

Randomized, Open-Label, Single-Dose, Parallel-Group Pharmacokinetic Study of PF-06410293 (adalimumab-afzb), an Adalimumab Biosimilar, by Subcutaneous Dosing Using a Prefilled Syringe or a Prefilled Pen in Healthy Subjects

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Abstract

This open-label, single-dose, randomized, parallel-group, 2-arm phase I bioequivalence (BE) study assessed the pharmacokinetics (PK), safety, and tolerability of PF-06410293 (ADL-PF), an adalimumab (ADL) biosimilar, following administration by prefilled pen (PFP) or prefilled syringe (PFS). A total of 164 healthy adult subjects were randomized (1:1) to receive ADL-PF (40 mg subcutaneously) in the lower abdomen or upper anterior thigh by PFS or PFP; 163 subjects were included in the primary PK analysis. The concentration-time profiles of the ADL-PF PFS and PFP treatment arms were similar. The 90% confidence intervals for the test/reference ratios of the primary end points (area under the serum concentration-time profile from time 0 to 2 weeks after dosing and maximum observed serum concentration) fell within the 80.00%-125.00% prespecified margin for BE. Comparable numbers of subjects experienced adverse events (AEs) between treatment groups, and injection-site pain was similar at all times and for the 2 injection-site locations. This study demonstrated the BE of ADL-PF following subcutaneous administration using either a PFS or PFP device. ADL-PF by PFS or PFP injection was well tolerated, with the distribution of AEs, including injection-site reactions, being similar between treatment arms.

Keywords

adalimumab, bioequivalence, PF-06410293, pharmacokinetics

Adalimumab (ADL) is a recombinant, fully human, immunoglobulin G (IgG) 1 monoclonal antibody specific for human tumor necrosis factor- α (TNF- α).¹ The primary mechanism of action of ADL is to bind to TNF- α and block its interaction with the p55 and p75 cell-surface TNF receptors, thereby neutralizing the effect of TNF found in inflammatory conditions.¹ ADL has been shown to reduce clinical symptoms in patients with rheumatoid arthritis (RA),² ankylosing spondylitis,³ inflammatory bowel disease,^{4,5} plaque psoriasis,⁶ and other inflammatory and autoimmune diseases.⁷

PF-06410293 (ADL-PF) is an approved ADL biosimilar that achieved regulatory authorization based on an extensive biosimilar development program performed in line with the relevant regulatory guidance,

comprising comparative analytical structural and functional assessment,⁸ clinical pharmacokinetics (PK),⁹

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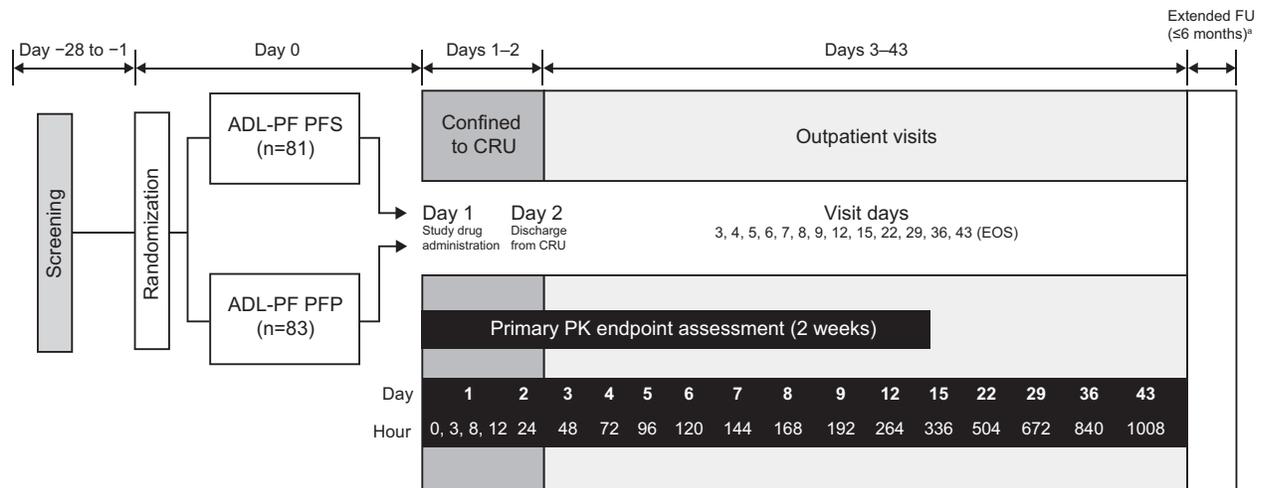


Figure 1. Study design. ^aSubjects with an unresolved AE that was possibly related to ADA formation were asked to return for ADA and drug concentration blood sampling at up to 3-month intervals until the AE or its sequelae resolved or stabilized at a level acceptable to the investigator and the sponsor concurred with the investigator's assessment. Visits continued up to 6 months from the visit on day 43 or the day of early withdrawal. ADA, antidrug antibody; ADL-PF, PF-06410293; AE, adverse event; CRU, clinical research unit; EOS, end of study; FU, follow-up; PFP, prefilled pen; PFS, prefilled syringe; PK, pharmacokinetics.

and efficacy and safety in a clinical trial in patients with RA.¹⁰ In a 3-way comparison of ADL-PF and ADL reference product (ADL-RP) sourced from the United States and European Union (EU), the 90% confidence intervals (CIs) for the geometric means of the test/reference ratios of maximum observed serum concentration (C_{max}), area under the serum concentration-time curve (AUC) from time 0 to the last point with a quantifiable concentration (AUC_T), and AUC extrapolated to infinity (AUC_{0-inf}) for all comparisons were within the predefined equivalence criteria of 80.00%-125.00%, supporting similarity in PK between ADL-PF and ADL-RP.⁹ Overall, the body of data accumulated in the development program demonstrated that the quality, PK, clinical efficacy, and safety profiles of ADL-PF were similar to those of ADL-RP. This study was conducted to determine whether the PK, safety, and tolerability of ADL-PF were similar following a single dose by prefilled pen (PFP) or by prefilled syringe (PFS) in healthy subjects.

Methods

Study Design

This was an open-label, single-dose, randomized, parallel-group, 2-arm phase 1 bioequivalence (BE) study registered at ClinicalTrials.gov (NCT02572245), conducted at ICON Early Phase Services, LLC, San Antonio, Texas (Figure 1). Healthy male and female subjects aged 18-55 years, with a body mass index of 17.5-32 kg/m² and a total body weight > 50 kg were eligible for inclusion. Female subjects were required to be postmenopausal, have undergone a documented hysterectomy and/or bilateral oophorectomy, or had med-

ically confirmed ovarian failure. Key exclusion criteria included a history of clinically significant disease or evidence thereof at screening; clinically relevant abnormal findings in laboratory test results or on physical examination; previous history of cancer other than adequately treated basal cell or squamous cell carcinoma of the skin; or prior or current exposure to anti-TNF biologic therapies or prior exposure to non-anti-TNF biologics with a washout period of less than 5 half-lives.

The study was conducted in compliance with the ethical principles originating in, or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice guidelines. The final protocol and informed consent documentation were reviewed and approved by the institutional review board (IntegReview IRB, Austin, Texas) for the investigational center participating in the study. A signed and dated informed consent form was required before any screening procedures were conducted.

A 40-mg dose of ADL-PF was chosen for the present study because it is the approved therapeutic dose of ADL-RP. This dose was expected to allow for full PK profiling of ADL-PF by PFS and PFP devices. Enrolled subjects were randomized (1:1) to receive a single dose of ADL-PF (40 mg subcutaneously) by PFS or PFP. In each study arm, alternating sequential subjects were assigned to receive their study dose in the lower abdomen or upper anterior thigh. Except for the safety assessor, who was blinded with regard to the type of injection device, the study was open label to subjects, the sponsor, investigators, and investigative-site drug-administration personnel.

The sample size was estimated to ensure that at least 146 subjects (73 per device study arm) had evaluable data for the PK BE assessment. An enrollment of approximately 82 subjects per arm was targeted to account for attrition. Primary study end points were C_{\max} and AUC from time 0 to 2 weeks after dosing (AUC_{0-2wk}) for ADL-PF administered by PFS or PFP. Safety, including treatment-emergent adverse events (TEAEs), for example, injection-site reactions (ISRs) and abnormalities in laboratory parameters, was assessed. Injection-site tolerability by device and injection location was also assessed. Secondary PK end points included the time to reach the maximum serum concentration (T_{\max}), AUC_T , AUC_{0-inf} , apparent volume of distribution (V_z/F), apparent clearance (CL/F), and terminal half-life ($t_{1/2}$). The incidence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) was included as exploratory end points. The assessment was limited in scope, in that samples were to be analyzed only if there was a need for immunogenicity data to help to interpret either PK or safety results.

Statistical Analysis

With a sample size of 73 subjects per device study arm and assuming a ratio of 1.05 and a percent coefficient of variation of $\leq 40\%$ in PK parameters for the 2 devices, the study had approximately 85% power to demonstrate that the 2-sided 90% CIs for the geometric mean ratios of test (ADL-PF PFP)/reference (ADL-PF PFS) for AUC_{0-2wk} and C_{\max} fell within the 80.00%-125.00% pre-specified BE margin.

Pharmacokinetic Evaluations

Blood samples for determining ADL-PF concentrations were collected within 6 hours predose on day 1 and 3, 8, and 12 hours following the injection; and on days 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 22, 29, 36, and 43 (Figure 1). Serum samples were analyzed for ADL-PF concentrations using a validated enzyme-linked immunosorbent assay as follows (conducted at QPS, LLC, Newark, Delaware). Recombinant human TNF- α was coated on the plate to capture ADL-PF in human serum samples. After the plate was washed and blocked, the standards, quality control (QC) samples and blank were diluted 1:100 (minimal required dilution), then incubated. The plate was subsequently washed, and a peroxidase-conjugated goat antihuman IgG antibody was added as a detection reagent. A tetramethylbenzidine substrate was used to generate a signal proportional to the amount of ADL-PF in the sample. ADL-PF concentrations were determined on a calibration curve using a 5-parameter logistic fit with quantitative range from 250 to 10 000 ng/mL. The PK method was fully validated with respect to precision, accuracy, selectivity, specificity, dilution linearity, target and ADA interference, tested stability, and parallelism using incurred samples.

The between-day assay accuracy, expressed as percent relative error, for QC concentrations ranged from -2.3% to 22.2% for the low, medium, high, and diluted QC samples. Assay precision, expressed as the interrun coefficient of variation of the mean estimated concentrations of QC samples, ranged from 1.5% to 6.8% for low (750 ng/mL), medium (2000 ng/mL), high (7500 ng/mL), and diluted (50 000 ng/mL) concentrations. The primary and secondary PK parameter end points were calculated from the concentration-time data of each eligible subject using standard noncompartmental methods. Samples below the lower limit of quantification (250 ng/mL) were set to 0 for data analysis. Actual sample collection times were used for the PK analysis.

Safety Evaluations

Safety was evaluated throughout the study in all enrolled subjects who received the study drug (safety analysis set). All observed or volunteered TEAEs—including type, timing, and seriousness—were recorded, as well as the investigator's assessment of causality and the severity of the events. Severity of adverse events (AEs) was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03). Injection-site tolerability was also recorded. Subjects assessed the severity of any injection-site pain immediately and 15 minutes after the injection and then at periodic intervals from 1 to 24 hours postinjection, using a visual analog scale (VAS) from 0 = no pain to 100 = worst possible pain. Local tolerability of the injection site was also rated by a blinded safety assessor using the Modified Draize Scale Numerical Grade (for erythema) at periodic intervals from 1 to 24 hours postinjection. Physical assessment and laboratory parameters were also evaluated.

Immunogenicity Assessment

ADA and NAb samples were analyzed only if there was a need for the data to help to interpret the PK or safety results. Blood samples for detection of ADAs and NAbs were collected on days 1 (predose), 15, 29, and 43. A fully validated semiquantitative electrochemiluminescent assay was used to detect the presence of ADAs in human serum following a tiered approach using screening, confirmation, and titer/quantitation. The assay was validated utilizing Meso Scale Discovery (MSD-A) technology and was conducted as follows (at QPS, LLC, Newark, Delaware).

Human serum samples, positive controls, and negative controls were treated with acetic acid to dissociate the binding between the drug (ADL-PF) and endogenous TNF- α (target). The acid dissociated samples were then neutralized with Tris-base and coincubated with the labeled drugs (biotinylated-ADL-PF/ruthenium-labeled ADL-PF Master mix). ADAs bound to both the labeled drug molecules to form an antibody complex

Table 1. Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristics	ADL-PF PFS (n = 81)	ADL-PF PFP (n = 83)	Total (n = 164)
Male, n (%)	38 (46.9)	44 (53.0)	82 (50.0)
Age (years), mean ± SD	36.2 (8.8)	37.0 (8.9)	36.6 (8.8)
Race, n (%)			
White	61 (75.3)	68 (81.9)	129 (78.7)
Black	17 (21.0)	13 (15.7)	30 (18.3)
Asian	1 (1.2)	0	1 (0.6)
Other	2 (2.5)	2 (2.4)	4 (2.4)
Weight (kg), mean ± SD	75.8 (12.3)	75.8 (12.6)	75.8 (12.4)
Weight group			
>50 to ≤60 kg	10 (12.3)	10 (12.0)	20 (12.2)
>60 to ≤80 kg	38 (46.9)	40 (48.2)	78 (47.6)
>80 kg	33 (40.7)	33 (39.8)	66 (40.2)
Height (cm), mean ± SD	167.2 (8.6)	167.4 (8.7)	167.3 (8.6)
Body mass index (kg/m ²), mean ± SD	27.0 (3.0)	27.0 (3.4)	27.0 (3.2)
Injection site, n (%)			
Abdomen	37 (45.7)	44 (53.0)	81 (49.4)
Thigh	44 (54.3)	39 (47.0)	83 (50.6)

ADL-PF, PF-06410293; PFP, prefilled pen; PFS, prefilled syringe; SD, standard deviation.

bridge that was added to a streptavidin-coated MSD plate. In the presence of tripropylamine-containing read buffer, ruthenium produces a chemiluminescent signal that is triggered when voltage is applied. The resulting chemiluminescence was measured in response units that was proportional to the amount of anti-ADL-PF antibody present. The ADA assay has been fully validated with respect to precision, specificity, matrix selectivity, assay sensitivity, drug tolerance, target interference, dilution linearity, and tested stability. Screening cut-point factor and confirmatory cut point were statistically established in both a normal healthy population (>50 individual lots) as well as for the RA disease population (>50 RA patient sera).

ADA-positive samples were tested for the presence of NAb activity with a fully validated, semiquantitative cell-based assay using ADL-PF as the critical agent (conducted at QPS, LLC, Newark, Delaware). The neutralizing anti-ADL-PF antibody method utilizes a cell-based assay format. WEHI-13VAR, a variant of WEHI 164 clone 13 (mouse fibrosarcoma cell lines), which is highly susceptible to lysis to TNF- α in the presence of actinomycin D, was used for this bioassay. ADL-PF blocks TNF- α -induced cell cytotoxicity. The neutralizing antibodies to ADL-PF bind to the drug and restore the TNF- α -induced cytotoxicity of WEHI-13VAR cells. In this homogenous assay, human serum samples, negative controls, and positive controls were preincubated with ADL-PF and TNF- α , then the mixture was incubated with cells to initiate the TNF- α -induced cytotoxicity. The presence of a NAb inhibits the function of ADL-PF. The screening cut point was determined from drug-naïve individual matrix lots. The

cell-based NAb assay was fully validated and key parameters established, including precision, screening cut point, matrix selectivity, drug tolerance, and assay sensitivity.

Results

A total of 164 subjects were randomized and assigned to treatment; ADL-PF PFS (n = 81) and PFP (n = 83); see Figure 1. Baseline characteristics were comparable between treatment arms (Table 1).

Overall, 163 subjects were included in the primary PK analysis. The concentration-time profiles were similar between the ADL-PF PFS and PFP treatment arms. C_{max} was achieved approximately 6-7 days following the injection, and drug concentrations declined thereafter (Figure 2). Consistent with the mean concentration-time profiles, the mean C_{max} , AUC_{0-2wk} , AUC_T , and AUC_{0-inf} estimates were similar between the ADL-PF PFS and PFP treatment arms (Table 2). For the PK BE assessment, the 90% CIs for test-to-reference geometric mean ratios for the primary PK parameters, AUC_{0-2wk} , and C_{max} , fell within the prespecified BE margin (Table 3). BE was also demonstrated for the secondary PK end points of AUC_T and AUC_{0-inf} (Table 3). The distributions for individual and geometric mean values of C_{max} , AUC_{0-2wk} , AUC_T , and AUC_{0-inf} were also similar between treatments (Supplementary Materials; Figure 1A-D).

In total, 50 and 51 TEAEs were reported in 31 subjects (38.3%) and 29 subjects (34.9%), respectively, in the ADL-PF PFS and PFP treatment arms (Table 4). One subject in the ADL-PF PFS treatment

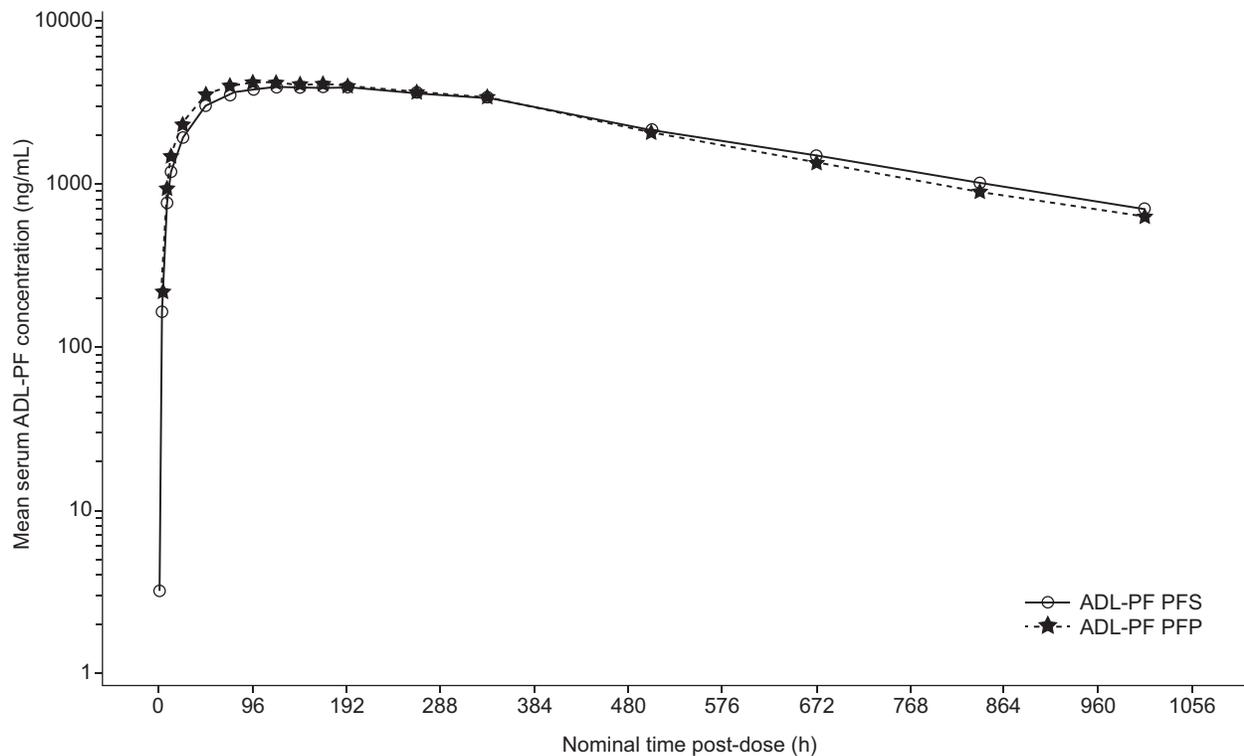


Figure 2. Mean serum concentration-time profiles of ADL-PF (40 mg subcutaneously) by PFS or PFP in healthy subjects. ADL-PF, PF-06410293; PFP, prefilled pen; PFS, prefilled syringe.

Table 2. Arithmetic Mean \pm Standard Deviation PK Parameter Estimates for ADL-PF PFS and PFP

PK Parameter	ADL-PF PFS (n = 80)	ADL-PF PFP (n = 83)
C_{max} , $\mu\text{g/mL}$	4.34 \pm 1.28	4.65 \pm 1.34
T_{max} , h ^a	166 (47.7, 674)	142 (45.4, 336)
AUC_{0-2wk} , $\mu\text{g}\cdot\text{h/mL}$	1160 \pm 342	1210 \pm 333
AUC_T , $\mu\text{g}\cdot\text{h/mL}$	2230 \pm 696	2240 \pm 792
AUC_{0-inf} , $\mu\text{g}\cdot\text{h/mL}$ ^b	2290 \pm 824	2340 \pm 757
CL/F , mL/h ^b	19.7 \pm 7.0	19.4 \pm 7.8
V_z/F , mL ^b	5470 \pm 2040	5280 \pm 2010
$t_{1/2}$, h ^b	210 \pm 84.5	209 \pm 96.7

ADL-PF, PF-06410293; AUC, area under the serum concentration-time profile; AUC_{0-2wk} , AUC from time 0 to 2 weeks after dosing; AUC_{inf} , AUC from time 0 extrapolated to infinity; AUC_T , AUC from time 0 to the point of the last quantifiable concentration; CL/F , apparent clearance; C_{max} , maximum observed serum concentration; PFP, prefilled pen; PFS, prefilled syringe; $t_{1/2}$, terminal half-life; T_{max} , time of maximum serum concentration; V_z/F , apparent volume of distribution.

^aMedian (range) values are reported for T_{max} .

^bNumber of subjects with a well-defined terminal phase (containing a minimum of 3 concentration-time data points and with $r^2 \geq 0.9$), permitting reliable estimation of AUC_{0-inf} , CL/F , V_z/F , and $t_{1/2}$, was 48 and 58 for the PFS and PFP treatment arms, respectively.

arm experienced a serious AE (SAE) of ovarian cyst rupture with anemia, but this was considered unrelated to treatment. The majority of the AEs were mild to moderate in severity. No subject experienced grade

4 or higher all-causality TEAEs. No subject discontinued, permanently or temporarily, from the study. There were no deaths during the study. In total, 21 and 25 treatment-related TEAEs were reported in 14 subjects (17.3%) and 14 subjects (16.9%) in the ADL-PF PFS and PFP treatment arms, respectively. There were no treatment-related SAEs. The most frequently reported AEs by system organ class and preferred term are shown in Table 5. A total of 14 subjects (8.5%) experienced ISR AEs, with the incidence and type being comparable for the ADL-PF PFS and PFP treatment arms (Table 5). (In the ADL-PF PFS and PFP groups, subjects also reported ISR AEs of hematoma [0 and 1 (1.2%)], rash [0 and 1 (1.2%)] and bruising [1 (1.2%) and 0, respectively].) The only treatment-related TEAE experienced by $\geq 5\%$ of subjects was headache, occurring in 10 subjects (6.1%) overall (6 subjects [7.4%] and 4 subjects [4.8%] in the ADL-PF PFS and PFP treatment arms, respectively).

Injection-site pain was similar between the ADL-PF PFS and PFP treatment arms at all times and for injection in the thigh or abdomen (Supplementary Materials; Table 1). The mean maximal VAS score over a 24-hour period postdose by device and injection site ranged from 3.79 mm (ADL-PF PFP injections in the thigh) to 10.68 mm (ADL-PF PFS injections in the thigh). The incidence of subjects reporting injection-site pain postinjection for the ADL-PF PFS and PFP

Table 3. Summary of Statistical Comparisons of PK Exposure Parameters Between Test and Reference Treatments (PK Analysis Set)

PK Parameter (Units)	Adjusted Geometric Mean		Ratio ^{a,b}	90%CI for Ratio ^b
	ADL-PF PFP (Test)	ADL-PF PFS (Reference)		
C _{max} , µg/mL	4.45	4.13	107.74	99.16-117.06
AUC _{0-2wk} , µg·h/mL	1150	1100	104.89	95.76-114.89
AUC _T , µg·h/mL	2040	2100	97.23	86.75-108.98
AUC _{0-inf} , µg·h/mL	2200	2150	102.27	91.12-114.78

ADL-PF, PF-06410293; AUC, area under the serum concentration-time profile; AUC_{0-2wk}, AUC from time 0 to 2 weeks after dosing; AUC_{inf}, AUC from time 0 extrapolated to infinity; AUC_T, AUC from time 0 to the point of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed serum concentration; PFP, prefilled pen; PFS, prefilled syringe; PK, pharmacokinetics.

^a Test/reference of adjusted geometric means.

^b Ratios and 90%CIs are expressed as percentages.

Table 4. Summary of TEAEs, All Causality (Safety Analysis Set), n (%)

Subjects	ADL-PF PFS (n = 81)	ADL-PF PFP (n = 83)	Total (n = 164)
Subjects with AEs	31 (38.3)	29 (34.9)	60 (36.6)
Subjects with SAEs	1 (1.2)	0	1 (0.6)
Subjects with AEs by grade			
Grade 1	13 (16.0)	13 (15.7)	26 (15.9)
Grade 2	14 (17.3)	14 (16.9)	28 (17.1)
Grade 3	4 (4.9)	2 (2.4)	6 (3.7)
Grade ≥4	0	0	0

ADL-PF, PF-06410293; AE, adverse event; PFP, prefilled pen; PFS, prefilled syringe; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 5. Incidence of TEAEs (SOC and PT, ≥2% of Subjects in Any Group), All Causality (Safety Analysis Set), n (%)

TEAEs	ADL-PF PFS (n = 81)	ADL-PF PFP (n = 83)	Total (n = 164)
Blood and lymphatic system disorders	1 (1.2)	2 (2.4)	3 (1.8)
Anemia	1 (1.2)	2 (2.4)	3 (1.8)
Gastrointestinal disorders	7 (8.6)	6 (7.2)	13 (7.9)
Nausea	4 (4.9)	3 (3.6)	7 (4.3)
General disorders and administration-site conditions	8 (9.9)	7 (8.4)	15 (9.1)
Injection-site erythema	3 (3.7)	4 (4.8)	7 (4.3)
Injection-site edema	4 (4.9)	1 (1.2)	5 (3.0)
Injection-site pruritus	2 (2.5)	4 (4.8)	6 (3.7)
Infections and infestations	3 (3.7)	2 (2.4)	5 (3.0)
Injury, poisoning, and procedural complications	3 (3.7)	1 (1.2)	4 (2.4)
Investigations	4 (4.9)	5 (6.0)	9 (5.5)
Neutrophil count decreased	2 (2.5)	2 (2.4)	4 (2.4)
Nervous system disorders	12 (14.8)	12 (14.5)	24 (14.6)
Dizziness	0	2 (2.4)	2 (1.2)
Headache	11 (13.6)	10 (12.0)	21 (12.8)
Respiratory, thoracic, and mediastinal disorders	2 (2.5)	5 (6.0)	7 (4.3)
Rhinitis allergic	1 (1.2)	2 (2.4)	3 (1.8)
Skin and subcutaneous tissue disorders	3 (3.7)	0	3 (1.8)
Rash	2 (2.5)	0	2 (1.2)

ADL-PF, PF-06410293; PFP, prefilled pen; PFS, prefilled syringe; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

treatment arms at each time and injection site is shown in the Supplementary Materials and Table 2. For the blinded safety-assessor evaluation of injection-site tolerability, there were no Modified Draize Scale Numerical Grade (for erythema) scores >1 in the ADL-PF

PFS or PFP treatment arms, and injection-site erythema was comparable between treatment arms at all times and for both injection-site locations. There were no reports of injection-site erythema at 3 or 24 hours postdose in any subject (Supplementary Materials;

Table 3). The mean \pm standard deviation maximal Modified Draize Scale Numerical Grade (for erythema) scores over a 24-hour period postdose by device and injection site location ranged from 0.026 ± 0.1601 for ADL-PF PFP injections in the thigh to 0.114 ± 0.3210 for ADL-PF PFP injections in the abdomen.

Immunogenicity testing was not needed to help interpret the PK data; therefore, testing was limited to only 15 subjects experiencing an ISR and/or rash AE (8 and 7 subjects in the ADL-PF PFS and PFP treatment arms, respectively). In addition, immunogenicity testing was performed on a control group of 15 subjects randomly selected from all those who did not experience ISR or rash AEs and who were matched to the test subjects by age, sex, weight, and delivery device. In subjects with an ISR and/or rash AE and the matched control group, 11 of 15 subjects (73.3%) and 7 of 15 subjects (46.7%), respectively, tested ADA positive. Among the ADA-positive subjects, a majority (12 of 18) also tested positive for NAb (7 of 11 subjects [63.6%] and 5 of 7 subjects [71.4%] among those with an ISR and/or rash AE and the matched control group, respectively).

Discussion

The findings from this open-label, single-dose, randomized PK study demonstrated BE of ADL-PF following administration using either a PFS or PFP device. The 90% CIs of the test-to-reference ratios for the primary PK parameters (C_{max} and AUC_{0-2wk}) were within the prespecified BE margin of 80.00%-125.00%.

Safety findings suggested that a single 40-mg subcutaneous dose of ADL-PF administered by PFS or PFP was well tolerated by healthy subjects. Similar rates of TEAEs were observed between the ADL-PF PFS and PFP treatment groups, with the majority of AEs being mild or moderate in severity, in line with the known safety profile of ADL, as was the incidence of ISR AEs.¹¹ Based on patient-reported scores of injection-site pain and the blinded safety-assessor evaluation of erythema, both ADL-PF PFS and PFP injections were well tolerated and unaffected by the site of administration.

Because immunogenicity assessment was limited, a full comparison of immunogenicity between ADL-PF PFS and PFP treatment arms was not conducted. The incidence of ADA-positive subjects among those with an ISR and/or rash AE was higher compared with the matched control group of subjects who did not experience an ISR and/or rash AE.

Since its first introduction, additional presentations of ADL-RP have been added to those initially authorized, such that it is now available in multiple dosage forms and strengths for optimal patient choice.¹² ADL-PF is 1 of 5 ADL biosimilars currently approved by

the US Food and Drug Administration and 1 of 6 currently approved by the European Medicines Agency for use in the European Union (Supplementary Materials; Table 4). Establishing PK similarity between individual ADL biosimilars and ADL-RP, coupled with demonstration of equivalent PK by different presentations provides options for patients who may have different preferences.¹³⁻¹⁶ Both ADL-PF PFS and ADL-PF PFP are biosimilars to ADL-RP (Humira), providing a degree of patient choice and convenience similar to that afforded by ADL-RP.

One limitation of this study is that the subjects were not blinded to the delivery device. These data were obtained in healthy subjects rather than a heterogeneous patient population.

Conclusions

This PK study demonstrated BE of ADL-PF following subcutaneous administration using either a PFS or PFP device. ADL-PF administered by PFS or PFP subcutaneous injection was well tolerated by healthy subjects, with the distribution of AEs, including ISRs, being similar for ADL-PF PFS and ADL-PF treatment arms.

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Conflicts of Interest

Donna Cox, Daniel Alvarez, and Amy Bock are employees of and hold stock or stock options from Pfizer. Carol Cronberger was an employee of and held stock or stock options from Pfizer at the time the study was conducted.

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This study was sponsored by Pfizer.

Data-Sharing Statement

On request and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data

dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply via a secure portal. To gain access, data requesters must enter into a data access agreement with Pfizer.

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