Title: A Multicenter, Randomized, Open-label, Parallel Phase 1 Comparability Study of Anifrolumab Administered Accessorized Pre-Filled Syringe or Autoinjector in Healthy Volunteers

Sponsor study code: D3465C00002

NCT number: NCT05339100

Date: 15-Nov-2023

2 SYNOPSIS

Title of Study:	A Multicenter, Randomized, Open-label, Parallel Phase I Comparability Study of Anifrolumab Administered using Accessorized Pre-Filled Syringe or Autoinjector in Healthy Volunteers	
Study Numbers:	Parexel Study No.: PXL263417 Sponsor Study No.: D3465C00002	
Study Intervention:	Test Product: Anifrolumab administered using autoinjector (AI) Reference Product: Anifrolumab administered using accessorized pre-filled syringe (APFS)	
Indication Studied:	Systemic Lupus Erythematosus (SLE)	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Centers:	Parexel Early Phase Clinical Unit Baltimore Habor Hospital 3001 S. Hanover St. Baltimore, MD 21225 USA Parexel International GmbH Campus DRK Kliniken Berlin, Westend, Haus 31 Spandauer Damm 130 14050 Berlin Germany Parexel Early Phase Clinical Unit London Level 7, Northwick Park Hospital Watford Road, Harrow Middlesex HA1 3UJ UK	
Publication:	None	
Study Duration:	First participant first visit: 22 March 2022	Last participant last visit: 13 April 2023

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Study Objective:

Primary objective:

- To demonstrate that the pharmacokinetic (PK) exposure following single subcutaneous (SC) administration of anifrolumab by AI is comparable to the PK exposure following single SC administration of anifrolumab using APFS.

Secondary objectives:

- To evaluate the PK of anifrolumab administered to various anatomical injection sites and in healthy participants within different body weight ranges.
- To evaluate the safety and tolerability of AI- vs APFS-administered anifrolumab.
- To evaluate the immunogenicity of anifrolumab delivered by AI or APFS.

Study Design:

This was a multicenter, randomized, open-label, parallel group Phase I study to compare anifrolumab PK exposure after a single SC administration of anifrolumab using AI to anifrolumab PK exposure after a single SC administration using APFS in healthy male and female (childbearing and non-childbearing potential) participants, aged 18 to 55 years.

The study comprised of:

- A Screening Period of up to 28 days.
- One treatment period during which eligible participants were admitted to the Clinical Unit on Day -1 (1 day before dosing) to reassess their eligibility. Participants who met eligibility criteria were randomized to receive a single SC dose of CCI mg anifrolumab by either APFS or AI device on Day 1. Participants were discharged on Day 3.
- Follow-up Visits on Days 6, 8, 12, 15, 22, 29, and 43.
- A final Follow-up Visit on Day 57.

The study was completed after the final Follow-up Visit on Day 57.

One hundred eighty participants were randomized 1:1:1:1:1:1 to one of the injection sites (upper arm, abdomen, or thigh) within a device group (APFS or AI) capped at 60 participants in each body weight category (50 to < 70 kg, 70 to < 90 kg, and 90 to 110 kg).

Study Participants:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
Approximately 180 participants	180 participants	179 participants

Main Inclusion Criteria:

1 Provision of signed and dated, written Informed Consent prior to any study specific procedures at screening.

2 Healthy male and female participants (childbearing and non-childbearing potential) aged 18 to 55 years (inclusive) at screening with suitable veins for cannulation or repeated venepuncture at screening.

3 Female participants of childbearing potential had to have a negative pregnancy test at screening and on admission to the Clinical Unit and must not have been lactating.

4 Female participants of childbearing potential had to adhere to the contraception methods.

5 Male participants had to adhere to the contraception methods.

6 Had a body mass index (BMI) between 18.5 and 30 kg/m^2 inclusive and weigh at least 50 kg and no more than 110 kg inclusive at screening and/or admission to the Clinical Unit.

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7 Participants had to have immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), either by having recovered from a SARS-CoV-2 infection (should have recovered from infection at least 6 weeks before Screening Visit as confirmed by a coronavirus disease of 2019 [COVID-19] test) or fully vaccinated against SARS-CoV-2 with vaccines approved in the local region (should have received the final vaccine dose at least 2 weeks before Screening Visit).

8 Participant had to meet all of the following tuberculosis (TB) criteria:

(a) No signs or symptoms of active TB prior to or during any Screening Visit.

(b) No medical history or past physical examinations suggestive of active TB.

(c) No recent contact with a person with active TB OR if there had been such contact, referral to a physician specializing in TB to undergo additional evaluation prior to randomization (documented comprehensively in source), and, if warranted, receipt of appropriate treatment for latent TB at or before the first administration of study intervention.

(d) No history of latent TB prior to initial Screening Visit, with the exception of latent TB with documented completion of appropriate treatment.

9 Negative result for an Interferon gamma (IFN-γ) release assay (IGRA) (eg, QuantiFERON-TB Gold test) test for TB at screening.

Investigational Medicinal Products/Study Interventions:

Formulations:	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
Autoinjector	CCI mg/mL CCI mL fill volume in CCI mM Histidine/Histidine-HCl, CCI mM Lysine HCl, CCI mM trehalose dihydrate, CCI % (weight in volume [w/v]) plant-derived polysorbate-80, pH CCI	CCI ; F Lot ID: CCI	CCI
Accessorized pre-filled syringe	CCI mg/mL CCI mL fill volume in CCI mM Histidine/Histidine-HCl, CCI mM Lysine HCl, CCI mM trehalose dihydrate, CCI % (w/v) plant-derived polysorbate-80, pH CCI	CCI ; F Lot ID: CCI	CCI

Duration of Treatment:

Each participant was involved in the study for up to 85 days (including Screening Period).

Treatment Compliance:

Dosing took place at the Clinical Unit and was performed by trained Clinical Unit staff.

The administration of all study intervention was recorded in ClinBase™ (e-data source) and transcribed into RAVE (electronic data capture system).

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Criteria for Evaluation:

Pharmacokinetic Parameters:

- Serum AUCinf, AUClast, Cmax, tmax, t1/2λz, MRT, CL/F, Vz/F, and tlast.

Pharmacodynamic Parameters:

Not applicable.

Safety Variables:

- Adverse events (AEs).
- Injection site pain and pruritus assessed using Visual Analog Scale (VAS) CCI
- Injection site erythema, induration and swelling assessed using the injection site reaction score.
- Vital signs (systolic and diastolic blood pressure, pulse and body temperature).
- 12-lead electrocardiograms (ECGs).
- Physical examination.
- Laboratory assessments (hematology, clinical chemistry, and urinalysis).

Immunogenicity:

- Anti-drug antibodies (ADA).

Exploratory Variables:

Not applicable.

Statistical Methods:

Determination of Sample Size:

The planned sample size was chosen to ensure 90% power to show that the 90% confidence intervals (CIs) for the estimated geometric mean ratios of AUCinf, AUClast, and Cmax between AI and APFS were within the bioequivalence limit of CCI and CCI In the calculation, CCI

Presentation and Analysis of Pharmacokinetic Data:

The serum concentrations and the PK parameters were listed and presented in tabular and graphical form as appropriate. The serum concentrations for each scheduled time point were summarized by device group, device group and injection site, device group and body weight category, and device group, injection site, and body weight category using appropriate descriptive statistics, based on the PK analysis set. All reportable PK parameters for anifrolumab, including individual diagnostic and λz-related parameters, were listed for each participant by device group (with injection site, and body weight category listed) based on the PK analysis set. The PK parameters were derived using non-compartmental methods.

Pharmacokinetic comparability was assessed between Reference (dose with APFS) and Test (dose with AI) treatments based on the PK analysis set.

A mixed effects model was employed on the natural log-transformed AUCinf, AUClast, and Cmax separately, as the response variables, treatment (device), injection sites, and continuous baseline body weight on log scale as fixed effects, and participant as a random effect. Transformed back from the logarithmic scale, geometric means together with 95% CIs (2-sided) for AUCinf, AUClast, and Cmax were calculated and presented.

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The estimated treatment (device) differences and the 90% CI (2-sided) on the log scale were back-transformed to obtain the geometric mean ratios of AI to APFS and their corresponding 90% CIs. No statistical comparison was made between injection sites or body weight groups.

Presentation and Analysis of Pharmacodynamic Data:

Not applicable.

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings and continuous variables were summarized using descriptive statistics (number of participants [n], mean, standard deviation [SD], minimum [min], median, maximum [max]) by device group. Categorical variables were summarized in frequency tables (frequency and proportion) by device group.

Adverse events were summarized by System Organ Class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) were made and the number of participants who had any AEs, SAEs, AEs with severe intensity and AEs that led to death were summarized. Adverse events that occurred before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs (listings only), injection site pain or reactions, were presented.

Presentation and Analysis of Immunogenicity Data:

The ADA assessments were conducted utilizing a tiered approach (screen, confirm, titer). The presence of neutralizing antibodies (nAb) was tested in all ADA-positive samples using a ligand binding assay.

The ADA to anifrolumab were summarized using descriptive statistics at each applicable visit (an ADA assessment made at that time point) by device group. Anti-drug antibody titer-time profiles of anifrolumab by device group were generated. The impact of ADA on PK was planned to be assessed.

Presentation and Analysis of Exploratory Data:

Not applicable.

Protocol Deviations:

There were no important protocol deviations in the study.

Pharmacokinetic Results:

- The 90% CIs for the geometric mean ratios of Cmax, AUCinf, and AUClast were contained within the 80% to 125% bioequivalence margins, therefore, systemic exposure following administration with AI device was comparable to APFS device.
- Trend in exposure to anifrolumab (AUCinf, AUClast, and Cmax) decreased numerically with an increase in body weight category. This was deemed not clinically relevant.
- tmax and t1/2 were consistent across body weight categories regardless of device group.
- CL/F and Vz/F increased numerically as body weight category increased for both the AI and APFS devices. This was not clinically relevant.
- For the 50 to < 70 kg body weight category, the moderate-high variability in the primary PK parameters for AI (up to 45%) was numerically higher than the moderate variability for APFS (up to 34%). The opposite relationship was seen for the other body weight categories, with moderate variability being observed for the AI (up to 39%), and a high variability being seen for the APFS (up to 76%).
- Exposure to anifrolumab (geometric mean AUCinf, AUClast, and Cmax) was higher (up to 21%) for the AI compared to APFS when the injection site was the abdomen, whereas the relationship was opposite for the thigh and upper arm. The AI parameter values were up to 14% and 13% smaller compared to the APFS values in the respective regions.
- Tmax, t1/2, MRTinf, tlast, CL/F and Vz/F were consistent between injection sites.

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Pharmacodynamic Results:

Not applicable.

Safety Results:

- No SAEs or deaths were reported for either device group, and no withdrawals due to AEs were reported during the study.
- Overall, 124 (68.9%) participants reported AEs with 75 (41.7%) participants reporting AEs that were possibly related to the study intervention.
  - In the AI device group, 69 (76.7%) participants reported AEs with 44 (48.9%) participants reporting AEs that were possibly related to the study intervention.
  - In the APFS device group 55 (61.1%) participants reported AEs with 31 (34.4%) participants reporting AEs that were possibly related to the study intervention.
- Highest recorded AEs were of injection site pain (40 [44.4%] and 27 [30.0%] participants in the AI and APFS device group, respectively) and injection site pruritus (25 [27.8%] and 15 [16.7%] participants in the AI and APFS device group, respectively). Injection site pain and pruritus were graded by participants using VAS [redacted], any value on the VAS greater than zero was considered an AE.
  - For the AI device group, all injection site pain and injection site pruritus AEs were mild in intensity and the mean VAS scores over time were below [redacted] and [redacted] mm for injection site pain and injection site pruritus, respectively.
  - For the APFS device group, all injection site pain and injection site pruritus AEs were mild in intensity and the mean VAS scores over time were below [redacted] and [redacted] mm for injection site pain and injection site pruritus, respectively.
- In the AI and APFS device groups, 9 (10.0%) and 5 (5.6%) participants, respectively, reported maximum injection site pain ≥[redacted] VAS for at least one injection site assessment during the study.
- In the APFS device group, 3 (3.3%) participants reported maximum injection site pruritus ≥[redacted] VAS for at least one injection site assessment during the study. None of the participants in the AI device group reported injection site pruritus ≥[redacted] VAS at any injection site assessments during the study.
- All AEs were mild or moderate in intensity.
- No clinically relevant trends were observed for vital signs, ECGs, weight, BMI, or laboratory assessments.
- None of the observed fluctuations in vital signs from baseline, 12-lead ECG findings, or laboratory assessments, with some observations being outside of the normal range, were considered to be of any clinical relevance.
- No clinically relevant trends were observed for injection site pain and injection site pruritus VAS or injection site erythema, injection site induration, and injection site swelling reaction scores for either the AI or APFS device group.

Immunogenicity Results:

- The immunogenicity of SC anifrolumab was very low and there were no differences in this regard in relation to device used (AI vs APFS) for anifrolumab administration.
- Overall, 3 (1.7%) participants were ADA-positive on Day 57 (1 [1.1%] participant in the AI device group and 2 [2.2%] participants in the APFS device group), demonstrating low incidence of ADA-positive participants for both device groups.
- Due to limited ADA sampling and the single dose of administration of anifrolumab, it was not possible to assess the effect of ADA on PK. In addition, the ADA-positive samples were all from Day 57; a time point at which anifrolumab concentration was below the LLOQ of the PK assay.

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Conclusion:

Primary Objective

- Systemic anifrolumab exposure following administration with AI device was comparable to APFS device.

Secondary Objectives

- Systemic exposure of anifrolumab following administration with AI device was comparable to APFS device irrespective of the injection site or body weight category.
- Anifrolumab administered as a single SC dose using AI or APFS device was found to have an acceptable safety profile and to be generally well tolerated in the studied participants.
- No new safety concerns were identified.
- Overall, immunogenicity of anifrolumab was low and consistent with both AI and APFS devices.
- Due to limited data, no assessment of an effect of ADA on PK could be made.

Overall Impact of COVID-19

The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: Final 1.0, 15 November 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.