**Supplementary information**

**SUPPLEMENTARY METHODS**

*Appendix I*

**1) Observer Assessment Tool (OAT)**

Q1: Based on your observations did the patient successfully inject the full dose into an acceptable injection site without your assistance?

* Was the self-administration successful? YES or NO
* If this attempt was not successful, why was it not successful? Provide the reason the patient did for not successfully complete this attempt (e.g., device failed to operate; patient damaged the device; patient delivered dose into air before insertion into the site; patient removed the injector prematurely from the injection site resulting in the drug continuing to be expelled from the injector after removal; user was physically unable to perform a step and required assistance; patient reached a point before injection where they stated they could not proceed without assistance, etc.):

Only answer Question 2 if the patient did not successfully inject the full dose into an acceptable injection site without assistance

**Q2: If patient was unable to successfully inject the full dose into an acceptable injection site without assistance, where did he/she stop?**

A. Removing the clear needle cap of the autoinjector

B. Pinch skin and position pen over injection site

C. Push and keep pushing the pen down against the injection site

* In your opinion, why did this step cause a problem? Please be specific. If you feel that the device could have been designed differently – or if the Instructions could have been written differently – or something else – please tell us.

**2) Participant Assessment Tool (PAT)**

Instructions to Study Staff:

Every study patient will be asked to complete the PAT after each injection, even if the patient did not successfully complete the injection.

* After self-injection training, if a patient fails his first attempt, the patient will be asked to make a second attempt only if no drug was administered, starting from the beginning with a new device.
* In case the second attempt also fails, and only if no drug was administered, the patient will be offered a PFS.
* If a patient has received a partial dose of study drug, following their first or second attempt, they should be withdrawn from the study.

**Instructions:**

Please answer the question below carefully.

* Please make a Comment in the space provided, if you have an observation or opinion you would like to share.

**Q1: Did you successfully self-administer the injection into an appropriate part of your body?**

* If you needed to use more than one device to achieve a successful injection, please consider that you achieved a successful injection for the response to this question, but describe the experience with the first device in the space provided below. YES or NO
* If no, or if your required more than one device to achieve a successful injection, in your opinion, why were you unsuccessful? Please be specific.

Only answer Question 2 if you could not complete all the Steps.

**Q2: If you were unable to complete all of the Steps, at which of the Steps below did you stop?**

A. Removing the clear needle cap of the autoinjector

B. Pinch Skin and Position Pen Over Injection Site

C. Push and keep pushing the pen down against the injection site

* In your opinion, why did this Step cause a problem? Please be specific. If you feel that the device could have been designed differently – or if the Instructions could have been written differently – or something else - please tell us.

*Appendix II*

*Outcome measures*

* The ACR-20 / -50 / -70 is a composite measure based on both the 20% / 50% / 70% improvement in the number of both tender joints and swollen joints, as well as a 20% / 50% / 70% improvement in 3 of 5 criteria: Physician Assessment of Disease Activity, Patient Assessment of Disease Activity, a functional ability measure (in this trial, the Health Assessment Questionnaire [HAQ]), a pain scale, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Disability index (DI) was calculated as the average of the scores from each section of the HAQ. Pain and health were summarized on the original scales from 0 to 100.
* Improvement in ACR was defined as follows:
  + Number of tender/swollen joints: Decrease of 20%/50%/70% from baseline (BL) in total number of tender and swollen joints.
  + Physician Assessment of Disease Activity (0 = Very Poor, 100 = Very Well): Increase of 20%/50%/70% from BL in the score.
  + Patient Assessment of Disease Activity (0 = Very Poor, 100 = Very Well): Increase of 20%/50%/70% from BL in the score.
  + Functional ability measure (in this trial, the HAQ): Decrease of 20%/50%/70% from BL in patient’s DI.
  + Pain scale (0 = No Pain, 100 = Worst Pain Imaginable): Decrease of 20%/50%/70% from BL in the score.
  + ESR or CRP: Decrease of 20%/50%/70% from BL in CRP.
* The Simple Disease Activity Index (SDAI) is the sum of 5 outcome parameters used to measure disease activity. The SDAI measures tender joint count based on a 28-joint assessment, swollen joint count based on a 28-joint measurement, Patient Assessment of Disease Activity on a visual analogue scale (VAS), Physician Assessment of Disease Activity on a VAS scale, and CRP. The total score from all 5 parameters results in the SDAI score.
* The DAS28 is a composite measure that is derived from the examination of swelling and tenderness in the joints, the measurement of the ESR or the CRP, and the Patient Assessment of Disease Activity. The combined results are calculated to produce an overall disease activity score. A DAS28 CRP score >5.1 implies active disease, <3.2 implies low disease activity, and <2.6 indicates remission. The number 28 describes the number of different joints that are examined, including the proximal interphalangeal joints (10 joints), the metacarpophalangeal joints (10 joints), wrists (2 joints), elbows (2 joints), shoulders (2 joints), and knees (2 joints).
* The HAQ is a health-related quality-of-life measure used to assess health-related life quality due to rheumatoid arthritis. The questionnaire is a patient-reported outcome, to be completed without the help of a physician. The HAQ assessed the following categories: Dressing and Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, and Common Daily Activities. The patients reported the degree of difficulty performing these activities, on a scale of 0 to 3 (‘WITHOUT ANY DIFFICULTY’ to ‘UNABLE TO DO’). For each section, the score given to that section was the worst score within the section, i.e., if 1 question was scored 1 and another 2, then the score for the section was 2. In addition, if an aide or device was used or if help was required from another individual, then the minimum score for that section was 2. If the section score was already 2 or more then no modification was made.

*Appendix III*

*Statistical analyses*

* AI robustness was calculated as:
* 100 − 100 × (Number of inspected autoinjectors with any signs of damage, malfunction, or injection incompleteness / Total number of inspected autoinjectors)

*Appendix IV*

* Analysis populations:
  + Full analysis set consistent with the intention-to-treat principles, was defined as all enrolled patients who received at least 1 dose of study drug
  + Safety set included the same patients as the full analysis set in the treatment group according to treatment received

**SUPPLEMENTARY FIGURES AND TABLES**

**Supplementary Table 1.** AI handling events (Full analysis set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| AVT02-AI  N = 107 | | | | |
| **Handling event** | **Week 4\*†, events,  % (95% CI)** | **Week 6†, events,  % (95% CI)** | **Week 8†, events,  % (95% CI)** | **Overall\***  **events,  % (95% CI)** |
| **OAT + PAT** | | | | |
| Any handling event | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 1.2) |
| Removing the clear needle cap of the autoinjector | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 1.2) |
| Pinch skin and position pen over injection site | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 1.2) |
| Push and keep pushing the pen down against the injection site | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 1.2) |
| Other | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 3.5) | 0 (0, 1.2) |

\*One patient missed one dose at Week 4. **†**N=105 for Week 4; N=106 for Weeks 6 and 8; N=317 for Overall. AI: autoinjector; CI: confidence interval; OAT: observer assessment tool; PAT: participant assessment tool

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**Supplementary Table 2.** SDAI (Full analysis set).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Actual Value | | | Change from Baseline | | |
|  | **Treatment** | **n** | **Mean** ± **SD** | **95% Cl** | **n** | **Mean** ± **SD** | **95% Cl** |
| Baseline | AVT02-AI | 107 | 55.0 ± 12.2 | 52.6, 57.3 | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | 38.0 ± 14.6 | 35.2, 40.8 | 106 | -16.9 ± 12.0 | -19.3, -14.6 |
| Week 8 | AVT02-AI | 106 | 26.8 ± 11.4 | 24.6, 29.0 | 106 | -28.1 ± 11.8 | -30.4, -25.9 |
| Week 14 | AVT02-PFS | 106 | 18.0 ± 7.9 | 16.4, 19.5 | 106 | -37.0 ± 11.6 | -39.2, -34.8 |
| Week 24 | AVT02-PFS | 106 | 15.7 ± 8.5 | 14.0, 17.3 | 106 | -39.3 ± 12.9 | -41.8, -36.8 |
| Week 36 | AVT02-PFS | 106 | 11.4 ± 6.4 | 10.2, 12.6 | 106 | -43.6 ± 12.6 | -46.0, -41.2 |
| Week 56 | AVT02-PFS | 106 | 10.2 ± 6.4 | 8.9, 11.4 | 106 | -44.8 ± 12.9 | -47.3, -42.3 |

AI: autoinjector; CI: confidence interval; NA: not applicable; PFS: prefilled syringe; SD: standard deviation; SDAI: simple disease activity index.

**Supplementary Table 3.** DAS28 CRP scores (Full analysis set).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Actual Value | | | Change from Baseline | | | |
|  | **Treatment** | **n** | **Mean** ± **SD** | **95% Cl** | **n** | **Mean** ± **SD** | | **95% Cl** |
| Baseline | AVT02-AI | 107 | 6.7 ± 0.8 | 6.5, 6.8 | 107 | NA | NA | |
| Week 4 | AVT02-AI | 106 | 5.3 ± 1.1 | 5.1, 5.6 | 106 | -1.3 ± 0.9 | -1.5, -1.2 | |
| Week 8 | AVT02-AI | 106 | 4.6 ± 1.0 | 4.4, 4.8 | 106 | -2.1 ± 0.9 | -2.3, -1.9 | |
| Week 14 | AVT02-PFS | 106 | 3.9 ± 0.9 | 3.7, 4.0 | 106 | -2.8 ± 0.9 | -3.0, -2.7 | |
| Week 24 | AVT02-PFS | 106 | 3.6 ± 1.0 | 3.4, 3.8 | 106 | -3.1 ± 1.0 | -3.2, -2.9 | |
| Week 36 | AVT02-PFS | 106 | 3.3 ± 0.9 | 3.1, 3.5 | 106 | -3.4 ± 1.0 | -3.6, -3.2 | |
| Week 56 | AVT02-PFS | 106 | 3.2 ± 0.9 | 3.0, 3.3 | 106 | -3.5 ± 1.0 | -3.7, -3.4 | |

AI: autoinjector; CI: confidence interval; DAS28 CRP: disease activity score 28 C-reactive protein; NA: not applicable; PFS: prefilled syringe; SD: standard deviation.

**Supplementary Table 4.** HAQ (Safety set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | | Change from Baseline | |
| **Time Point** | **Treatment** | **n** | **Mean** ± **SD** | **95% CI** |
| **Dressing and Grooming** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.6 ± 0.7 | -0.7, -0.4 |
| Week 8 | AVT02-AI | 106 | -0.8 ± 0.7 | -0.9, -0.7 |
| Week 14 | AVT02-PFS | 106 | -1.0 ± 0.8 | -1.1, -0.8 |
| Week 24 | AVT02-PFS | 106 | -1.2 ± 0.7 | -1.3, -1.0 |
| Week 36 | AVT02-PFS | 106 | -1.3 ± 0.7 | -1.4, -1.1 |
| Week 56 | AVT02-PFS | 106 | -1.2 ± 0.8 | -1.4, -1.1 |
| **Arising** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.4 ± 0.8 | -0.6, -0.3 |
| Week 8 | AVT02-AI | 106 | -0.6 ± 0.7 | -0.8, -0.5 |
| Week 14 | AVT02-PFS | 106 | -0.8 ± 0.8 | -0.9, -0.6 |
| Week 24 | AVT02-PFS | 106 | -1.0 ± 0.8 | -1.2, -0.9 |
| Week 36 | AVT02-PFS | 106 | -1.1 ± 0.8 | -1.2, -0.9 |
| Week 56 | AVT02-PFS | 106 | -1.1 ± 0.7 | -1.3, -1.0 |
| **Eating** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.7 ± 0.8 | -0.8, -0.5 |
| Week 8 | AVT02-AI | 106 | -1.0 ± 0.8 | -1.2, -0.9 |
| Week 14 | AVT02-PFS | 106 | -1.2 ± 0.8 | -1.5, -1.2 |
| Week 24 | AVT02-PFS | 106 | -1.3 ± 0.8 | -1.5, -1.2 |
| Week 36 | AVT02-PFS | 106 | -1.4 ± 0.8 | -1.5, -1.2 |
| Week 56 | AVT02-PFS | 106 | -1.5 ± 0.8 | -1.6, -1.3 |
| **Walking** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.3 ± 0.6 | -0.4, -0.2 |
| Week 8 | AVT02-AI | 106 | -0.7 ±0.7 | -0.8, -0.5 |
| Week 14 | AVT02-PFS | 106 | -1.1 ± 0.9 | -1.2, -0.9 |
| Week 24 | AVT02-PFS | 106 | -1.1 ± 0.9 | -1.3, -0.9 |
| Week 36 | AVT02-PFS | 106 | -1.2 ± 0.9 | -1.3, -1.0 |
| Week 56 | AVT02-PFS | 106 | -1.2 ± 0.9 | -1.4, -1.1 |
| **Hygiene** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.4 ± 0.6 | 0.5, -0.2 |
| Week 8 | AVT02-AI | 106 | -0.6 ± 0.6 | -0.8, -0.5 |
| Week 14 | AVT02-PFS | 106 | -0.8 ± 0.8 | -0.9, -0.6 |
| Week 24 | AVT02-PFS | 106 | -0.9 ± 0.8 | -1.1, -0.8 |
| Week 36 | AVT02-PFS | 106 | -1.1 ± 0.8 | -1.3, -1.0 |
| Week 56 | AVT02-PFS | 106 | -1.1 ± 0.8 | -1.2, -0.9 |
| **Reach** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.4 ± 0.8 | -0.6, -0.3 |
| Week 8 | AVT02-AI | 106 | -0.8 ± 0.8 | -1.0, -0.6 |
| Week 14 | AVT02-PFS | 106 | -0.9 ± 0.8 | -1.1, -0.8 |
| Week 24 | AVT02-PFS | 106 | -1.0 ± 0.8 | -1.2, -0.9 |
| Week 36 | AVT02-PFS | 106 | -1.3 ± 0.9 | -1.4, -1.1 |
| Week 56 | AVT02-PFS | 106 | -1.3 ± 0.9 | -1.5, -1.2 |
| **Grip** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.6 ± 1.0 | -0.8, -0.4 |
| Week 8 | AVT02-AI | 106 | -0.9 ± 0.8 | -1.0, -0.7 |
| Week 14 | AVT02-PFS | 106 | -1.1 ± 0.9 | -1.2, -0.9 |
| Week 24 | AVT02-PFS | 106 | -1.2 ± 0.9 | -1.4, -1.0 |
| Week 36 | AVT02-PFS | 106 | -1.3 ± 1.0 | -1.5, -1.1 |
| Week 56 | AVT02-PFS | 106 | -1.3 ± 0.9 | -1.4, -1.1 |
| **Common Daily Activities** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -0.4 ± 0.6 | -0.5, -0.3 |
| Week 8 | AVT02-AI | 106 | -0.5 ± 0.7 | -0.6, -0.4 |
| Week 14 | AVT02-PFS | 106 | -0.8 ± 0.7 | -0.9, -0.6 |
| Week 24 | AVT02-PFS | 106 | -1.0 ± 0.8 | -1.1, -0.8 |
| Week 36 | AVT02-PFS | 106 | -1.0 ± 0.7 | -1.1, -0.8 |
| Week 56 | AVT02-PFS | 106 | -1.1 ± 0.8 | -1.2, -0.9 |
| **Severity of Pain** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -17.4 ± 18.5 | -20.9, -13.8 |
| Week 8 | AVT02-AI | 106 | -28.6 ± 17.3 | -31.9, .25.2 |
| Week 14 | AVT02-PFS | 106 | -40.7 ± 18.4 | -44.3, -37.2 |
| Week 24 | AVT02-PFS | 106 | -45.8 ± 20.4 | -49.7, -41.9 |
| Week 36 | AVT02-PFS | 106 | -51.2 ± 21.6 | -55.4, -47.0 |
| Week 56 | AVT02-PFS | 106 | -56.4 ± 21.5 | -60.6, -52.3 |
| **Health** | | | | |
| Baseline | AVT02-AI | 107 | NA | NA |
| Week 4 | AVT02-AI | 106 | -17.0 ± 16.6 | -20.2, -13.8 |
| Week 8 | AVT02-AI | 106 | -28.9 ± 16.7 | -32.1, -25.6 |
| Week 14 | AVT02-PFS | 106 | -40.2 ± 18.2 | -43.7, -36.7 |
| Week 24 | AVT02-PFS | 106 | -45.5 ± 20.8 | -49.5, -41.5 |
| Week 36 | AVT02-PFS | 106 | -50.6 ± 22.3 | -54.9, -46.3 |
| Week 56 | AVT02-PFS | 106 | -55.7 ± 21.9 | -59.9, -51.5 |

AI: autoinjector; CI: confidence interval; HAQ: health assessment questionnaire; NA: not applicable; PFS: prefilled syringe; SD: standard deviation.

**Supplementary Table 5.** PK assessment (Safety set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Treatment Period | Time Point | Treatment | n | Mean ± SD ng/mL |
| Active Period | Week 0 | AI | 107 | 165.3 ± 537.9 |
| Week 2 | AI | 107 | 3237.3 ± 1614.5 |
| Week 8 | AI | 106 | 6027.3 ± 4916.2 |
| Extension Phase | Week 24 | PFS | 106 | 8141.3 ± 7694.6 |
| Week 36 | PFS | 106 | 7633.4 ± 7011.9 |
| Week 56 | PFS | 106 | 7024.5 ± 6124.5 |

AI: autoinjector; PFS: prefilled syringe; PK: pharmacokinetic; SD: standard deviation.

**Supplementary Table 6.** ADA titers (Safety set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Treatment | Visit | n | Mean ± SD | 95% CI |
| AVT02-AI | Week 0 | 18 | 123.6 ± 481.2 | -115.7, 362.9 |
| Week 2 | 69 | 38536.0 ± 259284.6 | -23750.9, 100823.0 |
| Week 8 | 69 | 10484.0 ± 64820.2 | -5087.5, 26055.6 |
| AVT02-PFS | Week 24 | 64 | 152209.4 ± 1049999.8 | -110072.7, 414491.5 |
| Week 36 | 58 | 21383.8 ± 75130.0 | 1629.4, 41138.3 |
| Week 56 | 52 | 90813.6 ± 406374.9 | -22321.9, 203949.1 |

ADA: anti-drug antibodies; AI: autoinjector; CI: confidence interval; PFS: prefilled syringe; SD: standard deviation.

**Supplementary Table 7.** Detection of ADA and NAb in patients (Safety set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | AVT02-AI+PFS  N = 107 | | | |
| **ADA detection** | | **NAb detection** | |
| **Visit** | **n** | **% (95% CI)** | **n** | **% (95% CI)** |
| **Week 0** | 107 | 16.8 (10.9, 25.0) | 18 | 16.7 (5.8, 39.2) |
| **Week 2** | 107 | 64.5 (55.1, 72.9) | 69 | 20.3 (12.5, 31.2) |
| **Week 8** | 106 | 65.1 (55.6, 73.5) | 69 | 62.3 (50.5, 72.8) |
| **Weeks 24** | 106 | 60.4 (50.9, 69.2) | 64 | 87.5 (77.2, 93.5) |
| **Week 36** | 106 | 54.7 (45.2, 63.9) | 58 | 94.8 (85.9, 98.2) |
| **Week 56** | 106 | 49.1 (39.7, 58.4) | 52 | 90.4 (79.4, 95.8) |

ADA: anti-drug antibodies; AI: autoinjector; CI: confidence interval; NAb: neutralizing antibodies; PFS: prefilled syringe.