

## Inclusion Criteria:

1. Adult men and women over 18 years, who present moderate to severe active RA (rheumatoid arthritis), diagnosed according to ACR/ EULAR 2010 criteria, who have failed prior MTX (methotrexate) therapy. Functional class I to III.
2. Moderate to severe disease activity, according to DAS28 (Erythrocyte Sedimentation Rate-ESR)  $\geq 3.2$ .
3. Must have at least a minimum of 6 tender joints and 8 swollen joints. If a patient has a joint surgery prior to the study, this joint is considered not evaluable throughout the study development.
4. Must have at least, one erosion in the baseline radiograph. Local assessment centers either radiologist or rheumatologist to decide on this criterion will be accepted.
5. Medical Indication to incorporate a biological treatment in their therapy.
6. Treatment with MTX for at least 3 months on dose  $\geq 15$  mg/ week, stable over the last 28 days before the Day 1. Doses lower than 15 mg and greater or equal than 10 mg/ week are accepted in cases with previously documented intolerance.
7. Subjects who have previously received treatment with a biologic (approved or investigational) except etanercept, may participate as long as the corresponding washout time has elapsed prior to the screening interview: At least
  - a. 8 weeks for infliximab (T<sub>1/2</sub> 8 to 9.5 days) and for tocilizumab (T<sub>1/2</sub> 3 to 12 days)
  - b. 10 weeks for adalimumab (T<sub>1/2</sub> 10 to 20 days), Golimumab (T<sub>1/2</sub> 11 to 14 days), certolizumab (T<sub>1/2</sub> 14 days), abatacept (T<sub>1/2</sub> 14 days),
  - c. 1 year for Rituximab (T<sub>1/2</sub> 77,5 days)
  - d. 5 T<sub>1/2</sub> for any other biological product, used for the treatment of rheumatoid arthritis, whether it has been used or not for research.
  - e. Subjects who are receiving leflunomide must have a previous washout of 8 weeks before Day 1, except had have treatment with colestyramine, according to manufacturer indications.
  - f. Can receive non-steroidal anti-inflammatory drugs (NSAIDs) or oral corticoids in doses  $< 10$  mg of prednisone, but treatment must have been stable over the last 28 days.

8 Subjects must be able to self-inject or willing to have a previously assigned caregiver do it for them.

9 Subjects must be able to meet the schedule of visits, understand and comply with other protocol requirements.

10 Women of childbearing age must commit to be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 12

weeks after the last dose of Enbrel®/Enerceptan®. Suitable methods of contraception are oral contraceptives, IUDs (intrauterine device), bilateral tubal ligation, vasectomy or double barrier methods such as condoms or spermicidal diaphragm, sponge, contraceptive foam or gel, heterosexual abstinence. Men should not conceive up to 12 weeks after stopping the MTX

11 Informed consent must be signed before making any study-specific procedure.

#### Exclusion Criteria:

1. Simultaneous treatment with other investigational drug or participation in another clinical study that the investigator considers inadvisable.
2. Women who are pregnant or breastfeeding.
3. Past history of nonresponsive to TNF (tumor necrosis factor) blocking agents or other biologic treatment.
4. Chronic antibiotic therapy, if the investigator considers this may affect the safety of the subject or the assessment of the study results.
5. Any previous or current serious medical conditions that, in the opinion of the investigator, constitute a contraindication for the study treatment, as:
6. Administration of vaccines:
  - a. Subjects who have received a live attenuated vaccine within 3 months prior to the randomization Visit (for example, varicella-zoster, oral polio, rabies, yellow fever vaccines.)
  - b. Subjects who have received the BCG (bacillus Calmette-Guerin) vaccine within 12 months before the Selection.
7. Presence of:
  - a. At the time of the inclusion i. Active infections. ii. Fever ( $\geq 38$  °C) or active, chronic or recurrent infections that require treatment with antibiotics, antiviral, or anti-fungal medications within 4 weeks prior to Screening Visit, or history of frequent recurrent infections unacceptable to the investigator's opinion.
  - iii. Non-healing infected skin ulcers. b. In the previous time: i. Background of recurrent bacterial, viral, fungal (excluding superficial infections or nail bed mycosis), mycobacterial or other severe infections within the last month previous to selection.
  - ii. Hospitalization for infection or Subjects who have received antibiotics intravenously within the last month or orally within the last 2 weeks.
  - iii. Subjects with herpes zoster in the last 2 months.
8. Past history of drug or alcohol abuse within the last year prior to the Screening Visit.

9. Known hypersensitivity to the study drug or history of severe allergy or anaphylactic reaction to monoclonal antibodies or fusion or human proteins.
10. Any condition that, in the investigator opinion, would not allow compliance with the guidelines of the study by the patient.
11. The subject presents absolute contraindications for the use of etanercept, according to the prospectus
12. Presence of significant laboratory abnormalities in the screening visit.