessments

- Total Back Pain, BASFI assessment
- Subject's Global Assessment of Disease Activity
- Investigational product (Biosimilar or Innovator Adalimumab) will be administered and subject compliance will be monitored.
- Documentation of AEs/SAEs: All the subjects will be instructed to contact their physician in case they have any symptom or complaint
- Concomitant medication review and documentation

11.4. Visit 4 (Week 4-Day 29) and Visit 6 (Week 8-Day 57)

- Physical examination
- Vital signs (pulse rate [beats/minute], respiratory rate [breaths per minute], systolic and diastolic blood pressure [mmHg] and body temperature [°F]) will be recorded. Vitals will be recorded in supine position after 5 minutes of rest
- ESR ad CRP
- ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 assessments
- Total Back Pain, BASFI assessment
- Subject's Global Assessment of Disease Activity
- Subject diary check
- Investigational product (Biosimilar or Innovator Adalimumab) and will be administered and subject compliance will be monitored.
- Documentation of AEs/SAEs: All the subjects will be instructed to contact their physician in case they have any symptom or complaint
- Concomitant medication review and documentation

11.5. Visit 5 (Week 6- Day 43)

- Physical examination
- Vital signs (pulse rate [beats/minute], respiratory rate [breaths per minute], systolic and diastolic blood pressure [mmHg] and body temperature [°F]) will be recorded. Vitals will be recorded in supine position after 5 minutes of rest
- ECG and 2D ECHO
- Blood sample collection for Anti-Adalimumab Antibody
- Blood sample collection for the following
  - Hematology- total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, HCT (PCV), lymphocytes, monocytes, granulocytes (neutrophils, basophils, eosinophils), platelet count, ANC
  - Biochemistry- ALT, AST, ALP, total bilirubin, Creatinine, CrCl, Serum proteins
  - ESR and CRP
- Urine Pregnancy test- for females of childbearing potential or who are ≤ 1 year postmenopausal

- Urine sample collection for routine urine analysis: color, transparency, pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leucocyte esterase and microscopic examination: RBC, Leucocytes, epithelial cells, bacteria, crystals
- ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 assessments
- Total Back Pain, BASFI assessment
- Subject's Global Assessment of Disease Activity
- Subject diary check
- Investigational product (Biosimilar or Innovator Adalimumab) and will be administered and subject compliance will be monitored.
- Documentation of AEs/SAEs: All the subjects will be instructed to contact their physician in case they have any symptom or complaint
- Concomitant medication review and documentation

11.6. Tuberculosis Assessment:

- Subjects will be monitored closely for TB during the course of study.
- Subjects will be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Adalimumab.

11.7. Visit 8 (Week 12- Day 85)/ End of study

- Physical examination
- Vital signs (pulse rate [beats/minute], respiratory rate [breaths per minute], systolic and diastolic blood pressure [mmHg] and body temperature [°F]) will be recorded. Vitals will be recorded in supine position after 5 minutes of rest
- ECG and 2D ECHO
- Blood sample collection for the following
  - Hematology- total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, HCT (PCV), lymphocytes, monocytes, granulocytes (neutrophils, basophils, eosinophils), platelet count, ANC
  - Biochemistry- ALT, AST, ALP, total bilirubin, Creatinine, CrCl, Serum proteins,
  - ESR and CRP
- Blood sample collection for Anti-Adalimumab Antibody
- Urine Pregnancy test- for females of childbearing potential or who are ≤ 1 year postmenopausal
- Urine sample collection for routine urine analysis: color, transparency, pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leucocyte esterase and microscopic examination: RBC, Leucocytes, epithelial cells, bacteria, crystals
- ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 assessments
- Subject's Global Assessment of Disease Activity

- Total Back Pain, BASFI assessment
- Subject diary review and collection
- Monitoring and capturing of AEs/SAEs
- Concomitant medication review and documentation

11.8. Blood sample collection for PK assessment

- Blood samples for PK assessment will be collected at following time points:

Sr. No.	Day	Time point (hour)	Window period
1	1	00.00 (Before dosing)	Within 10 minutes prior to dosing
2		4.00	± 5 minutes
3		8.00	
4		12.00	± 10 minutes
5	2	24.00	
6	3	48.00	
7	4	72.00	± 1 hour
8	5	96.00	
9	6	120.00	± 2 hour
10	7	144.00	
11	8	168.00	
12	11	240.00	
13	15	336.00*	Will be collected prior to next dosing of the study drug

- Monitoring and capturing AEs/SAEs, if any

11.9. Unscheduled Visit

During the study, subjects will be free to contact the investigator. Subject can come for Unscheduled Visit anytime during the study duration in case of AEs or aggravation of the existing disorder. During an Unscheduled Visit, laboratory tests and other investigations, if required, will be done at the investigator's discretion.

11.10. SUBJECT COMPLIANCE MONITORING

The investigator or his/her designated and qualified representatives will administer investigational product only to subjects who are eligible in the study in accordance with the protocol. The investigational product must not be used for reasons other than that described in the protocol.

If there are any significant irregularities in compliance in the opinion of the investigator, the subject should be discontinued from the study.

12. ASSESSMENTS

12.1. SAFETY ASSESSMENTS

Safety assessment will be carried out as outlined in section 11 of this protocol and adverse event (AE) or Serious Adverse Event (SAE) information will be collected and reported as discussed in Section 13 of the protocol.

Adverse event and Serious adverse events as and when occur, will be properly recorded, evaluated, managed and reported from signing informed consent till EOS visit.

Safety will be evaluated throughout the study based on complete physical examination, including signs and symptoms, adverse event monitoring, vital signs (Blood pressure, Pulse rate, respiratory rate and oral temperature), ECG, anti-Adalimumab antibody assessment and laboratory tests. Any clinically significant abnormalities including those present prior to the start of study medication will be recorded as medical history. Adverse events persisting at the end of the study will be followed up by the investigator until resolution or until a clinically stable endpoint is reached.

All AEs will be summarized according to appropriate medical dictionary.

12.2. PHARMACOKINETIC ASSESSMENTS

A comparative PK assessment will be performed to evaluate PK parameters of Biosimilar Adalimumab versus Innovator Adalimumab in a total of 24-evaluable subjects (i.e. 12 subjects in each treatment group).

The following PK parameters will be evaluated in the study: C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $t_{1/2}$

13. SUBJECT SAFETY

13.1. ASSESSING, RECORDING AND ANALYZING SAFETY PARAMETERS

13.1.1. Adverse Events

As per Indian GCP guidelines, adverse event (AE) is 'Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given'.

As per ICH-GCP E6(R2) guidelines, adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IP.

Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product. All AEs will be followed up to adequate resolution.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured in the AE section of the(e)CRF pages. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Severity of event

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1-5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 – 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

For evaluating severity, following classification will be used to quantify intensity:

Table 13.1: Severity classification of adverse event

Grade	Description
1	*Mild*: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	*Moderate*: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
3	*Severe or medically significant but not immediately life threatening*: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	*Life threatening consequences*: urgent intervention indicated
5	*Death:* related to AE

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to investigational products

The clinician's assessment of an AE's relationship to study medication is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AE's must have their relationship to investigational product assessed using the terms: Related or Unrelated. In a clinical trial, the study product must always be suspect. This assessment will be based on following criteria:

- Temporal relationship
- Pharmacological plausibility
- Rechallenge and Dechallenge information
- Other confounding factors like underlying concurrent conditions, co-suspects, concomitant medications etc.

If AE is ongoing at any visit, please follow the patient till the event gets resolved or condition gets stabilized.

13.1.2. ADVERSE EVENT OF SPECIAL INTEREST (AESI) of the reference product / Innovator Adalimumab

Serious Infections: pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis

Tuberculosis and Opportunistic Infections: miliary, lymphatic, peritoneal, and pulmonary TB

Liver Enzyme Elevations: ALT elevations ≥ 3 x ULN

Other Adverse Reactions: Headache, rash, Injection site reaction, Back pain, Urinary tract infection, Hypertension

Respiratory: Upper respiratory infection, Sinusitis, Flu syndrome

Gastrointestinal: Nausea, Abdominal pain

Laboratory Tests: Hypercholesterolemia, Hyperlipidemia, Hematuria, Alkaline phosphatase increased

Malignancies

Injection site reactions (erythema and/or itching, hemorrhage, pain or swelling)

13.1.3. SERIOUS ADVERSE EVENT

As per ICH-GCP E6(R2) and Indian GCP guidelines, serious adverse event (SAE) or serious adverse drug reaction is any medical occurrence that at any dose:

No.	Description
1	Results in death
2	Is life threatening: refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.
3	Requires inpatient hospitalization or prolongation of existing hospitalization*

4	Results in persistent or significant disability/incapacity: is defined as a substantial disruption in a person's ability to conduct normal life functions
5	is a congenital anomaly or birth defect
6	Is an important medical event: A medical event that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

* Examples of situations which do not fulfill this criterion in the absence of an AE include, but are not limited to, are as follows:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the site (e.g., stent removal after surgery). This should be recorded in the study file
- A hospitalization for a pre-existing condition that has not worsened
- Hospitalization for social reasons

All SAEs will be recorded on the appropriate SAE form, followed through resolution by the study investigator and must be reviewed and evaluated by a study investigator.

13.1.4. ABNORMAL LABORATORY VALUES OR ABNORMAL CLINICAL FINDINGS

Laboratory abnormalities that are considered clinically significant by the investigator constitute an adverse event and should be recorded on the Adverse Events (e)CRF. Abnormal laboratory values or abnormal clinical findings at the time of screening will be considered as medical history and not AE. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

13.1.5. ASSESSMENT OF OUTCOME OF ADVERSE EVENTS

The outcome of the AEs will be assessed and recorded as per the following categories:

- Recovered/resolved;
- Ongoing (Not resolved or stabilized on follow-up);

- Recovered with sequelae;
- Unknown;
- Death.

13.2. SAFETY REPORTING

Adverse Events:

All Adverse Events regardless of seriousness or relationship to Investigational Product, spanning from the first visit planned in the Clinical Trial Protocol/signature of the informed consent form (i.e., occurring during the screening period even in the absence of any administration of investigational and non-investigational product), up to End of study are to be recorded on the corresponding page of the Case Report Form i.e. AE/ SAE form.

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

Laboratory or vital sign abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

Serious Adverse Events

All SAEs should be immediately (within 24 hours of knowledge of the event) reported by the Investigator to the Licensing Authority, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial and the Ethics Committee that accorded approval to the study protocol, by sending a completed SAE form.

Following this, a due analysis report for all SAEs will have to be submitted by the investigator, to the Licensing Authority, Head of the Institution where the event occurred and Ethics Committee that accorded the protocol within 14 calendar days of the occurrence of the event. In case investigator fails to report any SAE within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the CLA along with the report of the SAE.

A report of SAE, after due analysis will also be submitted by the sponsor to the CLA, Head of the Institution where the event occurred and Ethics Committee that accorded of the protocol within 14 calendar days of occurrence of the event by the sponsor.

The above mentioned process and timelines for initial SAE reporting will also be followed for reporting of all follow-up information received for the SAE.

The further course of action for all SAEs; shall be observed as per current local applicable rules and regulations.

Ethics committee that accorded approval for the protocol will send its review report to CLA for all SAEs within 30 days of its occurrence.

Similarly, all AESIs should be reported within 24 hours of occurrence of the event to the sponsor only. Except for those AESIs which also fulfill the requirement of a SAE, these events will additionally have to be reported as per the local applicable rules and regulations for SAE reporting.

SAE Follow-up

Any follow-up information received for the SAE should be analyzed and reported as per the process and timelines mentioned above for initial SAE reporting.

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the patient returns to normal or consolidation of the patient's condition;

In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized.

This may imply that follow-up will continue after the patient has left the Clinical trial.

Pregnancy:

Pregnancy will lead to permanent treatment discontinuation in all cases. Pregnancy should be reported to sponsor by the investigator within 24 hours of knowledge of pregnancy via telephone or fax or email (immediately). The subject will also be followed to determine the outcome of the pregnancy. Any premature termination of the pregnancy will be reported to sponsor with-in 24hrs.

Overdose:

Overdose is defined as a dose greater than the dose specified in the protocol. Any overdose must be recorded in the AE section of the (e)CRF and the source documents. Any case of over dose leading to SAEs must be reported in an expedited manner using the SAE reporting form. Overdose (with associated symptoms or without any associated symptoms), should be reported as an adverse event using the Preferred Term "OVERDOSE''.

13.3. MEDICAL MONITORING

It is the responsibility of the investigator to oversee the safety of the study at his/her site. A separate Medical Monitoring plan may be prepared for the study. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and

implementation of site data and safety-monitoring plan. For any subject safety or eligibility concerns or protocol related queries, the investigator should contact the medical monitor.

14. STATISTICAL ANALYSIS

A detailed description of the statistical analysis will be provided in the statistical analysis plan (SAP). This plan will include a description of handling of missing and, if applicable, unused and spurious data. The descriptive statistics for continuous variables will be presented with number (n) of non-missing observations, mean, standard deviation, median, and minimum and maximum (range). For categorical data, the descriptive statistics will be presented with number of exposed patients and number (n) with percentage of observations in various categories of the endpoint, where percentage will be based on the exposed patients. Descriptive analyses will also include graphical presentations of data wherever appropriate. Individual data listings will be also provided.

14.1. SAMPLE SIZE ESTIMATION

The sample size is based on the number of achievers in assessment in Ankylosing spondylitis (ASAS20) response criteria at week 12 of 58% with Innovator Adalimumab and Biosimilar Adalimumab in subjects with active Ankylosing spondylitis (AS). Fifty-seven (57) patients in Biosimilar Adalimumab group and one hundred fourteen (114) patients in innovator Adalimumab group will provide 80 % power to detect non-inferiority of Biosimilar Adalimumab versus innovator Adalimumab, using a non-inferiority margin off 20 % and a 1-sided confidence interval of 5 %. Considering a drop-out rate of around 10 %, a total of 192 patients (128 patients in test group and 64 patients in comparator group) will be recruited.

14.2. ANALYSIS POPULATIONS

14.2.1. Intention-to-Treat (ITT) Population

All patients who have been randomized in the study.

14.2.2. Modified Intention-to-Treat (mITT) Population

The mITT population will comprise of all randomized subjects who receive at least one dose of study treatment and have at least one efficacy assessment.

14.2.3. Per Protocol Population

The PP population will comprise of all randomized subjects who complete the study visits as per protocol without any major protocol deviations.

14.2.4. Pharmacokinetic Population

PK analysis will be done in 24 evaluable male subjects who have all PK samples collected.

14.2.5. Safety Population

All randomized subjects who receive at least one dose of study treatment will be included in the safety population.

15. ETHICAL AND REGULATORY STANDARDS

15.1. ETHICAL PRINCIPLES, LAWS AND REGULATIONS

The clinical trial will be conducted as per the principles and requirements of Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, 2013) and are consistent with the ICH-GCP E6(R2) guidelines along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), New Drugs and Clinical Trial Rules, 2019 and ICMR's National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).

15.2. INSTITUTIONAL ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Sponsor or each participating institution/hospital must provide this protocol (protocol amendment, if applicable) and associated documents for the review and approval to Institutional Ethics Committee (IEC) or Institutional Review Board (IRB), registered with CDSCO, for the formal approval of the study conduct. The decision of the IEC/IRB signed by its chairman with IEC composition, concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IEC/IRB members and their affiliate to the sponsor. If requested, a progress report during the trial and a summary of the study at the end of the clinical trial is sent to the IEC/IRB.

15.3. INFORMED CONSENT PROCESS

The investigator or a person designated by the investigator, and under the investigator's responsibility, should completely inform the subjects and/or their families describing this study and providing sufficient information to them for making an informed decision about their participation in this study.

All the subjects should be informed to the complete extent possible about the study, in language and terms they are able to understand. Consent form must be IRB/IEC approved and the patient will be provided the same in local language(s).

Prior to patient's participation in this study, the written informed consent form must be signed, name filled in and personally dated by the patient 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.

As per New Drugs and Clinical Trial Rules 2019, audio-video recording of the informed consent process is not applicable for this study.

Patients may be paid an adequate (IEC/IRB approved) participation fee on account of their participation in the study. In case of withdrawal of a patient before completion of the study, patient will be paid

compensation corresponding to the extent of participation and any controversy pertaining to this will be forwarded to IEC and the decision of IEC will be final as well as binding on both the patients and CRO.

15.4. SUBJECT AND DATA CONFIDENTIALITY

Subject confidentiality along with the information disclosed/provided/produced by the sponsor during the clinical trial, including, but not limited to, the clinical trial protocol, the (e)CRF, ICFs and results are strictly held in trust by the sponsor, sponsor's authorized personnel, investigators and their staff members. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IEC/IRB) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

16. DATA HANDLING AND RECORD KEEPING

16.1. SOURCE DOCUMENTS

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject's memory aid (diaries) or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, laboratories and medico-technical departments involved in the clinical trial.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) guidelines and Indian GCP guidelines along with the regulatory and institutional requirements for the protection of confidentiality of subjects. Sponsor and IRB/IEC will have access to medical and research records. Each site will permit sponsor/sponsor representatives, study monitors, IEC/IRB and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

16.2. CASE REPORT FORMS/ELECTRONIC CASE REPORT FORM

The electronic Case Report/Record Form ((e)CRF) is the primary data collection instrument for the study. All data requested on the (e)CRF must be recorded. All missing data must be explained. The electronic data capture (EDC) system maintains an audit trail on entries, changes or corrections in the (e)CRF.

All the data entries on the (e)CRF will be authenticated by the Investigator.

16.3. DATA CAPTURE METHODS

Authorized staff of the investigators will record the data in the provided study (e)CRF, accurately and in a timely manner. Only the Investigator and authorized team member are entitled to make entries into the (e)CRF and all entries will be made in English.

Data cleaning and processing will be managed through the electronic data capture and data management system. The database development process will include the production of a code book containing annotated (e)CRF screens detailing the variable names used in the database. The EDC system will be programmed to capture all data in a dedicated database through the specified (e)CRF screens in a secure

manner. Clinical Data will be recorded directly into an electronic Case Report Form (eCRF) by assigned site personnel.

All data should be recorded as early as possible within the (e)CRF. Access via the internet to the (e)CRF is defined through permission based roles, for example data entry or read-only. All changes to the (e)CRF are recorded, along with a reason for change, in the system audit trail. Username, Password and web-address will be provided to study personnel.

Edit checks will be built into the design of the (e)CRF screens and global rules will be programmed into the QM (Query Management) system. Validation of the consistency checks will be provided in the data management specification through UAT (User Acceptance Testing).The CDMS automatically tracks any data anomalies such as missing data, outstanding queries, missed visits, unsigned subjects that block data cleaning.

Consistency checks were programmed and run as global rules to produce data queries. All queries were resolved at the clinical site. Any database updates will be managed through authorized person under data management security privileges. Final (e)CRF will be signed by the investigator, either electronically or by hardcopy.

Database management and quality control:

All data will be entered into the EDC system. When the database is complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the sponsor, the Trial Statistician and the Data Manager.

After the data have been entered and verified, various edit checks will be performed by Data Management Team for the purpose of ensuring the accuracy, integrity, and validity of the database against the (e)CRF. These should include:

a. Missing value checks
b. Range checks
c. Consistency checks
d. Sequence checks
e. Probabilistic checks and
f. Protocol adherence checks

It is the responsibility of the study site and investigator to resolve all data queries that arise during data management in a timely manner.

Coding dictionaries:

Coexistent diseases and adverse events will be coded using appropriate medical coding dictionary.

16.4. DATA MANGEMENT TEAM

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

The CRO will serve as the statistical and data coordinating center for the present study and will be responsible for data management, quality review, analysis, and reporting of the study data.

16.5. RECORD RETENTIONS

It is the responsibility of sponsor to make arrangements for safe and secure custody of all study related documents and material for a period of 5years after the completion of the study or submission of the data to the regulatory authority (ies) whichever is later or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period of time, if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator / institution as to when these documents no longer need to be retained.

17. STUDY MONITORING, AUDITING AND INSPECTING

17.1. RESPONSIBILITIES OF INVESTIGATORS

The Investigator(s) and delegated Investigator staff undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules).

The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the (e)CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the subject's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

17.2. RESPONSIBILITIES OF SPONSOR AND STUDY MANAGEMENT

The Sponsor of this Clinical Trial shall take all reasonable steps to ensure proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, integrity and validity of the data recorded on the (e)CRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and subject compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits, will include but not be limited to review of the following aspect: subject informed consent, subject recruitment and follow-up, Source data verification, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, IP allocation, subject compliance with the IP regimen, IP accountability, concomitant therapy use and quality of data.

17.2.1 MONITORING PROCEDURE

17.2.1. A Site Initiation Visit

Site initiation visit will be performed by the Sponsor/CRO before the first subject enrolment at site and after the receipt of ethics committee as well as competent authority approval. Sponsor/CRO will be responsible for providing training to the investigator and appropriate clinical site personnel.

The following study documents must be in place at an investigative site and at Sponsor/CRO before subject enrollment begins:

- Study protocol signed by the Investigator
- Signed Clinical Study Agreement
- Ethics Committee approval letter
- Central Regulatory approval letter
- Translated and English language Subject Information Sheet and Informed Consent Form (ICF) that has been approved by both the Ethics Committee and Sponsor
- Financial Disclosure (if applicable)
- Signed Investigator Undertaking
- Case Report Forms
- Documentation of protocol Training
- Completed Delegated Task List for site
- Insurance Certificate
- Recent signed and dated Curriculum Vitae of Principal Investigator and each of the co-investigators
- Site Activation Confirmation, to begin the subject enrolment at site

17.2.1.B Periodic Monitoring Visit

Site-monitoring visits will be conducted to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, to verify that study records and documents are being properly maintained for the duration of the study. Source data verification will be documented by study monitor by reviewing original source documents for each enrolled subject in order to have an overview of the checks over time. The frequency of the monitoring visits will be determined in a monitoring plan.

17.2.1.C Site Closeout Visit

Once the target enrolment is achieved and all study visits are completed for all the subjects and the (e)CRF data entry is completed, the study monitor will perform a site closeout visit to verify that study documents are complete, that all open actions are closed and that study document archival and record retention requirements are understood by the site. A thorough verification of the study documents, archival of documents and reconciliation and accountability of investigational products will be done during the visit. Additional investigational products and study related material will be returned to Sponsor.

17.3. AUDITING AND INSPECTING

The investigator will permit study-related monitoring, audits and inspections by the IEC/IRB, the sponsor, government regulatory bodies and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator agrees to allow the auditors or inspectors to have direct access to subjects 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 confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

The investigator will ensure the capacity for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, study documents etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and quality assurance offices. As soon as the investigator is notified of a future inspection by the authorities, he/she will inform the sponsor and authorize the sponsor to participate in these inspections. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the investigator to the sponsor.

17.4. QUALITY CONTROL AND QUALITY ASSURANCE

All sites conducting research under the sponsorship of the Enzene Biosciences Ltd. are required to have a plan in place for assuring the quality of the research being conducted. Each site should have Standard Operating Procedures for carrying out clinical trials related activities at the site.

Sponsor or the Sponsor's designee will monitor the study and site activity while ongoing, to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of the subjects are being protected
- Study is conducted in accordance with the currently approved protocol and amendments and any other study agreements, GCP, and all applicable regulatory requirements

18. ADMINISTRATIVE PROCEDURES

The investigator must maintain confidentiality of all study related documents, and takes measures to prevent accidental or premature destruction of these documents. The retention of the study related documents is depicted in section 16.5 (RECORD RETENTIONS) of the present protocol. The site master file and trial master file will be maintained on behalf of sponsor at the site and at CRO respectively, as per their SOPs.

18.1. PROTOCOL AMENDMENTS

Any change or addition to the protocol, other than administrative ones (i.e. typographical or logistical), can only be made in a written protocol amendment that must be approved by Sponsor, CLA where required, and the IRB/IEC. Only amendments that are required for subject safety may be implemented prior to IRB/IEC approval.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a violation of the protocol. In such cases, CRO and Sponsor should be notified of this action and the IRB/IEC at the study site should be informed immediately.

Changes to the protocol affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval but the IRB/IEC must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include:

- Changes in the staff used to monitor trials
- Changes in shipping address for (e)CRF

18.2. PROTOCOL DEVIATIONS AND VIOLATIONS

According to FDA Inspectional Manual, the term “Protocol Deviation” is “A protocol deviation/violation that is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change”. A protocol deviation or violation is any noncompliance with the requirements of clinical trial protocol, SOPs, ICH-GCP-E6(R2) guidelines and New Drugs and Clinical Trial Rules, 2019 (CDSCO) and other applicable regulations and guidelines. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations or violation, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to observe vigilance to identify and report deviations immediately upon identification of the protocol deviation. All deviations must be promptly reported to Sponsor/CRO through written communication. All deviations from the protocol must be addressed in study subject source documents. A completed copy of the protocol deviation form must be maintained in the

regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the local IRB/IEC, if required, per their guidelines. The site investigator / study staff is responsible for adhering to IRB/IEC requirements.

18.3. INSURANCE COMPENSATION

The sponsor certifies that it has taken a liability insurance policy covering this clinical trial. The insurance policy is in accordance with local laws and requirements. A copy of the insurance certificate will be provided to the IEC/IRB. In the case of an injury occurring to the subject during the study, free medical management will be provided to the subjects as long as required or till such time it is established that the injury is not related to the clinical study, whichever is earlier.

18.4. INDEMNITY AGREEMENT AND STUDY FINANCES

Sponsor undertakes to maintain an appropriate clinical study insurance and indemnity policy.

Deviation from the study Protocol-Especially the prescription of a dose other than that scheduled in the study Protocol, other modes of administration, other indication, and longer treatment periods – are not permitted and shall not be covered by the statutory subject Insurance scheme.

18.5. PREMATURE DISCONTINUATION OF THE STUDY

The sponsor on the basis of new information regarding safety or efficacy, reserves the right to terminate the investigational site or this clinical study at any time. However, the sponsor will take the approval of CDSCO before complete termination of the trial. Reasons for termination include, but not limited to, following:

- Unacceptable safety issues
- If the investigator has received from the sponsor all study drugs, means and information necessary to perform the clinical trial and has not included any subject after a reasonable period of time mutually agreed upon, site can be prematurely closed.
- The site can be prematurely closed if there is an event of breach by the investigator of the fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the applicable guidelines for GCP.
- Additionally,
  i. IRB/IEC can terminate the study for the safety of subjects.
  ii. Subsequent review of serious, unexpected, and related AEs by the medical monitor, IEC/IRB, the sponsor(s), or local regulatory authorities may also result in suspension/termination of further trial interventions/administration of study product at a site. The study sponsor(s) retain

the authority to suspend/terminate additional enrollment and study interventions/administration of study product for the entire study, as applicable.

18.6. PROPERTY RIGHTS AND DATA PROTECTION

All information, documents and study drug provided by the sponsor or its assignee are and remain the sole property of the sponsor. The investigator shall not mention any information or the product name in any application for a patent or for any other intellectual property rights. All the results, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the exclusive property of the sponsor. Any investigator involved with this study is obliged to provide the sponsor with complete test results and all data derived from the study. The sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

The data collected during the entire trial will be included in the sponsor database and shall be treated in compliance with the SOPs prepared according to applicable laws and regulations. When archiving or processing the data, sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

18.7. CLINICAL STUDY REPORT

A final clinical study Report will be prepared according to the New Drugs and Clinical Trial Rules, 2019, Table 6 on structure, content and format of Clinical Trial Report. A Final Clinical Study Report will be prepared regardless of whether the study is completed or prematurely terminated.

18.8. PUBLICATION POLICY

It is the responsibility of the sponsor to register this trial on Clinical Trial Registry-India (CTRI). On the basis of the statistical and clinical evaluation of the pooled results across the study centers, a clinical study report will be prepared. This can form the basis of a manuscript for publication in a peer-reviewed journal. The sponsor will hold the right to publish the results of present study at any time. An investigator may seek permission to publish results of the study from the sponsor.

19. REFERENCES

1. USFDA Prescribing Information of HUMIRA® (adalimumab) injection; Abbvie Inc.; Revised: 01/2019
2. EMA draft Guideline On Clinical Investigation Of Medicinal Products For The Treatment Of Ankylosing Spondylitis, CPMP/EWP/4891/03
3. De´sire´e van der Heijde et al., Efficacy and Safety of Adalimumab in Patients With Ankylosing Spondylitis, ARTHRITIS & RHEUMATISM, Vol. 54, No. 7, July 2006, pp 2136–2146
4. New Drugs and Clinical Trial Rules, 2019 of CDSCO (Central Drugs Standard Control organization), Ministry of health and family welfare, Government of India.
5. National Ethical guidelines for Biomedical and Health Research involving Human Participants (2017).
6. ICH (International Conference on Harmonization) E6(R2) 'Guideline for Good Clinical Practice'
7. Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013).
8. Common Terminology Criteria for Adverse Events [CTCAE]; National Cancer Institute, U.S. Department of Health and Human services, Version 5.0, Published: November 27, 2017

20. APPENDICES

20.1. SUBJECT INFORMATION SHEET AND INFORMED CONSENT FORM