Fenebrutinib versus Placebo or Adalimumab in Rheumatoid Arthritis: A Randomized, Double-Blind, Phase II Trial (ANDES Study)

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SUPPLEMENTARY MATERIAL
METHODS

Randomization and blinding

The sponsor provided the specifications of the randomization algorithm to the interactive voice and web response system (IxRS) vendor. For cohort 1, the randomization was stratified by geographic region. For cohort 2, the randomization was stratified by geographic region and prior exposure to a non-TNF inhibitor biologic.

To prevent potential blind breaks due to observed efficacy or laboratory changes, a dual assessor approach was used to evaluate efficacy and safety. Sites did not receive data related to selected laboratory parameters after screening in order to maintain the blind. PK samples were collected from patients assigned to all arms in order to maintain blind. Sponsor personnel responsible for performing PK assays were unblinded to identify appropriate PK samples to be analyzed. If unblinding was necessary for patient management (such as for a serious adverse event), the investigator was able to break the treatment code by contacting the IxRS.

Statistical analysis

The purpose of both cohorts was to estimate the treatment effect of fenebrutinib as assessed by ACR response, and evaluate the underlying mechanistic effects of BTK inhibition. In cohort 1, a sample size of 480 patients was targeted (110 per group except for the fenebrutinib 50 mg once daily dose group with 40 patients) to give 80% power to detect a 15% difference between adalimumab and each fenebrutinib regimen (150 mg once daily and 200 mg twice daily) for a ACR50 response rate of up to 50% with adalimumab, with a two-sided type-one error rate of 0.2 with the χ² test with continuity correction. The 50 mg once daily fenebrutinib group was powered for comparison with placebo but not with adalimumab. No adjustment for multiple comparisons was made. In cohort 2, approximately 120 patients (60 per group) provided approximately 80% power to detect a difference of 20% for an
ACR50 response rate of up to 20% in the placebo group with a two-sided type-one error rate of 0.2 using Fisher’s exact test. The conservative estimate for the planned sample size for cohort 2 was approximately 120 patients with a minimum sample size of 100 patients being sufficient to determine a treatment effect in this signal seeking cohort.

All efficacy analyses were performed on the intent-to-treat population (all randomized patients). Primary and key secondary efficacy analyses were carried out using the Cochran-Mantel-Haenszel test with adjustment for stratification factors. Non-responder imputation was used for patients who discontinued prior to week 12 and for those for whom an ACR response could not be determined. Patients who received >10 mg/day corticosteroid or increased the dose between weeks 8 and 12 were non-responders for the primary analysis. For continuous endpoints, such as DAS28, ESR, CRP, and HAQ-DI scores, comparisons were made with the use of analysis of covariance with adjustments for treatment, stratification factors, and baseline values.

For the exploratory, pre-specified biomarker analyses, the Kruskal-Wallis H test was used to assess the difference in biomarker change over time for fenebrutinib or adalimumab versus placebo. The test adjusted for baseline values and used a two-sided false discovery rate (FDR controlled Benjamini Hochberg) type I error threshold of 5%. The proportion of patients (with 95% confidence interval) achieving an ACR50 response or change in DAS28 score at week 12 relative to baseline levels of RF split into quartiles were compared.
**Supplementary Table 1. Description of efficacy measures**

| Efficacy measures                | Definition                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| ACR20, ACR50, and ACR70          | 20 0 70 of tender (66 joints) and swollen joints (68 joints) 20 0 70 3 of the remaining ACR core set measures, including patient global assessment, physician global assessment, functional ability measure (HAQ-DI), visual analog pain scale, and ESR or CRP, respectively, for ACR20, ACR50, and ACR70. |
| DAS28-4 (CRP) and DAS28-4 (ESR)  | Disease activity scores using tender joint counts 28 joints, swollen joint counts 28 joints, high sensitivity C-reactive protein [DAS28-4 (CRP)] or erythrocyte sedimentation rate [DAS28-4 (ESR)] and patient’s global assessment of disease activity on a visual analog scale (0-100 mm). |
| DAS-LDA and DAS-remission        | Disease activity scores for low disease activity (DAS-LDA) and remission (DAS-remission) included DAS scores of <3.2 and <2.6, respectively. |
| CDAI and SDAI                    | Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI). Remission by CDAI score was CDAI \( \leq 2.8 \). Remission by SDAI score was SDAI \( \leq 3.3 \). |
| Boolean remission                | Boolean-based definition of ACR/EULAR remission included tender and swollen joint count, CRP, and patient global assessment, with all scores at \( \leq 1 \). |
| SF-36 and FACIT-Fatigue          | Physical and mental component summary scores of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the fatigue scale according to Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue scale). |

1Prevoo et al. Arthritis Rheum. 1995;38:44-8.
**Supplementary Table 2.** Additional baseline characteristics and disease activity measures

| Region, n (%) | Cohort 1 (MTX-IR) | Placebo (n=110) | Fenebrutinib 50 mg once daily (n=40) | Fenebrutinib 150 mg once daily (n=109) | Fenebrutinib 200 mg twice daily (n=110) | Adalimumab 40 mg every other week (n=111) | Cohort 2 (TNF-IR) | Placebo (n=50) | Fenebrutinib 200 mg twice daily (n=48) |
|---------------|------------------|----------------|-------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------------|------------------|---------------|----------------------------------------|
| EEU/Asia      |                  | 66 (60)        | 33 (83)                             | 65 (60)                              | 66 (60)                                | 65 (59)                                   |                  | 30 (60)       | 30 (63)                  |
| LATAM         |                  | 40 (36)        | 5 (13)                              | 40 (37)                              | 40 (36)                                | 41 (37)                                   |                  | 15 (30)       | 15 (31)                  |
| USA           |                  | 4 (4)          | 2 (5)                               | 4 (4)                                | 4 (4)                                  | 5 (5)                                     |                  | 5 (10)        | 3 (6)                    |
| Previous biologic DMARDs |            |                |                                     |                                      |                                        |                                            |                  |               |                          |
| 1 TNF inhibitor, n (%) |        | N/A            | N/A                                 | N/A                                  | N/A                                    | N/A                                       |                  | 43 (86)       | 41 (85)                  |
| 2 TNF inhibitors, n (%) |       | N/A            | N/A                                 | N/A                                  | N/A                                    | N/A                                       |                  | 5 (10)        | 5 (10)                  |
| Previous biologic non-TNF |            |                |                                     |                                      |                                        |                                            |                  |               |                          |
| Patients, n (%) |              | N/A            | N/A                                 | N/A                                  | N/A                                    | N/A                                       |                  | 6 (12)        | 8 (16)                  |
| Phys. global assessment |          | n = 110        | 40                                  | 109                                  | 110                                    | 111                                       |                  | 50             | 48                       |
| Mean (SD)     |              | 62.4 (16.6)    | 64.2 (14.0)                         | 63.8 (14.8)                          | 65.1 (16.3)                            | 66.0 (18.8)                               |                  | 70.2 (20.5) | 64.6 (14.9)             |
| Pts. global assessment |        | n = 107        | 40                                  | 108                                  | 108                                    | 110                                       |                  | 49             | 48                       |
| Mean (SD)     |              | 60.9 (21.2)    | 66.1 (15.6)                         | 67.3 (17.9)                          | 65.0 (18.3)                            | 65.6 (22.7)                               |                  | 70.7 (19.6) | 65.4 (20.6)             |
| Pts. assessment of pain |         | n = 107        | 40                                  | 108                                  | 108                                    | 110                                       |                  | 49             | 48                       |
| Mean (SD)     |              | 63.5 (22.8)    | 65.3 (14.4)                         | 66.6 (18.2)                          | 65.5 (20.4)                            | 64.0 (23.0)                               |                  | 67.5 (22.5) | 66.4 (21.0)             |
| Methotrexate at baseline |          | Patients, n = 110 | 40                                  | 109                                  | 110                                    | 111                                       |                  | 49*            | 49*                      |
| Dose (mg/week), mean (SD) |        | 16.1 (3.4)     | 16.3 (3.2)                          | 16.2 (3.3)                           | 16.2 (3.8)                             | 15.7 (3.2)                                |                  | 16.6 (3.2)   | 15.7 (3.7)              |
| Corticosteroids at baseline |          | Patients, n = 67 | 14                                  | 63                                   | 67                                      | 62                                        |                  | 16*            | 19*                      |
| Dose (mg/day), mean (SD) |        | 7.4 (3.1)      | 7.8 (3.0)                           | 7.6 (2.7)                            | 7.9 (2.5)                              | 7.8 (2.4)                                 |                  | 8.3 (2.4)    | 7.5 (2.8)               |
| SF-36 at baseline |            | Patients, n = 105 | 39                                  | 102                                  | 107                                    | 109                                       |                  | 48             | 45                       |
| Physical component score, mean (SD) |        | 31.0 (6.1)     | 29.3 (6.2)                          | 31.0 (5.7)                           | 30.1 (6.6)                             | 29.5 (6.2)                                |                  | 30.6 (6.0)   | 31.3 (6.0)              |
| Patients, n | Mental component score, mean (SD) | FACIT-fatigue at baseline | Patients, n | Score, mean (SD) |
|------------|-----------------------------------|---------------------------|------------|-----------------|
|            |                                   |                           |            |                 |
| 105        | 46.0 (12.4)                       |                           | 102        | 43.9 (11.9)     |
| 39         | 44.3 (13.0)                       |                           | 106        | 44.9 (14.4)     |
| 102        | 43.9 (11.9)                       |                           | 109        | 45.0 (12.3)     |
| 106        | 44.9 (14.4)                       |                           | 48         | 41.1 (11.8)     |
| 109        | 45.0 (12.3)                       |                           | 45         | 46.9 (11.4)     |
| 48         | 41.1 (11.8)                       |                           | 45         | 46.9 (11.4)     |
| 45         |                                   |                           |            |                 |

EEU: Bolivia, Russia, Serbia, and Ukraine; LATAM: Argentina, Brazil, Colombia, and Mexico; Asia: Korea; Phys: Physician; Pts: Patients.

*Cohort 2 groups are $n=50$ for placebo and $n=48$ for fenebrutinib in the intent-to-treat population; one placebo patient received fenebrutinib in error. Thus the safety population has 49 patients in each arm. Methotrexate and corticosteroid are summarized based on the safety population.
### Supplementary Table 3. Secondary efficacy endpoints

| Week 12 Response | Placebo | Fenebrutinib 50 mg once daily (n=40) | Fenebrutinib 150 mg once daily (n=109) | Fenebrutinib 200 mg twice daily (n=110) | Adalimumab 40 mg every other week (n=111) | Placebo | Fenebrutinib 200 mg twice daily (n=48) |
|------------------|---------|--------------------------------------|----------------------------------------|-----------------------------------------|--------------------------------------------|---------|--------------------------------------|
| **DAS28-4 ESR**  |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 99      | 36                                   | 94                                     | 95                                      | 106                                        | 44      | 47                                   |
| Change from baseline, mean (SD) | -1.5 (1.3) | -1.8 (1.0) | -2.1 (1.4) | -2.1 (1.1) | -2.1 (1.1) | -1.1 (1.2) | -1.9 (1.2) |
| **DAS remission*** |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 110     | 40                                   | 109                                    | 110                                     | 111                                        | 90      | 48                                   |
| Responders, n (%)| 4 (4)   | 1 (3)                                | 8 (7)                                  | 9 (8)                                   | 10 (9)                                    | 2 (4)   | 2 (4)                               |
| 95% CI (%)       | (0-7)   | (0-7)                                | (2-12)                                 | (3-13)                                  | (4-14)                                    | (0-9)   | (0-10)                              |
| \(P\) value vs. PBO | -       | 0.7134                               | 0.2635                                 | 0.1749                                  | 0.1213                                    | -       | 0.7848                              |
| **DAS low disease activity*** |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 110     | 40                                   | 109                                    | 110                                     | 111                                        | 50      | 48                                   |
| Responders, n (%)| 4 (4)   | 3 (8)                                | 21 (19)                                | 16 (15)                                 | 19 (17)                                   | 2 (4)   | 7 (15)                              |
| 95% CI (%)       | (0-7)   | (0-16)                               | (12-27)                                | (8-21)                                  | (10-24)                                   | (0-9)   | (5-25)                             |
| \(P\) value vs. PBO | -       | 0.5490                               | 0.0003                                 | 0.0044                                  | 0.0010                                    | -       | 0.0584                              |
| **CDAI**         |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 99      | 36                                   | 95                                     | 94                                      | 105                                        | 44      | 47                                   |
| Change from baseline, mean (SD) | -17.0 (16.2) | -17.0 (11.2) | -22.1 (12.2) | -22.1 (11.8) | -22.2 (11.8) | -12.2 (12.1) | -20.4 (13.2) |
| **SDAI**         |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 99      | 36                                   | 94                                     | 94                                      | 103                                        | 43      | 47                                   |
| Change from baseline, mean (SD) | -17.5 (16.7) | -17.5 (11.4) | -22.9 (12.5) | -23.2 (12.5) | -23.3 (12.0) | -12.9 (12.6) | -22.0 (13.8) |
| **Boolean remission** |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 102     | 37                                   | 98                                     | 97                                      | 108                                        | 45      | 47                                   |
| Responders, n (%)| 1 (1)   | 0 (0)                                | 2 (2)                                  | 4 (4)                                   | 7 (7)                                      | 1 (2)   | 4 (9)                               |
| 95% CI (%)       | (0-3)   | (0-0)                                | (0-5)                                  | (0-8)                                   | (2-11)                                    | (0-7)   | (1-16)                             |
| \(P\) value vs. PBO | -       | 0.8787                               | 0.7101                                 | 0.2425                                  | 0.0559                                    | -       | 0.2457                              |
| **SF-36**        |         |                                      |                                        |                                         |                                            |         |                                      |
| Patients, n      | 99      | 35                                   | 98                                     | 100                                     | 106                                        | 44      | 45                                   |
| Physical score, change from | 3.5 (6.8) | 5.6 (6.0) | 5.7 (6.9) | 6.6 (7.5) | 6.4 (6.4) | 1.8 (6.4) | 5.4 (7.5) |
|                  | baseline, mean (SD) | Patients, n | 99  | 36  | 98  | 101 | 106 | 43  | 45  |
|------------------|---------------------|-------------|-----|-----|-----|-----|-----|-----|-----|
| Mental score, change from baseline, mean (SD) | 4.3 (10.5) | 7.0 (9.3) | 4.9 (10.6) | 6.9 (12.1) | 6.5 (10.8) | 5.1 (10.1) | 5.8 (10.2) |
| FACIT-fatigue     | Patients, n         | 99  | 36  | 94  | 94  | 107 | 45  | 47  |
| Change from baseline, mean (SD)                | 7.1 (10.9) | 9.0 (10.6) | 8.2 (10.2) | 9.0 (10.0) | 9.6 (9.0) | 5.7 (9.2) | 8.9 (9.6) |

*Non-responder imputation was used for this analysis.
**Supplementary Table 4.** Details of serious adverse events

| Cohort, dose                        | Patient                          | Adverse event preferred term | NCI CTCAE Grade | Onset, study day | Duration (days) | Action with fenebrutinib/placebo | Action with adalimumab/placebo | Outcome                  |
|-------------------------------------|----------------------------------|-----------------------------|-----------------|-----------------|----------------|---------------------------------|------------------------------|--------------------------|
| Cohort 1, fenebrutinib 150 mg once daily | 55 yr female, white              | Pneumonia                   | 3               | 15              | 25             | Withdrawn                       | Withdrawn                   | Recovered/resolved       |
| Cohort 1, fenebrutinib 200 mg twice daily | 44 yr female, white              | Pyelonephritis acute        | 2               | 59              | 14             | Withdrawn                       | Withdrawn                   | Recovered/resolved       |
|                                    | 49 yr female, white              | Cellulitis                  | 3               | 69              | 13             | Withdrawn                       | Withdrawn                   | Recovered/resolved       |
|                                    | 70 yr female, American Indian or Alaska Native | Myocardial infarction     | 5               | 74              | 1              | Not applicable                  | Not applicable              | Death*                   |
| Cohort 1, placebo                  | 68 yr female, white              | Pneumonia                   | 3               | 22              | 33             | Withdrawn                       | Withdrawn                   | Recovered/resolved       |
|                                    |                                 | Pleural effusion            | 3               | 22              |                | Not applicable                  | Not applicable              | Recovered/resolved       |
|                                    |                                 | Chronic obstructive pulmonary disease | 3               | 55              | 11             | Not applicable                  | Not applicable              | Recovered/resolved       |
| Cohort 1, adalimumab               | 51 yr female, American Indian or Alaska Native | Seizure                   | 2               | 1               | 8              | Withdrawn                       | Withdrawn                   | Recovered/resolved       |
|                                    | 40 yr female, white              | Small intestinal obstruction | 1               | 59              | 4              | Interrupted                     | Not changed                 | Recovered/resolved       |
Prior to the event of myocardial infarction, the patient was taking methotrexate (15 mg/week). The most recent dose of fenebrutinib was administered on Study Day 65. On Study Day 74, at 01:00 am, the patient experienced general discomfort and unspecified chest pain. Reportedly, she did not want to go to the hospital hoping that the pain would improve. She self-medicated with paracetamol and subsequently slept. The same day when she woke up at 08:00 am, she experienced suffocation, sweating with ongoing chest pain. The patient decided to go to the emergency room immediately. On the way to the hospital, she experienced intense chest pain and shortness of breath and a few minutes later, at 09:00 am, she died. The death was attributed to myocardial infarction. It was reported that when the patient arrived at the hospital, she had no vital signs and therefore, no tests/procedures were performed. The death certificate stated the possible cause of death as natural. An autopsy was not performed.
**Supplementary Table 5.** Laboratory data for post-baseline NCI CTCAE by worst grade for patient

|                      | **Cohort 1 (MTX-IR)** |                      |                      | **Cohort 2 (TNF-IR)** |                      |                      |
|----------------------|-----------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|
|                      | Placebo               | Fenebrutinib         |                     | Placebo               | Fenebrutinib         |                     |
|                      | (n=110)               | 50 mg once daily     |                     | (n=50)*               | 200 mg twice daily   |                     |
|                      |                       | (n=40)               |                     |                       | (n=49)               |                     |
| Alanine aminotransferase (U/L) |                     |                      |                     |                       |                      |                     |
| Patients, n          | 110                   | 39                   | 109                  | 110                   | 109                  | 49                    |
| Grade 1, n (%)       | 20 (18.2)             | 7 (17.9)             | 22 (20.2%)           | 23 (20.9)             | 20 (18.3)            | 8 (16.3)              |
| Grade 2, n (%)       | 1 (0.9)               | 0                    | 0                    | 0                     | 0                    | 0                     |
| Grade 3, n (%)       | 0                     | 0                    | 1 (0.9%)             | 3 (2.7%)              | 1 (0.9)              | 0                     |
| Aspartate aminotransferase (U/L) |                     |                      |                     |                       |                      |                     |
| Patients, n          | 110                   | 39                   | 109                  | 110                   | 109                  | 49                    |
| Grade 1, n (%)       | 16 (14.5)             | 8 (20.5)             | 15 (13.8)            | 14 (12.7)             | 18 (16.5)            | 5 (10.2)              |
| Grade 2, n (%)       | 1 (0.9)               | 0                    | 0                    | 2 (1.8)               | 2 (1.8)              | 0                     |
| Grade 3, n (%)       | 0                     | 0                    | 0                    | 0                     | 0                    | 0                     |
| Creatinine (umol/L)  |                       |                      |                     |                       |                      |                       |
| Patients, n          | 110                   | 39                   | 109                  | 110                   | 109                  | 49                    |
| Grade 1, n (%)       | 77 (70)               | 28 (71.8)            | 79 (72.5)            | 93 (84.5)             | 86 (78.9)            | 31 (63.3)             |
| Grade 2, n (%)       | 0                     | 1 (2.6)              | 7 (6.4)              | 3 (2.7)               | 3 (2.8)              | 2 (4.1)               |
| Grade 3, n (%)       | 0                     | 0                    | 0                    | 1 (0.9)               | 0                    | 0                     |

*Cohort 2 groups in the intent-to-treat population are n=50 for placebo and n=48 for fenebrutinib. One placebo patient received fenebrutinib in error.

The safety analysis population therefore has n=49 in each of the two groups.
Supplementary Table 6. Laboratory data for change from baseline to week 12

| Mean change from baseline to week 12 | Placebo (n=110) | Fenebrutinib 50 mg once daily (n=40) | Fenebrutinib 150 mg once daily (n=109) | Fenebrutinib 200 mg twice daily (n=110) | Adalimumab 40 mg every other week (n=111) | Placebo (n=49)* | Fenebrutinib 200 mg twice daily (n=49)* |
|-------------------------------------|-----------------|-------------------------------------|---------------------------------------|-----------------------------------------|---------------------------------------------|-----------------|-----------------------------------------|
| Alanine aminotransferase (U/L)      |                 |                                     |                                       |                                         |                                             |                 |                                         |
| Patients, n                         | 103             | 36                                  | 97                                    | 100                                     | 106                                         | 44              | 47                                      |
| Change, mean (SD)                   | 0.2 (11.6)      | -1.2 (9.7)                          | 1.9 (10.6)                            | 2.1 (12.4)                              | 1.9 (22.9)                                  | -1.0 (10.4)     | 4.4 (13.8)                             |
| Aspartate aminotransferase (U/L)    |                 |                                     |                                       |                                         |                                             |                 |                                         |
| Patients, n                         | 103             | 36                                  | 97                                    | 100                                     | 105                                         | 43              | 47                                      |
| Change, mean (SD)                   | 0.7 (7.8)       | 0.1 (18.1)                          | 1.2 (8.1)                             | 1.7 (8.5)                               | 0.9 (13.2)                                  | -3.3 (12.6)     | 2.5 (7.2)                             |
| Bilirubin (µmol/L)                  |                 |                                     |                                       |                                         |                                             |                 |                                         |
| Patients, n                         | 102             | 36                                  | 97                                    | 100                                     | 105                                         | 43              | 47                                      |
| Change, mean (SD)                   | 0.4 (2.7)       | 0.3 (3)                             | 0.7 (2.9)                             | 0.2 (2.4)                               | 0.3 (2.7)                                   | -0.4 (2.1)      | 0.5 (3.0)                             |
| Creatinine (µmol/L)                 |                 |                                     |                                       |                                         |                                             |                 |                                         |
| Patients, n                         | 103             | 36                                  | 97                                    | 101                                     | 107                                         | 44              | 48                                      |
| Change, mean (SD)                   | -1.0 (9.5)      | -0.4 (9.5)                          | 3.9 (9.8)                             | 8.6 (38.7)                              | 1.4 (8.5)                                   | -0.4 (8.7)      | 5.1 (12.4)                             |
| Hemoglobin (g/L)                    |                 |                                     |                                       |                                         |                                             |                 |                                         |
| Patients, n                         | 97              | 36                                  | 97                                    | 95                                      | 104                                         | 40              | 42                                      |
| Change, mean (SD)                   | -0.6 (7.5)      | -0.7 (9.5)                          | 0.4 (9.8)                             | 0.2 (10.5)                              | 2.1 (9.5)                                   | -2.4 (10.3)     | 0.0 (11.2)                             |
| LDL cholesterol (mmol/L)            |                 |                                     |                                       |                                         |                                             |                 |                                         |
| Patients, n                         | 95              | 33                                  | 94                                    | 95                                      | 94                                          | 42              | 48                                      |
| Change, mean (SD)                   | 0.10            | -0.04 (0.50)                        | -0.09 (0.52)                          | -0.12 (0.62)                            | -0.02 (0.54)                                 | 0.10            | -0.07 (0.61)                           |
|                          | Lymphocytes ($10^9$/L), absolute | Neutrophils ($10^9$/L), segmented, absolute |
|--------------------------|----------------------------------|----------------------------------------------|
| Patients, $n$            | 97                               | 97                                           |
| Change, mean (SD)        | 0.06 (0.56)                      | -0.34 (1.85)                                 |
|                          | 0.17 (0.47)                      | -0.14 (1.97)                                 |
|                          | 0.13 (0.75)                      | -0.18 (2.44)                                 |
|                          | 0.16 (0.65)                      | -0.69 (2.02)                                 |
|                          | 0.41 (0.67)                      | -0.70 (2.07)                                 |
|                          | 0.01 (0.51)                      | 0.49 (1.59)                                  |
|                          | 0.09 (0.65)                      | -0.42 (1.93)                                 |

*Cohort 2 groups in the intent-to-treat population are $n=50$ for placebo and $n=48$ for fenebrutinib. One placebo patient received fenebrutinib in error.*
Supplementary Figure 1. ANDES study design

| Arm A | FEN 50 mg QD + PBO |
| Arm B | FEN 150 mg QD + PBO |
| Arm C | FEN 200 mg BID + PBO |
| Arm D | PBO (FEN) + PBO |
| Arm E | PBO (FEN) + ADA |
| Arm F | FEN 200 mg BID |
| Arm G | PBO (FEN) |

Study Week: 0 2 4 6 8 10 12

Screening (~4 weeks) & randomization

| Screening (~4 weeks) & randomization | Treatment: 12 weeks | Follow-up: 8 weeks |
|--------------------------------------|---------------------|--------------------|
|                                      | Cohort 1 visits - Week 0, 1, 2, 4, 6, 8, 10, 12 | Cohort 1 (MTX-IR): Arms A, B, C, D, and E |
|                                      | Cohort 2 visits - Week 0, 1, 2, 4, 8, 12         | Cohort 2 (TNF-IR): Arms F and G |

Office visits:  
Subcutaneous injections: ▲
Supplementary Figure 2. ACR20 responses over time to week 12 for (A) cohort 1 and (B) cohort 2, and ACR70 for (C) cohort 1 and (D) cohort 2. Error bars indicate 95% confidence intervals.
**Supplementary Figure 3.** Change in ACR components from baseline over time to week 12. SJC for (A) cohort 1 and (B) cohort 2; TJC for (C) cohort 1 and (D) cohort 2; ESR for (E) cohort 1 and (F) cohort 2; CRP for (G) cohort 1 and (H) cohort 2. Error bars indicate 95% confidence intervals.
Supplementary Figure S3.

A. Mean change from baseline

SJC: Cohort 1

Time (weeks)

B. Mean change from baseline

SJC: Cohort 2

Time (weeks)

C. Mean change from baseline

TJC: Cohort 1

Time (weeks)

D. Mean change from baseline

TJC: Cohort 2

Time (weeks)

E. Mean change from baseline

ESR (mm/L): Cohort 1

Time (weeks)

F. Mean change from baseline

ESR (mm/L): Cohort 2

Time (weeks)

G. Mean change from baseline

CRP (mg/dL): Cohort 1

Time (weeks)

H. Mean change from baseline

CRP (mg/dL): Cohort 2

Time (weeks)

Cohort 1:
- Fenebrutinib 50 mg daily (n=40)
- Placebo (n=110)
- Fenebrutinib 150 mg daily (n=109)
- Adalimumab (n=111)
- Fenebrutinib 200 mg twice daily (n=110)

Cohort 2:
- Fenebrutinib 200 mg twice daily (n=48)
- Placebo (n=50)
Supplementary Figure 4. Change in ACR components from baseline over time to week 12. Physician global assessment for (A) cohort 1 and (B) cohort 2; mean change from baseline in patient global assessment for (C) cohort 1 and (D) cohort 2; mean change from baseline in patient pain assessment for (E) cohort 1 and (F) cohort 2. Error bars indicate 95% confidence intervals.
Supplemental Figure 5. Total IgM, IgG, RF and ACPA profiles in cohort 2
Absolute change from baseline in levels of total IgM and IgG (A) and percent change from baseline in levels of rheumatoid factor and ACPA (B) at week 12 for cohort 2 (median with interquartile range). Significance versus placebo is indicated by **. RF and ACPA analyses included patients who were positive at screening.
Supplementary Figure 6

Monocyte screen to identify BTK-dependent Fcγ receptor-induced myeloid biomarkers. Heatmap reflecting expression of genes regulated by BTK-dependent immune complex-mediated stimulation of Fcγ receptors. The expression levels of genes in human monocytes were assayed under conditions of a) no stimulation, b) with human serum albumin immune complex stimulation, c) with stimulation + low concentration of a BTK inhibitor tool compound (GDC-0852) with very similar binding action, potency and selectivity to fenebrutinib, and, d) with stimulation + high concentration of the BTK inhibitor compound. Genes were filtered by up-regulation by immune complex stimulation of at least 2-fold (FDR of 0.01), followed by their subsequent reduction by IC90 concentrations of the BTK inhibitor of at least 1.5-fold (FDR of 0.05). Genes annotated with the GO term GO:0005215 (cytokine activity) were then selected. For visualization, a donor-only model was fitted to the voom-transformed data, and residuals were counted. The donor-corrected values were then centered and scaled, yielding z-scores with the color bar representing normalized gene expression.
Supplementary Figure 7. Myeloid biomarker changes and peripheral CD19+ and CD3+ T cell profiles. Percent change from baseline to week 12 in cohort 1 (median with interquartile range) for CCL4 (A), IL-6 (B), CD19+ B cells (C), and CD3+ T cells (D). Significance versus placebo is indicated by **.
Supplementary Figure 8. CCL4 (A), IL-6 (B), CD19+ B cells (C), and CD3+ T cells (D) levels over time for cohort 2; percent change from baseline (median and interquartile range) over time are shown. Significance versus placebo is indicated by “*”. 
A. CCL4

%Change from baseline (median)

Day

PBO
n=44
FEN 200 mg BID
n=48

B. IL-6

%Change from baseline (median)

Day

PBO
n=44
FEN 200 mg BID
n=47

C. CD19+ B Cells

%Change from baseline (median)

Day

PBO
n=35
FEN 200 mg BID
n=32

D. CD3+ T Cells

%Change from baseline (median)

Day

PBO
n=35
FEN 200 mg BID
n=32
