BRIEF SUMMARY OF STUDY RESULTS

1 Study general Information

1.1 Sponsor:

Fundación Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz (FIIS-FJD). Avda. de los Reyes Católicos, 2
28040 - MADRID

1.2 Title

A 3-arm, randomized, open-label, parallel active controlled, multicenter international study to compare the response of ultrasound-assessed synovitis to baricitinib, alone and combined with methotrexate versus etanercept in rheumatoid arthritis patients with inadequate response to methotrexate. Searching for synovium predictors of response.

1.3 Protocol Identification

- Code: BIOP-US
- EudraCT number: 2018-004558-30
- Version and Date (last updated): Version 4.0, 28th August 2019

1.4 Coordinating Investigator

Dra. Esperanza Naredo
Servicio Reumatología, Fundación Jiménez Díaz
Madrid, España

1.5 Investigators and sites

13 centres from 5 different European countries participated in the study:

- 9 in Spain
- 1 in Portugal, 1 in France, 1 in Belgium, and 1 in Germany.

1.6 Design

Low-intervention clinical trial with an authorized drug, multicentre, international, randomised, open-label active comparator-controlled clinical trial searching for synovium predictors of response.

1.7 Objectives

The main objective of the study was to demonstrate non-inferiority of the response of MSKUS-assessed synovitis (i.e. B-mode and Doppler mode synovitis) to baricitinib treatment, alone plus combined with MTX (arm1 + arm2) vs. etanercept plus MTX (arm 3) in IR-MTX patients. Non-inferiority was established to be claimed if changes in MSKUS-assessed synovitis with baricitinib (alone and combined with MTX) after 12 weeks of treatment reached at least 80% of changes in the etanercept + MTX group in the same period using a noninferiority test for two means.

1.8 Study population

As per sample size calculation, 186 adult patients diagnosed with rheumatoid arthritis with moderate to severe disease activity who agree to participate in the study and meet the following criteria were planned to be included in the present study. Finally, and due to COVID-19 pandemic impact on study recruitment, 150 patients were finally included (80% of preplanned sample size).

1.9 Study Chronogram

- Date of First Patient included: 30th January 2020
- Date of Last Patient included: 12th April 2024
- End of study Date: 10th October 2024
- Date of brief study report: October 2025

2 Results Summary

Background. Several clinical trials and real-world studies have shown that baricitinib, a Janus kinase (JAK) 1/JAK2 inhibitor, is clinically effective in treating active rheumatoid arthritis (RA), either as monotherapy or in combination with methotrexate. Ultrasound-assessed synovitis is an imaging marker that has demonstrated both validity and responsiveness.

Objectives. The primary objective of this randomised, active-controlled, international, multicentre, phase IV clinical trial was to demonstrate non-inferiority of the response of ultrasound-assessed synovitis to baricitinib treatment, alone and in combination with methotrexate (MTX), compared to etanercept with MTX in RA.

Methods. Adult patients with active RA and inadequate response to MTX were randomised into three parallel treatment groups: baricitinib monotherapy, baricitinib plus MTX, and etanercept plus MTX. The patients underwent clinical, ultrasound, and local and central laboratory assessments at baseline, 4, 12, and 24 weeks. Ultrasound synovitis was scored 0-3 in B-mode, Doppler mode, and a combination of both in bilateral wrist and metacarpophalangeal joints, plus two additional large joints. The primary endpoint was the change in ultrasound synovitis scores at week 12. Non-inferiority was stated if baricitinib, monotherapy and with MTX, were above the lower limit of the non-inferiority range defined as 80% of the changes observed in etanercept with MTX. Several proinflammatory mediators in serum were analysed at the central Laboratory. Additionally, ultrasound-guided synovial tissue biopsy (UGSTB) of the most ultrasound-determined inflamed peripheral joint was optionally performed at baseline, and the synovial tissue was analysed for histopathological and molecular findings at the central Laboratory

Results. One hundred fifty patients (109 female, 41 male) were randomised: 32.7% assigned to baricitinib monotherapy, 34.7% to baricitinib plus MTX, and 32.7% to etanercept plus MTX. All clinical and ultrasound variables showed significant improvement starting from week 4 across the three treatment arms ($p<0.05$). The changes in ultrasound scores at the time points were similar across the three treatment groups ($p>0.05$). Non-inferiority of baricitinib, monotherapy and with MTX, was confirmed against etanercept with MTX for all ultrasound variables at week 12 ($p<0.05$). Moreover, 95% confidence interval of the mean change at week 12 was above lower limit of non-inferiority range for all ultrasound measurements.

The treatments evaluated in this study produced different effects on systemic inflammation, endothelial activation, and tissue remodeling pathways, with more favorable modulation of inflammatory biomarkers generally observed in the combined baricitinib and etanercept plus MTX groups. Likewise, our results suggested that the

different treatment strategies exerted distinct effects on lipid metabolism. Histopathological and gene expression analyses of synovial tissue are described.
There were three serious adverse events (SAEs) in three participants (two in the baricitinib plus MTX group and one in the etanercept plus MTX group) with favourable outcome**.**
The incidence of non-serious AEs (125 in total) during the study period varied numerically across the three treatment groups, although the differences were not statistically significant (p=0.188); most of them (85.6%) were mild, and 68.8% were reported as unlikely or unrelated to the medication. The most frequent AEs were mild respiratory infections.
Conclusions. The response of ultrasound-assessed synovitis to baricitinib, alone or in combination with MTX, was non-inferior to that of etanercept with MTX. The results of this study reinforce the already clinically demonstrated efficacy of baricitinib in patients with active rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs

A more detailed study report is being prepared for publication in the following weeks. Once ready, it will be uploaded in the Spanish Registry of Clinical Studies.