1. TITLE PAGE

Study Title:	Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06410293 and Adalimumab Sourced From US and EU Administered to Healthy Subjects
Investigational Product:	PF-06410293
Indication:	Inflammation
Sponsor:	Pfizer, Inc.
Protocol Number:	B5381001
Phase of Development:	Phase 1
Study Initiation Date:	First Subject First Visit (FSFV): 28 May 2013
Primary Completion Date:	03 February 2014
Study Completion Date:	Last Subject Last Visit (LSLV): 03 February 2014
Sponsor's Signatories:	[redacted]
	[redacted]
Final Signoff Date:	13 July 2018
Investigators:	See below.

Country	Center	Principal Investigator
Belgium	1002	[redacted]
United States	1001	[redacted]

GCP STATEMENT

This study was conducted in compliance with Good Clinical Practice (GCP) guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the countries of conduct, including the archiving of essential documents.

2. SYNOPSIS

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Individual Subject Data Listings to be submitted will be provided in Module 5 of the Common Technical Document (CTD) for New Drug Applications (USA)

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
%CV	percent coefficient of variation
%RE	percent relative error
λ_z	slope of the terminal disposition phase
abs	absolute
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the serum concentration-time profile
$AUC_{0\text{-}2wk}$	area under the serum concentration-time profile from time 0 to the nominal 2-week time point
AUC_{inf}	area under the serum concentration-time profile from time 0 extrapolated to infinite time
AUC_t	area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration
BMI	Body Mass Index
BP	blood pressure
bpm	beat(s) per minute
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent clearance
C_{last}	serum concentration at the last quantifiable time point estimated from the log linear regression analysis
C_{max}	maximum observed serum concentration
CO_2	carbon dioxide
CRU	Clinical Research Unit
C_t	last observable drug concentration at time t
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DMID	dosage material identification
ECG	electrocardiogram
ECL	electrochemiluminescent
eDISH	evaluation of drug-induced serious hepatotoxicity
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
eNCA	electronic non-compartmental analysis
EU	European Union
F/U	follow-up
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Abbreviation	Definition
HPF	high-powered field
HR/hr	hour
ICH	International Council for Harmonisation
ID	identification number
IEC	Independent Ethics Committee
IgG1	immunoglobulin G-1
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
IV	intravenous
k_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration time curve
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL/ML	milliliter
mm Hg	millimeters of mercury
MPV	mean platelet volume
MRT	mean residence time
msec	millisecond(s)
N	number of subjects
NAb	neutralizing antibodies
NCI	National Cancer Institute
NG	nanogram
OPV	outpatient visit
pH	hydrogen ion concentration (negative log)
PIMS	Phase 1 Management System
PK	pharmacokinetic(s)
PP	per-protocol
PR interval	time between the beginning of the P wave and the start of the QRS complex, corresponding to the end of atrial depolarization and onset of ventricular depolarization
PT	prothrombin time
QC	quality control
QRS interval	time from electrocardiogram Q-wave to the end of the S-wave, corresponding to ventricle depolarization
QT interval	time from electrocardiogram Q-wave to the end of the T-wave corresponding to electrical systole
QTc interval	QT interval, corrected for heart rate
QTcF interval	QT corrected for heart rate using Fridericia's formula
qual	qualitative
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SOC	system organ class

Abbreviation	Definition
SOP	standard operating procedure
SpO_2	saturation level of oxygen in blood
$t_{½}$	terminal half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
T_{last}	time point when C_{last} occurred
T_{max}	time of maximum observed serum concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
µg	microgram
US	United States
v	version
vs.	versus
V_z/F	apparent volume of distribution
WBC	white blood cell

5. ETHICS

5.1. Independent Ethics Committee or Institutional Review Board

The final protocol (Section 16.1.1), and informed consent documentation (Section 16.1.3) were reviewed and approved by the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) at each of the investigational centers participating in the study. The IRB and IEC are listed in Section 16.1.4. Investigators were required to inform their IRB or IEC of the study's progress and occurrence of any serious and /or unexpected adverse events (AEs).

5.2. Ethical Conduct of the Study

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002). In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

5.3. Subject Information and Consent

A signed and dated informed consent was required before any screening procedures were done. The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that they could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document (Section 16.1.3).

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was managed by Pfizer, Inc. (the sponsor) and conducted at Pfizer Clinical Research Units (CRU). The investigators (Section 16.1.4) were responsible for adhering to the study procedures described in the protocol, for keeping records of study drug, and for accurately completing and signing the data in the Phase 1 Management System (PIMS).

The study was conducted at 2 centers; 1 in the United States (US) and 1 in Belgium. Medical and clinical monitoring of this study was delegated to personnel at the unit in accordance with local procedures. The clinical laboratory sample analyses were performed by [redacted] and by [redacted] All pharmacokinetic (PK) and immunogenicity samples were sent to [redacted] for analysis. Data management, data analysis, biostatistics, and medical writing were completed by the sponsor or its designee.

7. INTRODUCTION

Adalimumab (marketed under the brand name Humira®) is a fully human immunoglobulin G-1 (IgG1) monoclonal antibody (mAb) specific for human tumor necrosis

factor (TNF). Hereafter, Humira sourced from the US is referred to as adalimumab-US and Humira sourced from the European Union (EU) is referred to as adalimumab-EU.

The primary mechanism of action of adalimumab 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. Adalimumab is licensed in the US and approved in the EU for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, and approved only in the EU for axial spondyloarthropathy (radiographic-negative) and juvenile Crohn's disease.

PF-06410293, hereafter referred to as adalimumab-Pfizer, is being developed as a potential biosimilar so as to be an alternative to the adalimumab product (Humira). Future market access to biosimilar agents is expected to reduce treatment cost and improve access. Access limitations due to economic issues are currently viewed as one of the major public health issues in areas in which advanced biological therapies serve as the modern standard of care.

Prior to clinical studies in patients with diseases treatable with adalimumab, adalimumab-Pfizer was administered to healthy male/female volunteers to investigate whether the PK profile was similar to that of the licensed adalimumab. Prior to the conduct of this study, adalimumab-Pfizer had not been studied in clinical trials. Awareness of prior experience with the licensed products is informative of what might be expected to be observed during the adalimumab-Pfizer clinical development program.

Pfizer is developing adalimumab-Pfizer to have the same dosage form, route of administration, and dosing regimen as adalimumab sourced from both the US and EU.

8. STUDY OBJECTIVES

The objectives of the study were:

- To compare the PK of adalimumab-Pfizer to adalimumab-EU, and adalimumab-Pfizer to adalimumab-US.
- To compare the PK of adalimumab-EU to adalimumab-US.
- To evaluate the single-dose safety and tolerability.
- To evaluate the immunogenicity.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description and Flow Chart

This was a Phase 1, double-blind (subject and investigator-blinded, sponsor-open), randomized (1:1:1), parallel-group, single-dose, 3-arm, comparative PK study of adalimumab-Pfizer and adalimumab sourced from the US and EU administered subcutaneously (SC) to healthy male or female volunteers. The planned sample size for this study was approximately 210 subjects (70 subjects for each treatment arm).

The assigned study treatment was administered to each subject as a single SC injection, given as a 40-mg dose on Study Day 1. Subject participation in this study was approximately 71 days including an inpatient confinement period for the first 9 days in the CRU, in addition to a screening period of up to 28 days.

The sampling duration for the PK similarity assessment was 42 days (1008 hours). The sampling duration for the anti-drug antibodies (ADA) assessment was 70 days (1680 hours), which was designed to allow detection of low titer ADA at low drug concentrations. Safety was evaluated throughout the study.

Subjects reached the end of study at Day 71 if there were no unresolved drug related AEs. Subjects having an unresolved AE that was possibly related to ADA formation were to be 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, up to 6 months from the Day 71 visit or the visit on the day of early withdrawal.

To comply with Clinical Data Interchange Standards Consortium (CDISC) standards, the day before Day 1 is Day -1 throughout the report, instead of "Day 0" used in the protocol (Section 16.1.1). The schedule of study activities is provided in Table 1.

Table 1. Schedule of Activities

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Protocol Activity	Screen	D-1	D1			D2	D3	D4	D5	D6	D7	D8	OPV D9	OPV D12	OPV D15	OPV D22	OPV D29	OPV D36	OPV D43	OPV D71	Extended F/U
Visit window (days)[a]	**(-29 to -2)**	**0**						**0**					**±1**	**±1**	**±1**	**±2**	**±3**	**±4**	**±4**	**±7**	**±7**
Time post-dose (hr)			**0[b]**	**3**	**8**	**12 24**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**264**	**336**	**504**	**672**	**840**	**1008**	**1680**	
Informed consent[c]	X																				
Medical history[d]	X	X																			
Demography and height	X																				
Weight	X																			X	
History of drug, alcohol, and tobacco use	X																				
Inclusion/exclusion criteria	X	X																			
Physical examination[e]	X	X				X						X			X		X		X	X	
Randomization		X																			
CRU admission and confinement[f]		X	X----------									----------X									
Safety laboratory — Hematology	X	X						X				X			X		X		X	X	
Safety laboratory — Chemistry	X	X						X				X			X		X		X	X	
Safety laboratory — Urinalysis	X	X										X					X		X	X	
Urine drug test	X	X																			
FSH[g]	X																				
HBsAg, HBcAb, HBsAb, anti-HCV serology, HIV-1, HIV-2	X																				
QuantiFERON®-TB Gold In-Tube Test	X																				
Chest X-ray[h]	X																				
Single 12-Lead ECG	X		X									X								X	
Vital signs[i]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Insert IV catheter for blood collection[j]			X																		
Pulse oximetry[k]			X	X																	
Continuous cardiac telemetry monitoring[l]			X------	X																	
Serum samples for study drug concentration[n]			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum samples for ADA and NAb			X												X		X		X	X[q]	X[q]
Study treatment administration[m]			X																		
Assess baseline symptoms/AE monitoring[o]			X----------																		----------X
Prior/concomitant medication[p]	X----------																				----------X

Table 1. Schedule of Activities (Continued)

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Source: Protocol (Section 16.1.1)

Day -1 is corresponding to Day 0 as defined in the protocol (Section 16.1.1).

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; BP=blood pressure; CRU=Clinical Research Unit; D=Day; ECG=electrocardiogram; F/U=follow-up; FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; hr=hour; IV=intravenous; mg=milligram; NAb=neutralizing antibodies; OPV=outpatient visit; SAE=serious adverse event; SC=subcutaneously; TB=tuberculosis.

a. All visits and procedures were to occur when scheduled, but visit windows provided some flexibility as necessary.
b. Activities scheduled at Time 0 were done pre-dose. Injection was administered at Time 0.
c. Informed consent was obtained prior to undergoing any study specific procedure and may have occurred prior to the 28-day screening period.
d. Medical history and medication history were updated at the Day -1 visit.
e. An initial complete physical examination (including a neurologic examination) was required to be performed between screening and Day -1. If a complete physical examination was performed before Day -1, a limited physical examination was required on Day -1. After Day -1, limited examinations based on signs and symptoms were performed if clinically indicated at the discretion of the investigator to assess changes from baseline/previous visits of any ongoing symptoms.
f. Subject could have been discharged from the CRU following the 168-hour post-dose blood collection and following assessments of AEs (Day 8). Subjects could have stayed in the research unit up until Day 9 at the discretion of the investigator.
g. To confirm non-childbearing status in females who were amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause.
h. The allowable window for the chest X-ray was 24 weeks prior to Day 1.
i. Vital signs included BP, heart rate, respiration rate (1 minute calculated from 30 seconds), and temperature at Time 0 (pre-dose) and 3 hours post-dose. BP should have been taken with the subject in the supine position after the subject had been resting quietly for at least 5 minutes.
j. Site may have inserted IV catheter for blood sample collection prior to study drug administration (optional).
k. On Day 1 (pre-dose [Hour 0] through and including Hour 3 after the injection).
l. To establish a baseline, telemetry was to be recorded for at least 2 hours before dosing. This may have been done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording was performed when the subject was awake. Telemetry monitoring could have been extended for safety purposes at the discretion of the investigator.
m. Adalimumab was administered SC in the lower abdomen at a dose of 40 mg.
n. Blood samples for determination of adalimumab drug concentration were collected within 6 hours prior to the start of drug administration (Time 0), and at 3 (±0.25 hrs), 12 (±1 hr), 24 (±2 hrs), 48 (±4 hrs), 72 (±6 hrs), 96 (±8 hrs), 120 (±12 hrs), 144(±14 hrs), 168 (±16 hrs), 192(±24 hrs), 264(±24 hrs), 336 (±36 hrs), 504 (±48 hrs), 672 (±72 hrs), 840 (±96 hrs), and 1008 (±96 hrs) hrs after dosing. Every effort was to be made to draw samples at the scheduled time points, but sampling within the specified time window was allowed. In the event that a subject was not able to receive the full planned dose of 40 mg on Day 1, the full sampling schedule as described above did not apply; instead, blood samples for drug concentrations were to be collected only at the following time points: within 6 hours prior to initiation of adalimumab administration (Time 0), and subsequently at time points concurrent with ADA sample collection (Day 15, Day 29, Day 43, and Day 71), at extended follow-up if applicable, or the time of early withdrawal.
o. Reporting of SAEs began at the time of informed consent. AEs were collected from the time the subject had taken study treatment through last subject visit. Long-term follow-up included reporting of SAEs. If subject discontinued early, every attempt was to be made to follow AEs for 70 days post study drug administration.
p. Collected at each visit/contact from the time the consent form was signed to the final study visit/contact. If subject discontinued early, every attempt was to be made to follow concomitant medications for 70 days post study drug administration.
q. A sample for measurement of drug concentration was collected at the same time of ADA/NAb sampling to facilitate the immunogenicity assessment at low drug concentrations. Subjects having 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 sponsor, up to 6 months from the visit on Day 71 or the visit on the day of early withdrawal.

9.2. Discussion of Study Design, Including Choice of Control Groups

The sponsor planned to demonstrate PK similarity by conducting this single-dose, 3-arm, Phase 1 PK trial in healthy volunteers. This PK study using a single dose in healthy volunteers was designed to avoid factors in patient populations that could confound the interpretation of PK results, such as the potential for variability associated with a multi-dose and multi-center regimen, and complications inherent with disease indications, co-morbidities and concomitant therapies and medications.

9.3. Selection of Study Population

Subjects had to meet all inclusion criteria and not meet any exclusion criteria to participate in this study.

9.3.1. Inclusion Criteria

Subjects were required to meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Healthy females of non-childbearing potential and healthy males between the ages of 18 and 55 years, inclusive. Healthy was defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead electrocardiogram (ECG) and clinical laboratory tests. Female subjects of non-childbearing potential were required to meet at least 1 of the following criteria:

    a. Achieved postmenopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and had a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;

    b. Had undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Had medically confirmed ovarian failure.

    All other female subjects (including females with tubal ligations and females who did not have a documented hysterectomy or bilateral oophorectomy) were considered to be of childbearing potential.

2. Body Mass Index (BMI) of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lbs).

3. Evidence of a personally signed and dated informed consent document indicating that the subject had been informed of all pertinent aspects of the study.

4. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5. Chest X-ray with no evidence of current, active tuberculosis (TB) or previous inactive TB, general infections, heart failure, malignancy, or other clinically significant

abnormalities taken at screening or within 24 weeks prior to Day 1 and read by a qualified radiologist.

9.3.2. Exclusion Criteria

Subjects were ineligible to participate in this study if any of the following criteria were met:

1. Evidence or history of clinically significant infectious, hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, autoimmune, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

2. Evidence or history of heart failure, or nervous system demyelinating diseases (including multiple sclerosis, optic neuritis, Guillain-Barré syndrome).

3. Previous history of cancer, except for adequately treated basal cell or squamous cell carcinoma of the skin.

4. Screening supine BP ≥140 millimeters of mercury (mm Hg) (systolic) or ≥90 mm Hg (diastolic) on a single measurement (confirmed per local standard operating procedure [SOP]).

5. Clinically significant abnormalities in laboratory test results.

6. 12-lead ECG demonstrating time from electrocardiogram Q-wave to the end of the T-wave corresponding to electrical systole (QT interval), corrected for heart rate (QTc interval) >450 milliseconds (msec) or time from electrocardiogram Q-wave to the end of the S-wave, corresponding to ventricle depolarization (QRS interval) >120 msec at screening. If QTc exceeded 450 msec or QRS exceeded 120 msec, the ECG was to be repeated 2 more times and the average of the 3 QTc and QRS values was to be used to determine the subject's eligibility.

7. Pregnant females; breastfeeding females; females of childbearing potential.

8. Males who were unwilling or unable to use a highly effective method of contraception as outlined in the protocol (Section 16.1.1) for the duration of the study and for 6 months following study drug administration.

9. Previous exposure or current use of anti-TNF therapies including adalimumab.

10. Prior exposure to biologics (with the exception of anti-TNF therapies) with a washout period of less than 5 half-lives.

11. Prior exposure to biologics if the following criteria were met:

    a. ≥3 subjects among the first ~20 subjects who have had previous exposure to biologics tested positive for ADA at baseline, and;

b. The rate of baseline ADA in the first ~20 subjects with previous exposure to biologics was ≥2 folds of that observed in no less than 20 subjects with no prior biologics exposure who were first enrolled into the study.

12. Exposure to any live vaccines within 28 days prior to study drug administration. Exposure to any live vaccines was also prohibited for at least 3 months after study drug administration.

13. History of drug and/or alcohol abuse within 5 years prior to study participation, or a positive urine drug screen at screening or Day -1.

14. History of febrile illness within 5 days prior to dosing.

15. Current use of tobacco or nicotine containing products in excess of the equivalent of 5 cigarettes per day.

16. History of regular alcohol consumption exceeding 7 (US)/14 (EU) drinks/week for females or 14 (US)/21 (EU) drinks/week for males (1 drink=5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months of screening.

17. History of allergic or hypersensitivity reaction to inactive components of the study drugs.

18. History of anaphylactic reaction to a therapeutic drug.

19. Treatment with an investigational drug within 30 days or 5 half-lives (or as determined by the local requirement, whichever was longer) preceding the first dose of study medication.

20. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever was longer) prior to the first dose of study medication. Herbal supplements must be discontinued 28 days prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of non-prescription medications that were not believed to affect subject safety or the overall results of the study was permitted on a case-by-case basis following approval by the sponsor.

21. Blood donation of approximately 1 pint (500 mL) or more within 56 days prior to dosing.

22. History of sensitivity to heparin or heparin-induced thrombocytopenia.

23. Unwillingness or inability to comply with the lifestyle guidelines described in the protocol (Section 16.1.1).

24. Positive hepatitis B, hepatitis C or human immunodeficiency virus (HIV) tests at screening indicative of a current or past infection.

25. History of TB or a positive latent TB test at screening, or evidence of TB on chest X-ray.

26. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the subject inappropriate for entry into this study.

27. Subjects who were investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who were sponsor employees directly involved in the conduct of the study.

9.3.3. Removal of Subjects from Therapy or Assessment

Subjects could have withdrawn from the study at any time at their own request or could have been withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons.

If a subject did not return for a scheduled visit, every effort should have been made to contact the subject. The investigator should have attempted to contact the subject twice. After 2 attempts, CRU staff could have sent a registered letter. If no response was received from the subject, the subject was to be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts were to be documented in the subject's medical record. In any circumstance, every effort was to be made to document subject outcome, if possible. The investigator was to inquire about the reason for withdrawal, request the subject to return for a final visit (if applicable), and follow up with the subject regarding any unresolved AEs.

If appropriate, subjects were to return to the clinic for final safety assessments and were to be questioned regarding their reason for withdrawal. Assessments could have included: physical examination, vital signs (including body temperature, supine BP, heart rate, and respiratory rate measurements), 12-lead ECG measurement, blood and urine specimens for safety laboratory assessments, blood sample for serum concentration analysis, blood sample for ADA and neutralizing antibody (NAb) evaluation, information regarding the use of concomitant medication, and the occurrence of AEs. If the subject withdrew from the study and also withdrew consent for disclosure of future information, no further evaluations were to be performed and no additional data were to be collected. The sponsor was permitted to retain and continue to use any data collected before the withdrawal of consent.

9.4. Treatments

9.4.1. Treatments Administered

Following an 8-hour overnight fast, trained investigative site personnel administered study medication with a single SC injection of adalimumab 40 mg to the subject's lower abdomen, with the exception of 2 inches around the naval area. Subjects were instructed to look away when receiving study drug as the formulations had different color plungers.

All subjects were required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

9.4.2. Identity of Investigational Products

Adalimumab-Pfizer, adalimumab-US and adalimumab-EU prefilled syringes were provided by the sponsor as single-dose pre-filled syringes containing 40 mg/0.8 mL of adalimumab. Adalimumab-Pfizer was supplied as open label supplies, whereas adalimumab-US and adalimumab-EU were supplied in their commercially packaged form.

The study treatments were prepared by 2 operators, 1 of whom was a qualified pharmacist designated as participating in this study as an unblinded pharmacist. No information concerning subject treatment assignments was communicated from the unblinded pharmacist to investigators, site study staff, or study subjects unless a serious adverse event (SAE) had resulted in study unblinding.

The lot numbers and dosage material identification numbers are provided in Table 2.

Table 2. Lot and Formulation Identification/DMID Numbers

Drug	Formulation	Potency	Lot Number	DMID
PF-06410293 solution for injection (0.8 mL nominal fill)	Syringe	50 mg/mL	[redacted]	[redacted]
Adalimumab (US-sourced)	Syringe	40 mg/0.8 mL	[redacted]	[redacted]
Adalimumab (EU-sourced)	Syringe	40 mg/0.8 mL		

Source: Section 16.1.6
Abbreviations: DMID=dosage material identification; EU=European Union; mg=milligram; mL=milliliter; US=United States.

9.4.3. Method of Assigning Subjects to Treatment Groups

Approximately 210 subjects were randomly assigned (1:1:1) to 1 of 3 study treatment groups to receive either a single dose of adalimumab-Pfizer, adalimumab-US or adalimumab-EU.

Subjects were given a unique identification number on PIMS. Then, prior to dosing, a randomization number was allocated. This number was retained throughout the study and corresponded to a treatment schedule determined by a sponsor-generated randomization code. The number also appeared on the study medication containers. Randomization was stratified by study site.

9.4.4. Selection of Doses in the Study

A single 40-mg SC dose of adalimumab had been previously evaluated in healthy subject studies where its safety and tolerability were established. In addition, the dose of 40 mg was chosen for this study because it would allow full PK profiling and PK similarity determination at clinically relevant concentrations.

9.4.5. Timing of Dose for Each Subject

Subjects received study medication following an 8-hour fast on Day 1 at Time 0.

9.4.6. Blinding

This study was subject and investigator-blinded (with the exception of nominated staff preparing and administering study drug and not otherwise involved); and sponsor-open. Sponsor personnel were unblinded to subject treatments in order to permit real-time interpretation of the safety and PK data. To minimize the potential for bias, treatment randomization information was kept confidential by sponsor personnel and was not released to the investigator or investigative site personnel until the study database had been locked.

9.4.7. Prior and Concomitant Medications and Procedures

Subjects were to abstain from all concomitant medications, except for the treatment of AEs, as described in Section 9.3.2.

All concomitant medications taken during the study were recorded with indication, daily dose, and start and stop dates of administration. Concomitant medications were collected at each visit/contact from the time the consent form was signed to the final study visit/contact. If a subject discontinued early, every attempt was to be made to follow concomitant medications for 70 days post study drug administration.

Medications taken within 28 days before the first dose of study medication were documented as prior medications. Medications taken after the first dose of study medication were documented as concomitant medications.

A summary of prior exposure to non-TNF biologics was also provided.

9.4.8. Treatment Compliance

Study treatment was administered by trained investigative site personnel.

9.5. Efficacy, Safety, Pharmacokinetic and Pharmacodynamic Evaluations

9.5.1. Appropriateness of Measurements

The measures of PK and safety in this study were standard measurements, widely used and generally recognized as reliable, accurate, and relevant. The safety measurements recorded in this clinical study are those employed in most clinical studies, including the recording of AEs. Medical Dictionary for Regulatory Activities (MedDRA, version 16.1) coding was applied.

9.5.2. Efficacy Evaluations (Not Applicable)

There were no efficacy evaluations done in this study.

9.5.3. Immunogenicity Evaluations

9.5.3.1. Serum for Analysis of Immunogenicity

Blood samples for the detection of ADA and NAb were collected at Day 1 (pre-dose), Day 15, Day 29, Day 43, Day 71, and at extended follow-up (Table 1). A blood sample volume of 10 mL was required to harvest approximately 4 mL serum for ADA and NAb analysis.

Blood samples were allowed to clot at room temperature for at least 20 minutes, and then centrifuged at 1700 × g for approximately 15 minutes in a refrigerated centrifuge to harvest the serum. Samples were frozen in an upright position at approximately -70°C within about 90 minutes of sample collection.

Samples were analyzed using validated analytical methods in compliance with SOPs of a sponsor designated bioanalytical laboratory. Two (2) parallel ADA assays with the same immunoassay platform but different capture (target) antibodies were used to detect ADA against adalimumab-Pfizer and ADA against adalimumab (Humira®), respectively. Samples were first tested in the assay specific for the product which the subject received. If a sample was positive for antibodies to the dosed product, the sample was then analyzed in the alternative assay. Samples confirmed as positive for ADA were further tested for neutralizing activity using validated NAb assays.

9.5.3.2. Immunogenicity Analytical Methods

Serum for Analysis of Anti-Drug Antibodies

Human serum ADA (anti-adalimumab antibodies or anti-PF-06410293 antibodies) samples were analyzed for the presence or absence of anti-adalimumab antibodies or anti-PF-06410293 antibodies at [redacted], following a tiered approach using screening, confirmation and titer/quantification. The semi-quantitative electrochemiluminescent (ECL) assays were validated in compliance with the sponsor's SOPs. The performance of the methods during validation was documented in the method validation reports (QPS Validation Reports [redacted], [redacted] and [redacted]/Pfizer Validation Reports [redacted] and [redacted]). The ADA sample analysis was guided by the approved Bioanalytical Plan for the detection of anti-adalimumab antibodies and anti-PF-06410293 antibodies. A cross reactivity sample analysis was done for samples testing positive in the ADA assay for the dosed product, using the alternate ADA assay with titration and confirmatory analysis as described in the Bioanalytical Plan.

The ADA sample analysis report is included in Section 16.2.5.10.2.

Serum for Analysis of Neutralizing Antibodies

Human serum samples testing positive for the presence of ADA were analyzed for the presence or absence of NAb at [redacted] following a tiered approach using screening and titer. Semi-quantitative cell-based assays were validated in compliance with the sponsor's SOPs. The performance of the methods during validation was documented in method validation reports [redacted] Validation Reports [redacted], [redacted] and [redacted]

[redacted]/Pfizer Validation Reports [redacted] and [redacted]). The NAb sample analysis was guided by the approved Bioanalytical Plan for the detection of NAb. The cross reactivity sample analysis was done for those samples which tested positive in the NAb assay for the dosed product and tested positive in the cross-reactivity ADA assay, using the alternate NAb assay, with titration and confirmatory analysis as described in the Bioanalytical Plan.

The NAb sample analysis report is included in Section 16.2.5.10.3.

9.5.4. Pharmacokinetic Evaluations

9.5.4.1. Pharmacokinetic Sampling

Blood samples (5 mL) to provide approximately 2 mL serum for measurement of drug concentration were collected at the times specified in Table 1.

Blood samples were allowed to clot at room temperature for at least 20 minutes, after which they were centrifuged at 1700 × g for approximately 15 minutes in a refrigerated centrifuge to harvest the serum. Samples were frozen in an upright position at approximately -70°C or colder within 90 minutes of sample collection.

The actual times may have differed from the nominal times, but the number of samples remained the same. All efforts were made to obtain the drug concentration samples at the exact nominal time relative to dosing. However, samples obtained within the specified time window were not to be captured as a protocol deviation, as long as the exact time of the sample collection was noted on PIMS.

Samples were analyzed using a validated analytical method in compliance with SOPs at a sponsor designated bioanalytical lab.

As part of understanding the PK of the study drug, samples may have been used for evaluation of the bioanalytical method. These data were to be used for internal exploratory purposes and are not be included in this clinical study report. Samples collected for this purpose were to be retained in accordance to local regulations and if not used within this timeframe, were to be destroyed.

9.5.4.2. Pharmacokinetic Analytical Methods

Human PK serum samples were analyzed for adalimumab (EU, US and Pfizer [PF-06410293]) concentrations at [redacted] using a validated analytical assay in compliance with the sponsor's SOPs. Adalimumab samples were assayed using a validated, sensitive and specific enzyme-linked immunosorbent assay (ELISA) method. The performance of the method during validation was documented in [redacted] Validation Reports [redacted] and [redacted]/Pfizer Validation Report [redacted]. The serum specimens were stored at approximately -70°C until analysis and assayed within the established matrix stability data that covered a time period of 184 days ([redacted] Validation Projects [redacted] and [redacted]). Sample concentrations were determined by interpolation from calibration standard curves (over the range of 250 to 10,000 ng/mL) that had been fit using a 5-parameter logistic regression model. Those samples with concentrations above the upper limit of quantification (10,000 ng/mL) were adequately

diluted into calibration range. The lower limit of quantification (LLOQ) for adalimumab was 250 ng/mL. Clinical specimens with serum adalimumab concentrations below the LLOQ were reported as <250 ng/mL.

The inter-run assay accuracy, expressed as percent relative error (%RE) for quality control (QC) concentrations, ranged from 0.0% to 3.9% for adalimumab low, medium, and high QC samples. Assay precision, expressed as the inter-run percent coefficient of variation (%CV) of the estimated concentrations of QC samples, was 3.2 to 4.3% for the low (750 ng/mL), medium (2000 ng/mL), and high (7500 ng/mL) concentrations.

The PK sample analysis report is included in Section 16.2.5.10.1.

9.5.4.3. Calculation of Pharmacokinetic Parameters

The PK parameters listed in Table 3 were calculated from concentration-time data of each eligible subject using standard non-compartmental methods. Samples below the LLOQ were set to 0 for analysis. Actual sample collection times were used for the PK analysis. Unless otherwise noted, parameters marked "if data permitted" were reported only where a well-characterized terminal phase was observed.

Table 3. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum observed serum concentration	Observed directly from data
$AUC_{0\text{-}2wk}$	Area under the serum concentration-time profile from time 0 to the nominal 2-week time point	Linear/log trapezoidal method
AUC_t	Area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration	Linear/log trapezoidal method
AUC_{inf}[a]	Area under the serum concentration-time profile from time 0 extrapolated to infinite time	$AUC_t + (C_{last}*/k_{el})$, where $C_{last}*$ was the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis, and k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
T_{max}	Time of maximum observed serum concentration	Observed directly from data
CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$
V_z/F[a]	Apparent volume of distribution	$(CL/F)/k_{el}$
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$

Pharmacokinetic parameter values were calculated using an internally validated software system, eNCA (version 2.2.4).
Abbreviation: eNCA=electronic non-compartmental analysis.
a. If data permitted.

The actual time of sample collection was used in the PK parameter calculation. In the event that the actual sampling time was not available, the nominal time may have been used if there was no evidence that the actual sampling time deviated substantially from the nominal time.

9.5.5. Pharmacodynamic Evaluations (Not Applicable)

There were no pharmacodynamic evaluations done in this study.

9.5.6. Pharmacogenomic Evaluations (Not Applicable)

There were no pharmacogenomic evaluations done in this study.

9.5.7. Safety Evaluations

9.5.7.1. Adverse Events

An AE was any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs included but were not limited to the following: abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, drug abuse, or drug dependency.

Additionally, AEs may have included the signs or symptoms resulting from drug overdose, drug withdrawal, drug misuse, drug interactions, extravasation, exposure in utero, exposure via breastfeeding, medication error, or occupational exposure.

The investigator obtained and recorded all observed or volunteered AEs, the severity (by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, version 4.03]: Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe], Grade 4 [life-threatening], Grade 5 [death]) of the events, and the investigator's opinion of the relationship to the study treatment. AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator was to record as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (eg, ECG, laboratory).

For all AEs, the investigator pursued and obtained information adequate to determine both the outcome of the AE and to assess whether it met the criteria for classification as an SAE (Section 9.5.7.2) requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information was to be obtained by the investigator to determine the causality of the AE. The investigator was required to assess causality. For AEs with a causal relationship to the investigational product, follow-up was required until the event or its sequelae resolved or stabilized at a level acceptable to the investigator and sponsor.

9.5.7.2. Serious Adverse Events

An SAE was any untoward medical occurrence at any dose that resulted in death, was life-threatening (immediate risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions), or resulted in congenital anomaly/birth defect.

Medical and scientific judgment was exercised in determining whether an event was an important medical event. An important medical event may not have been immediately

life-threatening and/or resulted in death or hospitalization. However, if it was determined that the event could have jeopardized the subject or required intervention to prevent one of the other AE outcomes, the important medical event was to be reported as serious. Examples of such events were intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that did not result in hospitalization; or development of drug dependency or drug abuse.

Regardless of the above criteria, any AE that the sponsor or investigator considered serious was to be immediately reported as an SAE.

For SAEs, the reporting period to the sponsor or its designated representative began from the time that the subject provided informed consent, which was obtained before the subject's participation in the study (ie, prior to undergoing any study-related procedure and/or receiving investigational product) through and including 70 calendar days after the last administration of the investigational product or through the subject's final immunogenicity follow-up visit, whichever occurred later. Any SAE occurring any time after the reporting period was to be promptly reported.

9.5.7.3. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) concurrent with abnormal elevations in total bilirubin that met the criteria outlined below in the absence of other causes of liver injury were considered potential cases of drug-induced liver injury (potential Hy's Law cases) and was always to be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depended on the subject's individual baseline values and underlying conditions. Subjects who presented with the following laboratory abnormalities were to be evaluated further to definitively determine the etiology of the abnormal laboratory values:

a. Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently presented with AST or ALT ≥3 × the upper limit of normal (ULN) concurrent with a total bilirubin ≥2 × the ULN with no evidence of hemolysis and an alkaline phosphatase (ALP) ≤2 × ULN or not available.

b. For subjects with preexisting ALT, AST or total bilirubin values above the ULN, the following threshold values were to be used to determine liver injury:

   - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 × the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever was smaller).

   Concurrent with:

   - For subjects with pre-existing values of total bilirubin above the normal range: total bilirubin increased by 1 × the ULN or ≥3 × the ULN (whichever was smaller).

The subject was to return to the investigational site for evaluation as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation was to include laboratory tests, detailed history, and physical assessment. In addition to repeating AST and ALT, laboratory tests were to include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/ international normalized ratio (INR), and ALP. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, were to be collected. Further testing for acute hepatitis A, B, or C virus infection and liver imaging (eg, biliary tract) may have been warranted. All cases confirmed on repeat testing as meeting criteria a or b, with no other cause for liver function test (LFT) abnormalities identified at the time, would have been considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases were to be reported as SAEs.

9.5.7.4. Laboratory Evaluations

The following safety laboratory tests in Table 4 were performed at times specified in Table 1. Additional laboratory results may have been generated on the samples (without additional blood volume drawn) as a result of the method of analysis, the type of analyzers used, or as derived or calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may have been obtained at any time during the study to assess any perceived safety concerns.

Table 4. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and creatinine	pH	FSH[b]
Hematocrit	Glucose (fasting)	Glucose (qual)	Urine drug screen[c]
RBC count	Calcium	Protein (qual)	QuantiFERON-TB Gold
MCV	Sodium	Blood (qual)	In-Tube Test[c]
MCH	Potassium	Ketones	HIV-1[c]
MCHC	Chloride	Nitrites	HIV-2[c]
Platelet count	Total CO_2 (bicarbonate)	Leukocyte esterase	HBsAg[c]
MPV	AST, ALT	Urobilinogen	HBsAb[c]
WBC count	Total bilirubin	Urine bilirubin	HBcAb[c]
Total neutrophils (abs)	Alkaline phosphatase	Microscopy[a]	Anti-hepatitis C virus serology[c]
Eosinophils (abs)	Uric acid		
Monocytes (abs)	Albumin		
Basophils (abs)	Total protein		
Lymphocytes (abs)			
	Additional Tests[d]		
	AST, ALT (repeat)		
	Total bilirubin (repeat)		
	Albumin (repeat)		
	Alkaline phosphatase (repeat)		
	Direct bilirubin		
	Indirect bilirubin		
	Creatine kinase		
	GGT		
	PT/INR		

Source: Protocol (Section 16.1.1)
Abbreviations: abs=absolute; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO_2=carbon dioxide; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MPV=mean platelet volume; pH=hydrogen ion concentration (negative log); PT=prothrombin time; qual=qualitative; RBC=red blood cell; TB=tuberculosis; WBC=white blood cell.
a. Only if urine dipstick was positive for blood, protein, nitrites or leukocyte esterase.
b. At screening only, in females who were amenorrheic for at least 1 year.
c. At screening and Day -1 only.
d. Additional testing for potential Hy's Law cases only.
e. Only performed at screening.

The minimum requirement for drug testing included: cocaine, tetrahydrocannabinol, opiates/opioids, benzodiazepines, and amphetamines. Subjects may have undergone random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing had to be negative in order for subjects to receive study medication.

The criteria for laboratory test values of potential clinical concern are listed in Table 5.

Table 5. Criteria for Laboratory Values of Potential Clinical Concern

Hematology	
Hemoglobin	<0.8× lower limit of the reference range
Hematocrit	<0.8× lower limit of the reference range
RBC count	<0.8× lower limit of the reference range
Platelets	<0.5 or >1.75× the limits of the reference range
Leukocytes	<0.6 or >1.5× the limits of the reference range
Total neutrophils (absolute)	<0.8 or >1.2× the limits of the reference range
Eosinophils (absolute)	>1.2× the upper limit of the reference range
Basophils (absolute)	>1.2× the upper limit of the reference range
Lymphocytes (absolute)	<0.8 or >1.2× the limits of the reference range
Monocytes (absolute)	>1.2× the upper limit of the reference range
Chemistry	
Total bilirubin	>1.5× the upper limit of the reference range
Direct bilirubin	>1.5× the upper limit of the reference range
Indirect bilirubin	>1.5× the upper limit of the reference range
AST	>3× upper limit of the reference range
ALT	>3× upper limit of the reference range
Alkaline phosphatase	>3× upper limit of the reference range
Creatinine	>1.3× upper limit of the reference range
BUN	>1.3× upper limit of the reference range
Glucose (fasting)	<0.6 or >1.5× the limits of the reference range
Uric acid	>1.2× upper limit of the reference range
Sodium	<0.95 or >1.05× the limits of the reference range
Potassium	<0.9 or >1.1× the limits of the reference range
Chloride	<0.9 or >1.1× the limits of the reference range
Bicarbonate	<0.9 or >1.1× the limits of the reference range
Calcium	<0.9 or >1.1× the limits of the reference range
Albumin	<0.8 or >1.2× the limits of the reference range
Total protein	<0.8 or >1.2× the limits of the reference range
Creatine kinase	>2.0× upper limit of the reference range
Urinalysis	
Urine WBC	≥20/HPF
Urine RBC	≥20/HPF

Source: Protocol (Section 16.1.1)
Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HPF=high-powered field; RBC=red blood cell; WBC=white blood cell.

9.5.7.5. Physical Examination

Physical examinations were conducted by a physician, trained physician's assistant, or nurse practitioner, as acceptable according to local regulation. A complete physical examination included head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. Limited physical examinations focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

An initial complete physical examination was performed between screening and Day -1. If a complete physical examination was performed before Day -1, a limited physical examination was to be performed on Day -1. After Day -1, limited examinations based on signs and symptoms were performed if clinically indicated at the discretion of the investigator to assess

changes from baseline/previous visits of any ongoing symptoms. The limited or abbreviated physical examination focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution was used and was placed on a stable, flat surface. Subjects removed shoes, bulky layers of clothing, and jackets so that only light clothing remained. They also removed the contents of their pockets and remained still during measurement of weight.

9.5.7.6. Vital Signs

Vital signs (BP, heart rate, respiratory rate, temperature) were measured at times specified in Table 1.

Blood Pressure and Heart Rate

Additional collection times, or changes to collection times of BP and heart rate were permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP was measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after at least 5 minutes of rest. The same arm (preferably the dominant arm) was used throughout the study. Subjects were instructed not to speak during the measurements.

The same size BP cuff, which had been properly sized and calibrated, was used to measure BP each time. The use of automated devices for measuring BP and pulse rate were acceptable, although, when done manually, pulse rate was to be measured in the brachial/radial artery for at least 30 seconds. If the timing of these measurements coincided with a blood collection, BP and pulse rate were to be obtained prior to the nominal time of the blood collection.

Table 6 presents criteria for vital signs results of potential clinical concern.

Respiratory Rate

Respiratory rate was measured after 5 minutes of rest in the supine position by observing and counting the respirations of the subject for 30 seconds and multiplying by 2. When BP was to be taken at the same time, respiration measurement would have started after the 5-minute rest and before BP measurement.

Temperature

Temperature was measured using oral or tympanic methods. The same method was used consistently throughout the study. No eating, drinking or smoking was allowed for 15 minutes prior to the measurement.

Table 6. Criteria for Vital Sign Values of Potential Clinical Concern

Vital Signs	Criteria Description
Pulse Rate	Supine/Sitting: <40 or >120 bpm Standing: <40 or >140 bpm
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture
	Systolic <90 mm Hg
	Diastolic ≥20 mm Hg change from baseline in same posture
	Diastolic <50 mm Hg

Source: Protocol (Section 16.1.1)
Abbreviations: bpm=beat per minute; mm Hg=millimeter of mercury.

9.5.7.7. Electrocardiogram

A standard supine 12-lead ECG was collected at times specified in Table 1.

All scheduled ECGs were performed after the subject had rested quietly for at least 10 minutes in a supine position. ECGs were compared to Day 1 pre-dose ECGs (baseline) and any clinically significant changes were to be recorded as AEs and evaluated further as clinically warranted.

Table 7 presents criteria for ECG results of potential clinical concern.

Table 7. Criteria for ECG Results of Potential Clinical Concern

Electrocardiogram	Criteria Description
PR interval	≥300 msec; ≥25% increase when baseline >200 msec; ≥50% increase when baseline ≤200 msec
QRS interval	≥140 msec; ≥50% increase from baseline
QTc interval	≥500 msec

Source: Protocol (Section 16.1.1)
Abbreviations: ECG=electrocardiogram; msec=millisecond(s); PR interval=time between the beginning of the P wave and the start of the QRS complex, corresponding to the end of atrial depolarization and onset of ventricular depolarization; QRS interval=time from electrocardiogram Q-wave to the end of the S-wave, corresponding to ventricle depolarization; QT interval= time from electrocardiogram Q-wave to the end of the T-wave corresponding to electrical systole; QTc interval=QT interval, corrected for heart rate.

To ensure the safety of the subjects, a qualified individual at the investigative site made comparisons to baseline measurements. If the QTc interval was increased by >45 msec from the baseline, or an absolute QTc value was ≥500 msec for any scheduled ECG, then 2 additional ECGs were to be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remained above the threshold value (>45 msec above the baseline or was ≥500 msec), then a single ECG was to be repeated at least hourly until QTc values from 2 successive ECGs fell below the threshold value that triggered the repeat measurement.

If QTc values remained above 500 msec (or >45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTc intervals got progressively

longer, the subject was to undergo continuous ECG monitoring. A cardiologist was to be consulted if QTc intervals did not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

In some cases, it may have been appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It was important that leads were placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value was prolonged, as defined above, repeat measurements may not have been necessary if a qualified physician's interpretation determined that the QTc values were in the acceptable range.

9.5.7.8. Chest X-Ray

Subjects were required to have a chest radiograph (posterior-anterior and lateral views were recommended; however, local guidelines were to be followed) with no evidence of current, active TB or previous inactive TB, general infections, heart failure, malignancy, or other clinically significant abnormalities taken at screening or within 24 weeks prior to Day 1 and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

9.5.7.9. Continuous Cardiac Monitoring by Telemetry

All abnormal rhythms were recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event were to be recorded in PIMS. In addition, a printed record of the tracings of the clinically significant rhythms was to be made and retained with other source documents.

Telemetry was to be collected using a centralized system that also allowed for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring was not used in parallel with continuous telemetry, unless it was the only means of data storage available at the study site, or verifiable arrhythmia quantification was required. To establish a baseline, telemetry was recorded for at least 2 hours before dosing in Period 1. This may have been done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording was performed when the subject was awake. Telemetry was stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it was expected that the telemetry leads were to be in place and the system connected prior to dosing. Continuous cardiac monitoring by telemetry began prior to the start of injection (-5 minutes) and continued through 8 hours after injection.

9.5.7.10. Pulse Oximetry

Saturation level of oxygen in blood (SpO_2) was measured using pulse oximetry and was obtained in a supine position. This was performed on Day 1, immediately prior to treatment administration, and after the injection at Hours 0 and 3.

9.6. Data Quality Assurance

As this study was performed at Pfizer CRUs, personnel at the unit were responsible for reviewing study procedures, comparing PIMS data to original clinical records, resolving data queries and providing details of protocol deviations in accordance with the unit's SOPs. The overall study conduct was subject to internal quality review by the sponsor.

This clinical study report has been subjected to QC review by the sponsor or the sponsor's designee. The QC processes were reviewed by the sponsor's own independent quality assurance group.

In addition, this study report was audited.

9.7. Statistical Methods Planned in the Protocol

9.7.1. Statistical and Analytical Plans

Detailed methodology for summarization and statistical analyses of the data collected in this study was documented in a statistical analysis plan (SAP, Section 16.1.9.1). There were no modifications of the primary endpoint definition and/or its analysis subsequent to the protocol finalization.

9.7.2. Determination of Sample Size

Approximately 210 subjects were planned to be randomized 1:1:1 to adalimumab-Pfizer, adalimumab-EU or adalimumab-US.

The similarity objective of the study required similarity in area under the serum concentration-time profile (AUC), including area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_t) and area under the serum concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}) between adalimumab-Pfizer and adalimumab-US and between adalimumab-Pfizer and adalimumab-EU. Based on literature, an estimate of %CV for AUC_t was 30%.[1] A sample size of 65 subjects per arm would have provided 90% power for the 2 comparisons to achieve similarity in AUC_t for the similarity objective, and 94% for a single comparison in AUC_t, if %CV was equal to 30% and the true ratio of AUC_t values was equal to 1.05 or less for each AUC_t comparison. Since AUC_t and AUC_{inf} are highly correlated, the power for similarity in AUC_t is about the same as that for AUC_{inf}.[1]

The similarity objective of the study also required similarity in maximum observed serum concentration (C_{max}) between adalimumab-Pfizer and adalimumab-US and between adalimumab-Pfizer and adalimumab-EU. With an estimated %CV of 35% for C_{max}[1] the same sample size would have provided 77% power to achieve similarity in C_{max} for the similarity objective, and 86% for a single comparison in C_{max} if the true ratio of C_{max} was equal to 1.05 or less for each C_{max} comparison.

The bridging objective of the study was to evaluate similarity between adalimumab-US and adalimumab-EU based on comparison in AUC (AUC_t and AUC_{inf}) and C_{max} with the same 80.00% to 125.00% acceptance criteria. A sample size of 65 subjects per arm provided 99%

power for comparison in AUC if the %CV was equal to 30% and the true ratio of AUC for adalimumab-US to adalimumab-EU was equal to 1.0; and 94 % power for comparison in C_{max} if the %CV was equal to 35% and the true ratio of C_{max} for adalimumab-US to adalimumab-EU was equal to 1.0.

To account for a non-evaluable rate of approximately 5%, the total sample size was increased to approximately 70 subjects per treatment arm. The assigned study treatment was administered to each subject as a single SC 40-mg dose on Study Day 1.

9.7.3. Analysis Populations

The full analysis set (FAS) was defined as all subjects randomized and who received the randomized treatment. The FAS population was used for assessment of immunogenicity.

The per-protocol (PP) analysis set was defined as all subjects who were randomized to and received the planned study treatment, and had no major protocol violations. Protocol violations were determined based on blinded medical data review. The PP analysis set was used as the population for PK analyses.

The safety analysis set was defined as all subjects who received the study medication. The safety analysis set was used for safety and tolerability analyses.

9.7.4. Statistical Analysis

9.7.4.1. Efficacy Parameters (Not Applicable)

There were no efficacy parameters in this study.

9.7.4.2. Pharmacokinetic Parameters

The single-dose serum drug concentration-time data from Day 1 to Day 43 were analyzed using standard non-compartmental analysis to estimate PK parameters for each individual subject. The PK parameters included: C_{max}, time of maximum observed serum concentration (T_{max}), area under the serum concentration-time profile from time 0 to the nominal 2-week time point ($AUC_{0\text{-}2wk}$), and AUC_t. In addition, if data permitted, AUC_{inf}, apparent clearance (CL/F), apparent volume of distribution (V_z/F) and terminal half-life ($t_{½}$) were also estimated. The PK parameters were summarized using descriptive statistics according to treatment group.

A one-way analysis of variance (ANOVA) with treatment as a factor was performed for each natural log transformed PK parameter ($AUC_{0\text{-}2wk}$, AUC_t, AUC_{inf} or C_{max}). Estimates of mean differences (adalimumab-Pfizer minus adalimumab-EU; adalimumab-Pfizer minus adalimumab-US; or adalimumab-EU minus adalimumab-US) and corresponding 90% confidence intervals (CIs) were obtained from the model. The mean differences and the CIs for the differences were exponentiated to provide estimates of the ratio of geometric means and the 90% CIs for the ratios. PK similarity for a given test-to-reference comparison was considered demonstrated if the 90% CIs for the test-to-reference ratios of C_{max}, AUC_t, and AUC_{inf} fell within the 80.00% to 125.00% bioequivalence window.

Additional exploratory PK analyses were planned for assessing potential effects of ADA at low drug concentrations, which included the companion drug concentration collected as part of the ADA assessment at 1680 hours. The same ANOVA analysis (AUC_t, AUC_{inf}, and C_{max}), as based on the first 42-day concentration was planned to be repeated with the inclusion of concentration at 1680 hours. However, due to the high rate of ADA observed, and the small number of subjects with measurable concentrations at 1680 hours, there were insufficient data to perform the analysis.

Exploratory analysis was also performed to examine the relationship between weight and PK parameters. Analysis of covariance (ANCOVA) with treatment as factor and baseline weight as covariate was used for this analysis. The 90% CI between 2 treatment groups was constructed for C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, and AUC_{inf} in the same way as ANOVA.

The PK analysis was carried out with the PP analysis set. Detailed analysis is described in the SAP (Section 16.1.9.1).

9.7.5. Immunogenicity Analysis

The FAS population was used for assessment of immunogenicity.

For the immunogenicity data, the percentage of subjects with positive ADA directed against the assigned study treatment was summarized for each of the 3 treatment groups. For subjects with a positive ADA test by either assay, the percentage of positive ADA also showing cross-reactivity in the alternate ADA test was summarized for each of the 3 treatment groups. In addition, for subjects with a positive ADA test by either assay, the percentage of positive ADA with neutralizing activity was summarized for each of the 3 treatment groups. If neutralizing activity was positive for the assigned study treatment, cross-reactivity for NAb was also evaluated. For subjects with positive ADA and neutralizing antibodies, the magnitude (titer), time of onset, and duration of ADA response were also described, as data permitted.

Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the subjects, the incidence of ADA observed in the planned study may have differed from the incidence reported in historical clinical trials.

In addition, potential effects of ADA formation on the PK profiles of adalimumab were examined individually (PP analysis set), and evaluated between the groups with and without positive ADA and evaluated between the groups with and without positive NAb.

9.7.6. Safety Parameters

The safety analysis was performed in accordance with the sponsor reporting standards. The safety analysis was carried out with the safety analysis set based on safety data including AEs, laboratory data, vital signs, and ECG data. Change from baseline on continuous endpoints was summarized by treatment and visit. Baseline for these endpoints was defined as the most recent measurement prior to dosing.

9.7.6.1. Adverse Events

AEs were coded by MedDRA (version 16.1) and summarized by treatment, severity (NCI CTCAE version 4.03 grade: 1=mild, 2=moderate, 3=severe, 4=life threatening, 5=death), and relationship with the study drug. In addition, AEs reported by ≥ 5% subjects in at least 1 treatment group were summarized by treatment.

SAE presentations were derived from a combination of data in the clinical study database and the corporate safety database. The corporate safety database was a separate, centralized, SAE monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the sponsor (as per Section 9.5.7.2). The clinical study database was based on information provided in PIMS. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

9.7.6.2. Clinical Laboratory Parameters

Laboratory data were listed in accordance with the sponsor's reporting standards. Mean, median, standard deviation (SD), and range for change from baseline were summarized by treatment over time. Laboratory values of special interest and potential clinical concern were summarized by treatment.

9.7.6.3. Other Safety Parameters

9.7.6.3.1. Vital Signs

Change from baseline in vital signs was summarized by treatment over time. Vital signs of special interest and of potential clinical concern were summarized by treatment.

9.7.6.3.2. Electrocardiogram

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, time between the beginning of the P wave and the start of the QRS complex, corresponding to the end of atrial depolarization and onset of ventricular depolarization (PR interval) and QRS interval were summarized by treatment and time.

In addition to categories of abnormal values defined in Table 7, the number (%) of subjects with maximum post-dose QTc values and maximum increases from baseline in the following categories (Table 8) were tabulated by treatment:

Table 8. Safety QTc

	Borderline (msec)	Prolonged (msec)
Absolute value	≥450 - <480	≥480
Absolute change	30 - <60	≥60

Source: Protocol (Section 16.1.1)
Abbreviations: msec=millisecond(s); QT= time from electrocardiogram Q-wave to the end of the T-wave corresponding to electrical systole; QTc=QT interval, corrected for heart rate.

The number of subjects with corrected and uncorrected QT values ≥500 msec was also summarized.

Post-dose ECGs (Day 8 and Day 71) were compared to the Day 1 pre-dose ECG for each subject, and any clinically significant changes were recorded as AEs and evaluated further, as clinically warranted.

9.7.7. Interim Analysis

An interim analysis of the ADA status at baseline was conducted after approximately 20 subjects with prior non-TNF biologics exposure and no fewer than 20 subjects without prior non-TNF biologics exposure had been enrolled into the study. Serum samples collected from these subjects for ADA assessment at baseline, prior to dosing with study drug, were tested with validated ADA assays. The pre-dose positive ADA rates were calculated for subjects with prior non-TNF biologics exposure and subjects without prior non-TNF biologics exposure.

The ADA interim analysis was used to decide whether subjects with prior non-TNF biologics exposure should be excluded from subsequent enrollment in the study. Subjects with prior biologics exposure would be entirely excluded from subsequent study enrollment if the pre-specified criteria (Section 9.3.2) were met based on the review of the data.

In addition, this was a sponsor-open study. Unblinded safety and immunogenicity data were reviewed by the study team (clinicians, statistician, and clinical pharmacologist) on an ongoing basis to ensure the safety of the study subjects.

9.8. Changes in the Conduct of the Study or Planned Analyses

To better characterize the similarity among the adalimumab-Pfizer, adalimumab-US and adalimumab-EU treatments, $AUC_{0\text{-}2wk}$ was analyzed using the same statistical analysis as for AUC_t, AUC_{inf}, and C_{max} of Day 1 to Day 43.

Statistical analysis of AUC_t, AUC_{inf}, and C_{max} including companion drug concentration collected as part of the ADA assessment at 1680 hours on Day 71 was planned as an exploratory analysis to help describe the effect of immunogenicity on the drug exposure. However, due to low number of subjects with measurable adalimumab serum concentrations at 1680 hours, this analysis was not informative and thus was not performed.

For change from baseline in laboratory values over time, the visits (scheduled assessment time points) were based on time window (Section 16.1.9.3) in order to include the tests deviating from protocol defined time points.

10. STUDY SUBJECTS

10.1. Disposition of Subjects

A total of 210 subjects were randomized to 1 of the 3 study treatment groups (Table 9). Sixty-nine (69) subjects received adalimumab-Pfizer, 71 subjects received adalimumab-US, and 70 subjects received adalimumab-EU. Two (2) subjects discontinued from the study due to withdrawal by subject (1 subject each in the adalimumab-Pfizer group and adalimumab-EU group), of whom the 1 subject ([redacted]) in the adalimumab-EU group was still evaluable in the PK population (Tables 16.2.1.1 and 16.2.1.2). Eleven (11) subjects were excluded from the primary PK analysis (3 subjects in the adalimumab-Pfizer group,

4 subjects in the adalimumab-US group, and 4 subjects in the adalimumab-EU group). All subjects who received study drug were analyzed for safety; the FAS and safety populations are identical as all subjects were correctly dosed.

Table 9. Subject Disposition and Evaluation Groups

	Adalimumab			Total
Number (%) of Subjects	**Pfizer**	**US**	**EU**	
Assigned to Study Treatment:	**69 (100.0%)**	**71 (100.0%)**	**70 (100.0%)**	**210 (100.0%)**
Treated	69 (100.0%)	71 (100.0%)	70 (100.0%)	210 (100.0%)
Not treated	0	0	0	0
Completed	68 (98.6%)	71 (100.0%)	69 (98.6%)	208 (99.0%)
Discontinued	1 (1.4%)	0	1 (1.4%)	2 (1.0%)
Withdrawal by subject	1 (1.4%)	0	1 (1.4%)	2 (1.0%)
Full analysis set	69 (100.0%)	71 (100.0%)	70 (100.0%)	210 (100.0%)
Per-protocol analysis set	66 (95.7%)	67 (94.4%)	66 (94.3%)	199 (94.8%)
Safety analysis set	69 (100.0%)	71 (100.0%)	70 (100.0%)	210 (100.0%)

Source: Table 14.1.1.1 and Table 14.1.1.2
Abbreviations: EU=European Union; US=United States.

An interim analysis was performed to decide whether subjects with prior non-TNF biologics exposure should be excluded from subsequent enrollment in the study. Subjects with prior biologics exposure would be entirely excluded from subsequent study enrollment if the pre-specified criteria (Section 9.3.2) were met based on the review of the data. Based on interim analysis performed for 21 subjects with prior non-TNF biologics exposure and 20 subjects with no prior non-TNF biologics exposure, with only 1 pre-dose positive ADA test in a subject with no prior biologics exposure, the pre-specified criteria were not met and thus the study continued without exclusion of subjects with prior non-TNF biologics exposure.

10.2. Protocol Deviations

There were only 2 protocol deviations during the conduct of this study (Section 16.2.2). One subject ([redacted] was non-compliant with the 48-hour activity restriction prior to a study visit. Another subject ([redacted] engaged in strenuous activity within 48 hours of a study visit. Neither of these protocol deviations was considered to be potentially important. A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained.

10.3. Prior and Concomitant Treatments

Concomitant Treatments

Concomitant drug treatments are listed in Table 16.2.5.2 and concomitant non-drug treatments are listed in Table 16.2.5.3.

The most commonly used concomitant drug treatment across the 3 groups was paracetamol mainly for headache/fever/common cold/flu-like symptoms.

The most common concomitant non-drug interventions were office visits in the adalimumab-Pfizer group, dental care in the adalimumab–US group and vital sign measurements in the adalimumab–EU treatment group.

Prior Exposure to Biologics

The status of subjects' prior exposure to biologics other than TNF inhibitors is summarized in Table 14.1.2.4 and listed in Table 16.2.4.1.2. Most subjects (183 out of 210 subjects; 87.1%) had no prior exposure to non-TNF biologics: 59 (85.5%) subjects in the adalimumab-Pfizer group, 63 (88.7%) subjects in the adalimumab-US group, and 61 (87.1%) subjects in the adalimumab-EU group.

11. PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

11.1. Data Sets Analyzed

Among the 210 subjects who received the assigned study drug, 11 subjects (3 in adalimumab-Pfizer, 4 in adalimumab-US, and 4 in adalimumab-EU) were excluded from the PP analysis set (Table 10). Of these 11 subjects, 2 (Subjects [redacted] and [redacted]) were excluded because the measured serum concentration of adalimumab in the pre-dose sample was greater than 5% of the C for each of the subjects. An additional 9 subjects (Subjects [redacted], and [redacted]) were excluded because their PK profiles exhibited an insufficient terminal phase, due to missing concentrations at later time points (PK samples were not collected at these time points) or because of the impact of ADA on the terminal phase. For each subject, the terminal phase was considered sufficient if the profile showed: 1) measurable concentrations to at least the 504-hour time point; and 2) measurable concentrations at a minimum of 3 time points after the observed T_{max}.

With the exception of the exclusions listed below, all concentration-time data were included in the PK data analysis.

Table 10. Subjects Excluded from PP Analysis Set

	Adalimumab		
	Pfizer	**US**	**EU**
Number of Subjects Excluded from PP Analysis Set	3	4	4
Reason for Exclusion			
Pre-dose serum concentration >5% of C_{max}	0	1	1
Incomplete PK lacking a defined terminal phase	3	3	3

Source: Table 16.2.5.1.2
Abbreviations: C_{max}=maximum observed serum concentration; EU=European Union; PK=pharmacokinetic; PP = per-protocol; US=United States.

11.2. Demographic and Other Baseline Characteristics

The demographic and baseline characteristics are summarized in Table 11 (safety analysis set), Tables 14.1.2.2 and 14.1.2.2.1 (FAS), and Table 12 (PP analysis set).

All subjects were male, except for 1 female in the adalimumab-EU group. The majority of the subjects were White (131 out of 210 subjects, 62.4%). There were no notable differences between mean weight, height, or BMI across the cohorts. Combining all 3 cohorts, the mean age was 35 years (range: 18 to 54 years), the mean weight was 81.1 kg (range: 50.8 to 107.7 kg), and the mean BMI was 25.8 kg/m^2 (range: 17.7 to 30.5 kg/m^2).

Table 11. Demographic and Baseline Characteristics (Safety Analysis Set)

	Adalimumab			Total
	Pfizer (N=69)	US (N=71)	EU (N=70)	(N=210)
Gender, n:				
Male	69	71	69	209
Female	0	0	1	1
Age (years), n (%):				
18-44	57 (82.6%)	55 (77.5%)	56 (80.0%)	168 (80.0%)
45-64	12 (17.4%)	16 (22.5%)	14 (20.0%)	42 (20.0%)
≥65	0	0	0	0
Mean (SD)	34.3 (9.9)	35.3 (9.2)	35.2 (9.1)	35.0 (9.4)
Range	19-54	18-54	20-54	18-54
Race, n (%):				
White	43 (62.3%)	44 (62.0%)	44 (62.9%)	131 (62.4%)
Black	19 (27.5%)	17 (23.9%)	18 (25.7%)	54 (25.7%)
Asian	0	4 (5.6%)	0	4 (1.9%)
Other	7 (10.1%)	6 (8.5%)	8 (11.4%)	21 (10.0%)
Weight (kg):				
Mean (SD)	80.5 (12.1)	80.6 (10.6)	82.1 (11.6)	81.1 (11.4)
Range	50.8-107.7	59.8-101.6	58.7-105.6	50.8-107.7
BMI (kg/m^2)[a]:				
Mean (SD)	25.5 (3.2)	25.9 (2.9)	25.9 (3.0)	25.8 (3.0)
Range	17.7-30.5	19.7-30.4	19.8-30.4	17.7-30.5
Height (cm):				
Mean (SD)	177.7 (7.4)	176.6 (6.7)	177.8 (6.5)	177.4 (6.9)
Range	159.0-194.0	161.0-197.0	163.0-192.0	159.0-197.0

Source: Tables 14.1.2.1 and 14.1.2.1.1
Abbreviations: BMI=Body Mass Index; EU=European Union; N=number of evaluable subjects; n=number of subjects meeting specified criteria; SD=standard deviation; US=United States.
a. BMI was defined as weight/(height × 0.01)^2.

Table 12. Demographic and Baseline Characteristics (Per-Protocol Analysis Set)

	Adalimumab			Total
	Pfizer (N=66)	US (N=67)	EU (N=66)	(N=199)
Gender, n:				
Male	66	67	65	198
Female	0	0	1	1
Age (years), n (%):				
18-44	55 (83.3%)	52 (77.6%)	53 (80.3%)	160 (80.4%)
45-64	11 (16.7%)	15 (22.4%)	13 (19.7%)	39 (19.6%)
≥65	0	0	0	0
Mean (SD)	34.5 (9.8)	35.3 (9.3)	35.1 (9.1)	35.0 (9.4)
Range	19-54	18-54	20-54	18-54
Race, n (%):				
White	42 (63.6%)	41 (61.2%)	41 (62.1%)	124 (62.3%)
Black	18 (27.3%)	17 (25.4%)	18 (27.3%)	53 (26.6%)
Asian	0	3 (4.5%)	0	3 (1.5%)
Other	6 (9.1%)	6 (9.0%)	7 (10.6%)	19 (9.5%)
Weight (kg):				
Mean (SD)	80.4 (12.2)	80.2 (10.4)	82.3 (11.6)	81.0 (11.4)
Range	50.8-107.7	59.8-101.6	58.7-105.6	50.8-107.7
BMI (kg/m^2)[a]:				
Mean (SD)	25.5 (3.2)	25.8 (2.9)	26.0 (3.0)	25.7 (3.0)
Range	17.7-30.5	19.7-30.4	19.8-30.4	17.7-30.5
Height (cm):				
Mean (SD)	177.6 (7.4)	176.4 (6.8)	177.9 (6.5)	177.3 (6.9)
Range	159.0-194.0	161.0-197.0	163.0-192.0	159.0-197.0

Source: Tables 14.1.2.3 and 14.1.2.3.1
Abbreviations: BMI=Body Mass Index; EU=European Union; N=number of evaluable subjects; n=number of subjects meeting specified criteria; SD=standard deviation; US=United States.
a. Body Mass Index was defined as weight/(height × 0.01)^2.

11.3. Measurements of Treatment Compliance

Study treatment was administered under the supervision of investigator site personnel. Details of the administration schedule were recorded in PIMS and listed in Table 16.2.5.1.1.

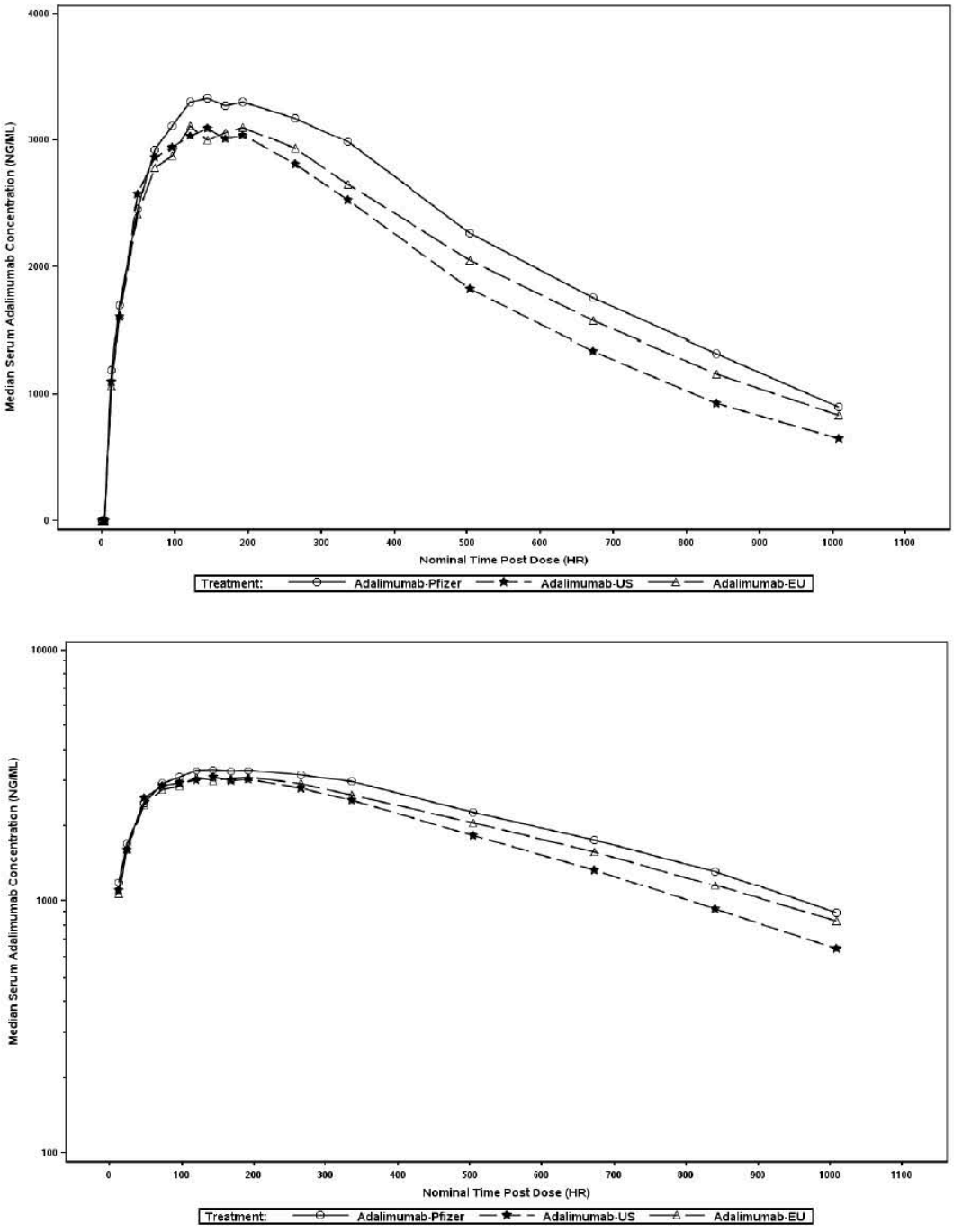
11.4. Pharmacokinetic and Immunogenicity Results

11.4.1. Pharmacokinetic Results

A total of 199 subjects were included in the PK data analysis, among whom 66, 67, and 66 subjects received adalimumab-Pfizer, adalimumab-US, and adalimumab-EU, respectively. The 3 groups of PK eligible subjects showed similar demographic characteristics (Table 12).

Median serum concentration-time profiles for adalimumab-Pfizer, adalimumab-US, and adalimumab-EU (Day 1-43) are presented in Figure 1. The 3 study drugs exhibited a similar PK profile, which was characterized by an increase of serum drug concentration after SC dosing, with C_{max} achieved after approximately 1 week, followed by a multi-phasic decline in drug concentrations.

Figure 1. Median Serum Concentration-Time Profiles of Adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU Following a Single 40-mg SC Dose to Healthy Subjects (Day 1-43, PP Analysis Set)



Source: Figure 14.4.2.2.1 and Figure 14.4.2.2.2
Upper and lower panels are linear and semi-logarithmic scales, respectively.
For corresponding mean plots, see Figure 14.4.2.2.3 and Figure 14.4.2.2.4.
Abbreviations: EU=European Union; HR=hour; ML=milliliter; NG=nanogram; PP=per-protocol; SC=subcutaneous; US=United States.

The mean (±SD) PK parameters (from Day 1 to Day 43) for adalimumab-Pfizer, adalimumab-US, and adalimumab-EU are summarized in Table 13. Consistent with the mean concentration-time profiles, the mean C_{max}, $AUC_{0\text{-}2wk}$, AUC_t and AUC_{inf} estimates were similar among the 3 study drugs. In addition, the inter-subject variability for each of the PK parameters was similar across the 3 study drugs, with %CV values of 30% to 31% for C_{max}, 31% to 32% for $AUC_{0\text{-}2wk}$, 30% to 33% for AUC_t, and 39% to 43% for AUC_{inf} (Table 14.4.3.1.1.1).

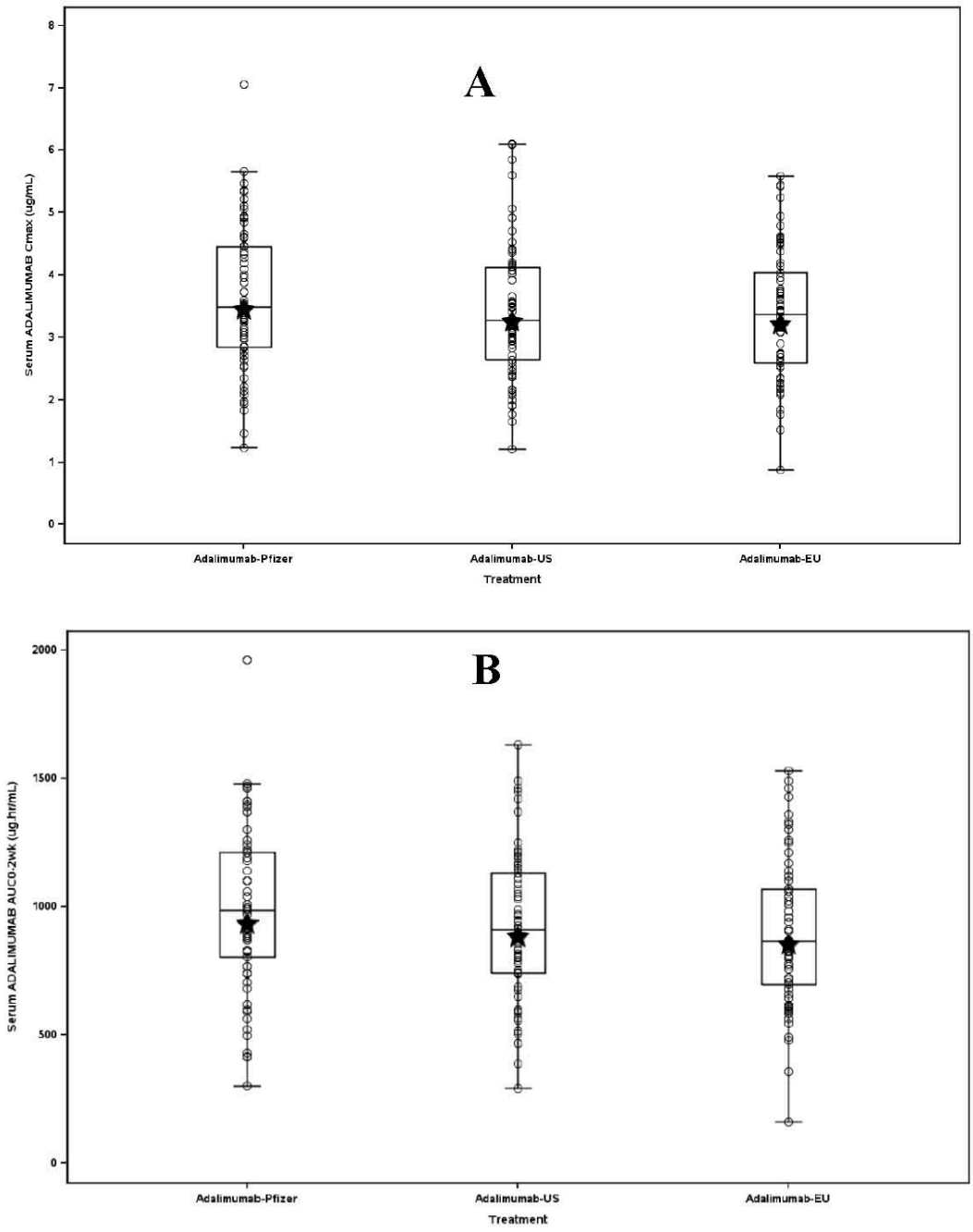
Table 13. Mean (±SD) PK Parameter Estimates of Adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU (Day 1-43, PP Analysis Set)

Parameters (units)	Adalimumab-Pfizer (N=66)	Adalimumab-US (N=67)	Adalimumab-EU (N=66)
C_{max} (µg/mL)	3.63 ± 1.13	3.41 ± 1.07	3.37 ± 1.02
$AUC_{0\text{-}2wk}$ (µg•hr/mL)	988.5 ± 318.40	927.5 ± 286.06	903.7 ± 286.92
AUC_t (µg•hr/mL)	2200 ± 723.80	1869 ± 598.48	1958 ± 579.48
AUC_{inf} (µg•hr/mL)	2969 ± 1284.7	2357 ± 918.4	2587 ± 1039.7
CL/F (mL/hr)	16.39 ± 7.77	20.04 ± 8.88	18.32 ± 8.74
V_z/F (mL)	8575 ± 3135.9	9088 ± 3532.7	9080 ± 2891.9
$t_{½}$ (hr)	427.5 ± 200.65	367.3 ± 187.64	403.4 ± 199.64
T_{max} (hr)[a]	168	168	168

Source: Table 14.4.3.1.1.1
PK parameters are defined in Table 3.
Abbreviations: EU=European Union; hr=hour; mL=milliliter; N=number of subjects; PK=pharmacokinetic(s); PP=per-protocol; SD=standard deviation; µg=microgram; US=United States.
a. T_{max} is reported as median.

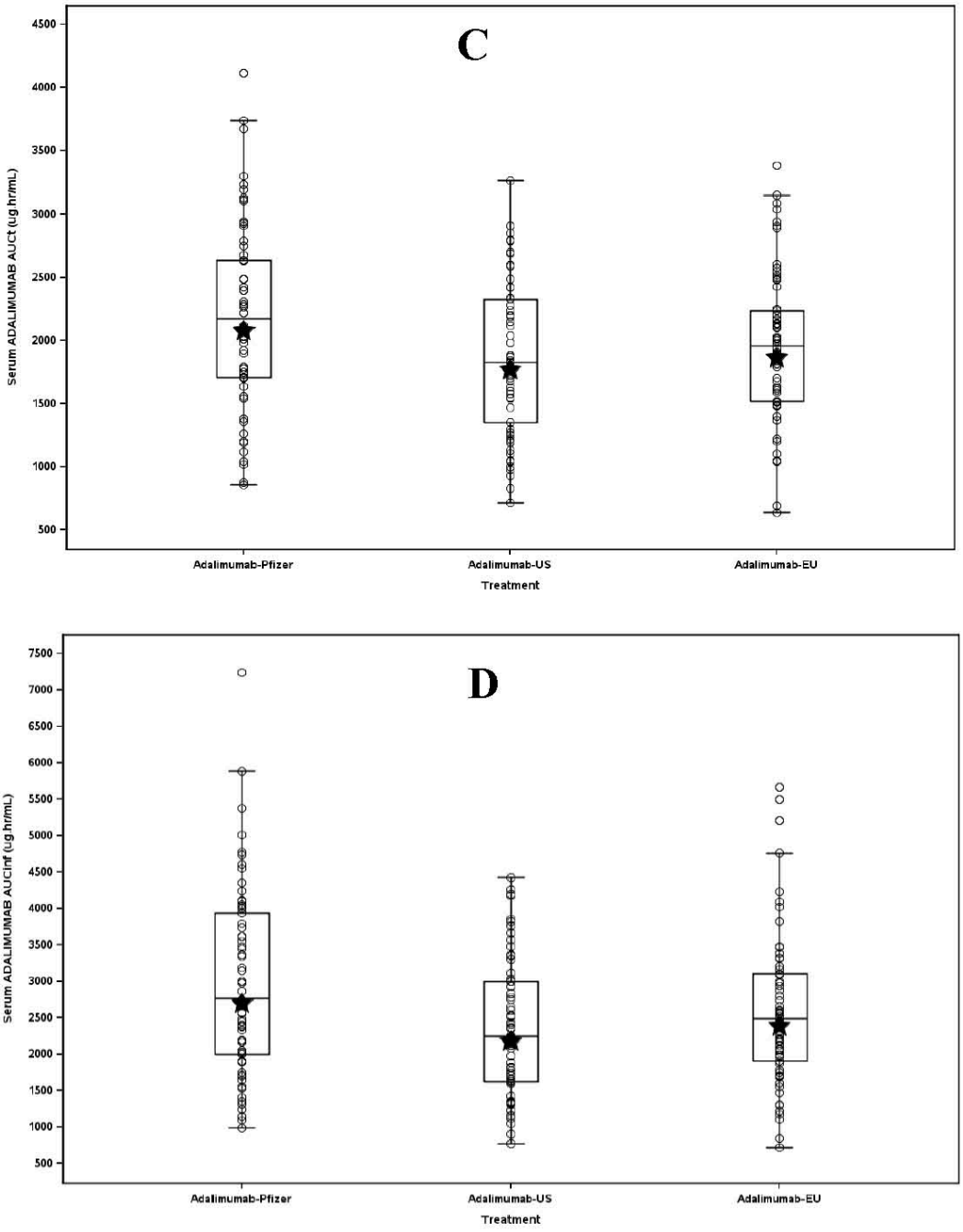
The distributions of individual and geometric mean C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, and AUC_{inf} (from Day 1 to Day 43) are plotted by treatment in box and whisker plots in Figure 2 and Figure 3.

Figure 2. Individual and Geometric Mean Values of C_{max} (Panel A) and $AUC_{0\text{-}2wk}$ (Panel B) of Adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU (Day 1-43, PP Analysis Set)



Source: Figure 14.4.3.2.3.1 and Figure 14.4.3.2.4.1
PK parameters are defined in Table 3.
Stars represent geometric mean and circles represent individual subject values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times inter-quartile range.
Abbreviations: EU=European Union; hr=hour; mL=milliliter; PK=pharmacokinetic(s); PP=per-protocol; µg=microgram; US=United States.

Figure 3. Individual and Geometric Mean Values of AUC_t (Panel C) and AUC_{inf} (Panel D) of Adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU (Day 1-43, PP Analysis Set)



Source: Figure 14.4.3.2.1.1 and Figure 14.4.3.2.2.1
PK parameters are defined in Table 3.
Stars represent geometric mean and circles represent individual subject values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times inter-quartile range.
Abbreviations: EU=European Union; hr=hour; mL=milliliter; PK=pharmacokinetic(s); PP=per-protocol; µg=microgram; US=United States.

Table 14 summarizes the ratio of adjusted geometric means and the 90% CIs for the test-to-reference comparisons (Day 1-Day 43). For the PK similarity comparison of adalimumab-Pfizer to the adalimumab-EU reference product, the 90% CIs for the test-to-reference ratios of C_{max}, AUC_{0-2wk}, and AUC_t were all within the bioequivalence window of 80.00% to 125.00%, while the 90% CI for the test-to-reference ratio of AUC_{inf} was outside the bioequivalence window of 80.00% to 125.00%. For the PK similarity comparison of adalimumab-Pfizer to the adalimumab-US reference product, the 90% CIs for the test-to-reference ratios of C_{max} and AUC_{0-2wk} were within the bioequivalence window of 80.00% to 125.00%, while the 90% CIs for the test-to-reference ratios of AUC_t and AUC_{inf} were outside the bioequivalence window of 80.00% to 125.00%. For the comparison of adalimumab-EU to adalimumab-US, the 90% CIs of the ratios of C_{max}, AUC_{0-2wk}, AUC_t, and AUC_{inf} were all within 80.00% to 125.00%.

Table 14. Summary of Statistical Comparisons of PK Exposure Parameters (C_{max}, AUC_{0-2wk}, AUC_t, and AUC_{inf}) Between Test and Reference Products (Day 1-43, PP Analysis Set)

Parameter (units)	Adjusted Geometric Means		Ratio[a] (Test/Reference) of Adjusted Means	90% CI for Ratio[a]
	Test	Reference		
Adalimumab-Pfizer (Test) vs. Adalimumab-EU (Reference)				
C_{max} (µg/mL)	3.44	3.20	107.58	97.73, 118.42
AUC_{0-2wk} (µg•hr/mL)	932.7	851.9	109.48	98.77, 121.35
AUC_t (µg•hr/mL)	2075	1866	111.21	100.77, 122.72
AUC_{inf} (µg•hr/mL)	2700	2388	113.10	100.08, 127.82
Adalimumab-Pfizer (Test) vs. Adalimumab-US (Reference)				
C_{max} (µg/mL)	3.44	3.25	106.07	96.39, 116.72
AUC_{0-2wk} (µg•hr/mL)	932.7	880.0	105.99	95.65, 117.44
AUC_t (µg•hr/mL)	2075	1768	117.39	106.41, 129.50
AUC_{inf} (µg•hr/mL)	2700	2177	124.04	109.81, 140.11
Adalimumab-EU (Test) vs. Adalimumab-US (Reference)				
C_{max} (µg/mL)	3.20	3.25	98.59	89.60, 108.49
AUC_{0-2wk} (µg•hr/mL)	851.9	880.0	96.81	87.37, 107.27
AUC_t (µg•hr/mL)	1866	1768	105.56	95.69, 116.45
AUC_{inf} (µg•hr/mL)	2388	2177	109.67	97.09, 123.88

Source: Table 14.4.3.3.1.1
PK parameters are defined in Table 3.
Statistical analysis was performed on the log-transformed parameters. Values presented in the table had been back-transformed from the log scale to the original scale.
Abbreviations: CI=confidence interval; EU=European Union; hr=hour; mL=milliliter; PK=pharmacokinetic(s); PP=per-protocol; µg=microgram; US=United States; vs=versus.
a. The ratios (and 90% CIs) are expressed as percentages.

Examining the test-to-reference ratios of C_{max} and AUC_{0-2wk} for the comparisons of adalimumab-Pfizer versus adalimumab-EU and of adalimumab-Pfizer versus adalimumab-US reveals that the C_{max} and AUC_{0-2wk} ratios were slightly higher than 100%.

It was also observed from the test-to-reference ratios of AUC for the comparisons of adalimumab-EU versus adalimumab-US and of adalimumab-Pfizer versus adalimumab-US in Table 14 that the ratios increase from AUC_{0-2wk} to AUC_t, and further to AUC_{inf}, for a total

increase of approximately 13% (96.81% to 109.67%) for adalimumab-EU versus adalimumab-US, and approximately 18% (105.99% to 124.04%) for adalimumab-Pfizer versus adalimumab-US. This was consistent with the observation of a relatively accelerated terminal disposition phase and shorter $t_{½}$ estimates for the adalimumab-US group (Table 13), which could be attributed to a trend toward higher ADA/NAb responses (incidence and titer) in subjects from the adalimumab-US group.

11.4.2. Supporting Data

Individual serum concentration-time data (Day 1-43) are listed in Table 16.2.5.4.1.1.1, along with nominal and actual sample collection times. Sample time deviations and comments are (Day 1-43) listed in Table 16.2.5.4.1.3.1. Individual plasma concentration-time profiles (Day 1-43) by subject and by treatment (in linear and semi-log scales) are presented in Figures 16.2.5.4.2.1.1, 16.2.5.4.2.3.1, 16.2.5.4.2.2.1, and 16.2.5.4.2.4.1, respectively. A summary of serum concentrations (Day 1-43) by time and treatment is presented in Table 14.4.2.1.1.

Table 16.2.5.5.1.1 lists the individual subject values for all PK parameters (Day 1-43), including the following supportive parameters: serum concentration at the last quantifiable time point estimated from the log linear regression analysis (C_{last}), time point when C_{last} occurred (T_{last}), T_{max}, $t_{½}$, CL/F, V_z/F, and mean residence time (MRT).

Individual and geometric mean C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, and AUC_{inf} (Day 1-43) are plotted by treatment in Figures 14.4.3.2.3.1, 14.4.3.2.4.1, 14.4.3.2.1.1, and 14.4.3.2.2.1, respectively.

Supporting output for statistical summary of PK parameters (C_{max}, $AUC_{0\text{-}2wk}$, AUC_t, and AUC_{inf}) is presented in Table 16.1.9.2.1.1 (Day 1-43). Supporting data for estimation of $t_{½}$ is presented in Table 16.2.5.5.2.1.

Exploratory analyses were also conducted as described in the SAP. The statistical summary of PK parameters with weight as a covariate (Day 1-43) is presented in Table 14.4.3.3.2.1, and the supporting statistical output (Day 1-43) is presented in Table 16.1.9.2.2.1. A descriptive summary of PK parameters (Day 1-43) by NAb status is presented in Table 14.4.3.1.1.2. An exploratory analysis based on Day 1-71 PK data was also conducted. Serum drug concentrations for individual subjects on Day 71 are listed in Table 16.2.5.4.1.1.2 and summarized in Table 14.4.2.1.2. Sample deviations and comments for Day 71 are listed in Table 16.2.5.4.1.3.2. Individual PK parameters for subjects with measurable serum concentrations of adalimumab on Day 71 are presented in Table 16.2.5.5.1.2. Supporting data for the estimation of $t_{½}$ for these subjects is presented in Table 16.2.5.5.2.2. A descriptive summary of the PK parameters based on the subjects with measurable serum concentrations of adalimumab on Day 71 is presented in Table 14.4.3.1.2.1. No further analyses were conducted due to the low number of subjects with measurable adalimumab serum concentrations on Day 71.

11.4.3. Immunogenicity Results

The incidence of ADA and NAb is presented in Table 15. On Study Day 1 prior to dosing, the number of subjects positive for ADA was 3 (4.3%), 2 (2.8%) and 2 (2.9%) subjects in the

adalimumab-Pfizer, adalimumab-US and adalimumab-EU treatment groups, respectively (Table 14.4.5.1.1.1). None of the 7 pre-dose ADA positive subjects except for Subject 10011073 in the adalimumab-EU treatment group had prior exposure to non-TNF biologics (Tables 16.2.4.1.2 and 16.2.8.5.1). All 7 subjects continued to test ADA positive following dose administration and were included in the primary PK analysis (Tables 16.2.8.5.1 and 16.2.1.1).

Following dose administration, 59/69 (85.5%), 67/71 (94.4%) and 63/70 (90.0%) subjects in each treatment group tested ADA positive at 1 or more time points with a titer ≥1.88 (Table 14.4.5.1.1.1). Overall, the 3 treatment groups had a comparable ADA profile, with a trend toward slightly higher ADA incidence in the adalimumab-US group at each time point (Table 14.4.5.1.1.1). The ADA titer is summarized by treatment group in Table 14.4.5.1.3.1 (FAS).

Table 15. Summary of ADA and NAb Incidence by Treatment Groups: Adalimumab-Pfizer, Adalimumab-US, and Adalimumab-EU (Full Analysis Set)

Number (%) of Subjects	Adalimumab-Pfizer (N=69)	Adalimumab-US (N=71)	Adalimumab-EU (N=70)
≥1 incidence of positive ADA post-dose	59 (85.5%)	67 (94.4%)	63 (90.0%)
≥1 incidence of positive NAb post-dose	37 (53.6%)	47 (66.2%)	43 (61.4%)

Source: Table 14.4.5.1.1.1 and Table 14.4.5.2.1.1
Abbreviations: ADA=anti-drug antibodies; EU=European Union; N=number of subjects; NAb=neutralizing antibodies; US=United States.

In all treatment groups, the greatest number of ADA positive samples was detected on Day 71 (ie, 1680 hours post-dose) (Table 14.4.5.1.1.1). A summary of ADA day of onset is provided in Table 14.4.5.1.4.1 (FAS).

A majority of the 189 subjects who tested positive for ADA post-dose also tested positive for cross-reactivity using the alternative assay: 57/59 (97%) in adalimumab-Pfizer, 65/67 (97%) in adalimumab-US and 63/63 (100%) in adalimumab-EU (Table 14.4.5.1.1.1 and Table 14.4.5.1.2.1.1). For the 412 samples that tested positive for ADA post-dose, 110/129 (85%), 145/154 (94%) and 118/129 (91%) samples also tested positive for cross-reactivity using the alternative assay in the adalimumab-Pfizer, adalimumab-US and adalimumab-EU groups, respectively (Table 14.4.5.1.2.2.1).

The samples that tested positive for ADA were also further tested for NAb. Of the 189 subjects who tested positive for ADA post-dose, 127 (67%) subjects tested positive for NAb at 1 or more time points: 37/59 (63%) for adalimumab-Pfizer, 47/67 (70%) for adalimumab-US and 43/63 (68%) for adalimumab-EU (Table 14.4.5.1.1.1 and Table 14.4.5.2.1.1). A summary of the NAb titer results is presented in Table 14.4.5.2.4.1. A summary of the NAb titer results by treatment and quartile for subjects with positive NAb test is presented in Table 14.4.5.2.3.1. Summaries of NAb cross-reactivity results for the NAb positive samples and for all subjects (FAS) are presented in Table 14.4.5.2.2.2.1 and Table 14.4.5.2.2.1.1, respectively.

A listing of the ADA results for individual subjects is presented in Table 16.2.8.5.1. A listing of the NAb results for individual subjects is presented in Table 16.2.8.5.2.

11.4.4. Statistical/Analytical Issues

No statistical or analytical issues were identified. Procedures for the handling of abnormal values or missing data can be found in the SAP (Section 16.1.9.1).

11.4.5. Pharmacokinetic and Immunogenicity Conclusions

There was a high incidence of immunogenicity following a single 40-mg SC dose of adalimumab-Pfizer, adalimumab-EU, and adalimumab-US in healthy subjects. The 3 treatment groups had a comparable ADA profile, although adalimumab-US showed a trend towards higher incidence of ADA response compared to that of the adalimumab-Pfizer or adalimumab-EU group. A majority of the ADA positive subjects also developed NAb. ADA cross-reactivity was quite high (97%-100% of the subjects with ADA) (Day 1-71).

Overall, there appeared to be minimal differences in drug product characteristics, as indicated by similar C_{max} and $AUC_{0\text{-}2wk}$; the PK similarity of adalimumab-Pfizer to both adalimumab-EU and adalimumab-US, and of adalimumab-EU to adalimumab-US, has been demonstrated for these parameters.

The development of ADA/NAb had profound effects on the estimates of AUC_t and AUC_{inf}. For AUC_t, the 80.00% to 125.00% acceptance criterion was met for the comparisons of adalimumab-Pfizer to adalimumab-EU and adalimumab-EU to adalimumab-US, but not for the comparison of adalimumab-Pfizer to adalimumab-US; the upper limit of the 90% CI for the latter comparison was slightly outside of the acceptance criterion, which was attributed largely to a trend toward higher observed immunogenicity response in subjects from the adalimumab-US group. The AUC_{inf} estimation was not reliable due to the formation of ADA/NAb.

The demonstration of similarity of adalimumab-EU to adalimumab-US fulfilled the PK bridging objective, supporting use of only 1 of the 2 innovator products as the reference comparator in future clinical trials.

12. SAFETY EVALUATION

12.1. Extent of Exposure

All subjects in the study received study medication according to their randomized sequence (Table 16.1.7.2).

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

All-Causality Adverse Events:

An overview of all-causality treatment-emergent adverse events (TEAEs) is presented in Table 16.

A total of 219 TEAEs were reported in 114 subjects, including 49 TEAEs in the adalimumab-Pfizer group, 77 TEAEs in the adalimumab-US group, and 93 TEAEs in the adalimumab-EU group.

Overall, 114 of 210 subjects (54.3%) experienced a TEAE (32 subjects [46.4%] for adalimumab-Pfizer; 38 subjects [53.5%] for adalimumab-US; 44 subjects [62.9%] for adalimumab-EU). One (1) subject experienced an SAE (adalimumab-EU group). Three (3) subjects (1.4%) experienced Grade 3 (severe) or Grade 4 (life-threatening) TEAEs (1 subject [1.4%] for adalimumab-US; 2 subjects [2.9%] for adalimumab-EU) (see ERRATA). No subjects discontinued (permanently or temporarily) from the study or had dose reductions due to an AE. No deaths occurred during this study.

Table 16. Summary of Treatment-Emergent Adverse Events, All-Causality

	Adalimumab			Total
Number (%) of Subjects	**Pfizer (N=69)**	**US (N=71)**	**EU (N=70)**	**(N=210)**
Number of AEs	49	77	93	219
Subjects with AEs	32 (46.4%)	38 (53.5%)	44 (62.9%)	114 (54.3%)
Subjects with SAEs	0	0	1 (1.4%)	1 (0.5%)
Subjects with Grade 3 or 4 AEs	0	1 (1.4%)	2 (2.9%)	3 (1.4%)
Subjects with Grade 5 AEs	0	0	0	0
Subjects discontinued from study due to AEs	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0

Source: Table 14.3.1.2.1, see ERRATA
Subjects 10021505 and 10021577 had 2 laboratory abnormalities that were reported as Grade 2 AEs, however, the abnormalities were actually Grade 3; numbers and percentages affected by these 2 subjects are not corrected in this table and relevant text.
Except for the number of AEs, subjects were counted only once per treatment in each row.
Included all data collected since the first dose of study treatment.
Abbreviations: AE=adverse event; EU=European Union; N=number of subjects; SAE=serious adverse event, US=United States.

Treatment-Related Adverse Events:

An overview of treatment-related TEAEs is presented in Table 17.

A total of 97 treatment–related TEAEs were reported in 63 subjects, including 19 TEAEs in the adalimumab-Pfizer group, 39 TEAEs in the adalimumab-US group, and 39 TEAEs in the adalimumab-EU group.

Overall, 63 of 210 subjects (30.0%) experienced a treatment-related AE (15 subjects [21.7%] for adalimumab-Pfizer; 24 subjects [33.8%] for adalimumab-US; 24 subjects [34.3%] for adalimumab-EU). Two (2) subjects (1.0%) experienced treatment-related Grade 3 (severe) or Grade 4 (life-threatening) AEs (1 subject [1.4%] for adalimumab-US; 1 subject [1.4%] for adalimumab-EU). There were no treatment-related SAEs.

Table 17. Summary of Treatment-Emergent Adverse Events, Treatment-Related

Number (%) of Subjects	Adalimumab			Total
	Pfizer (N=69)	US (N=71)	EU (N=70)	(N=210)
Number of AEs	19	39	39	97
Subjects with AEs	15 (21.7%)	24 (33.8%)	24 (34.3%)	63 (30.0%)
Subjects with SAEs	0	0	0	0
Subjects with Grade 3 or 4 AEs	0	1 (1.4%)	1 (1.4%)	2 (1.0%)
Subjects with Grade 5 AEs	0	0	0	0
Subjects discontinued from study due to AEs	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0

Source: Table 14.3.1.3.1
Except for the number of AEs, subjects were counted only once per treatment in each row.
Included all data collected since the first dose of study treatment.
Abbreviations: AE=adverse event; EU=European Union; N=number of subjects; SAE=serious adverse event; US=United States.

12.2.2. Incidence of Adverse Events

12.2.2.1. All-Causality Adverse Events

The incidence of all-causality TEAEs is summarized in Table 18. The most frequently reported AEs were in the MedDRA system organ class (SOC) of Infections and Infestations (14 subjects [20.3%] for adalimumab-Pfizer; 13 subjects [18.3%] for adalimumab-US; 20 subjects [28.6%] for adalimumab-EU) and Gastrointestinal Disorders (9 subjects [13.0%] for adalimumab-Pfizer; 14 subjects [19.7%] for adalimumab-US; 14 subjects [20.0%] for adalimumab-EU). In the Infections and Infestations SOC, the most common all-causality AEs were nasopharyngitis (17 subjects, 8.1%), influenza (7 subjects, 3.3%), and oral herpes (6 subjects, 2.9%); and in the Gastrointestinal Disorders SOC, the most common all-causality AEs were diarrhea (7 subjects, 3.3%), nausea (7 subjects, 3.3%), and abdominal pain (5 subjects, 2.4%) (Table 14.3.1.2.2.1).

There was 1 reported SAE in this study (Table 14.3.2.2) (See Section 12.3.2.2 for more details).

Table 18. Incidence of Treatment-Emergent Adverse Events, All-Causality

Number (%) of Subjects with AEs by MedDRA (version 16.1) SOC	Adalimumab			Total
	Pfizer N=69	US N=71	EU N=70	N=210
Any AEs	**32 (46.4%)**	**38 (53.5%)**	**44 (62.9%)**	**114 (54.3%)**
Ear and Labyrinth Disorders	1 (1.4%)	0	0	1 (0.5%)
Eye Disorders	0	1 (1.4%)	1 (1.4%)	2 (1.0%)
Gastrointestinal Disorders	9 (13.0%)	14 (19.7%)	14 (20.0%)	37 (17.6%)
General Disorders and Administration Site Conditions	4 (5.8%)	9 (12.7%)	5 (7.1%)	18 (8.6%)
Infections and Infestations	14 (20.3%)	13 (18.3%)	20 (28.6%)	47 (22.4%)
Injury, Poisoning and Procedural Complications	1 (1.4%)	0	3 (4.3%)	4 (1.9%)
Investigations	0	1 (1.4%)	3 (4.3%)	4 (1.9%)
Metabolism and Nutrition Disorders	0	1 (1.4%)	1 (1.4%)	2 (1.0%)
Musculoskeletal and Connective Tissue Disorders	5 (7.2%)	8 (11.3%)	8 (11.4%)	21 (10.0%)
Nervous System Disorders	6 (8.7%)	11 (15.5%)	15 (21.4%)	32 (15.2%)
Psychiatric Disorders	3 (4.3%)	2 (2.8%)	1 (1.4%)	6 (2.9%)
Renal and Urinary Disorders	0	0	1 (1.4%)	1 (0.5%)
Reproductive System and Breast Disorders	1 (1.4%)	0	0	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders	5 (7.2%)	4 (5.6%)	5 (7.1%)	14 (6.7%)
Skin and Subcutaneous Tissue Disorders	0	2 (2.8%)	3 (4.3%)	5 (2.4%)
Surgical and Medical Procedures	0	1 (1.4%)	0	1 (0.5%)
Vascular Disorders	0	0	1 (1.4%)	1 (0.5%)

Source: Table 14.3.1.2.2.1
For each of any AEs by SOC, each subject was only counted once under the highest grade.
Abbreviations: AE=adverse event; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of evaluable subjects; SOC=system organ class; US=United States.

The incidence of all-causality TEAEs occurring in ≥5% of subjects by study arm is summarized in Table 19. The most frequently reported AEs were headache (5 subjects [7.2%]) for adalimumab-Pfizer; 6 subjects [8.5 %] for adalimumab-US; 12 subjects [17.1%] for adalimumab-EU) and nasopharyngitis (4 subjects [5.8%]) for adalimumab-Pfizer; 4 subjects [5.6 %] for adalimumab-US; 9 subjects [12.9%] for adalimumab-EU). No opportunistic infections occurred, influenza was observed most frequently in the adalimumab-US group (1 subject [1.4%]) for adalimumab-Pfizer; 5 subjects [7.0%] for adalimumab-US; 1 subject [1.4%] for adalimumab-EU), and oral herpes was observed most frequently in the adalimumab-Pfizer group (4 subjects [5.8%]) for adalimumab-Pfizer; 0 subject for adalimumab-US; 2 subjects [2.9%] for adalimumab-EU). An additional case of herpes dermatitis was reported for 1 subject [1.4%] in the adalimumab-US group (Table 16.2.7.1).

Table 19. Incidence of Treatment-Emergent Adverse Events in ≥5% of Subjects, All-Causality

Number (%) of Subjects with AEs by SOC MedDRA version 16.1 Preferred Term	Adalimumab Pfizer N=69	Adalimumab US N=71	Adalimumab EU N=70	Total N=210
Gastrointestinal Disorders	**1 (1.4%)**	**2 (2.8%)**	**4 (5.7%)**	**7 (3.3%)**
Nausea	1 (1.4%)	2 (2.8%)	4 (5.7%)	7 (3.3%)
Infections and Infestations	**9 (13.0%)**	**8 (11.3%)**	**11 (15.7%)**	**28 (13.3%)**
Nasopharyngitis	4 (5.8%)	4 (5.6%)	9 (12.9%)	17 (8.1%)
Influenza	1 (1.4%)	5 (7.0%)	1 (1.4%)	7 (3.3%)
Oral herpes	4 (5.8%)	0	2 (2.9%)	6 (2.9%)
Musculoskeletal and Connective Tissue Disorders	**1 (1.4%)**	**4 (5.6%)**	**2 (2.9%)**	**7 (3.3%)**
Back pain	1 (1.4%)	4 (5.6%)	2 (2.9%)	7 (3.3%)
Nervous System Disorders	**5 (7.2%)**	**6 (8.5%)**	**12 (17.1%)**	**23 (11.0%)**
Headache	5 (7.2%)	6 (8.5%)	12 (17.1%)	23 (11.0%)

Source: Table 14.3.1.2.3
Subjects were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Abbreviations: AE=adverse event; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of evaluable subjects; SOC=System Organ Class; US=United States.

12.2.2.2. Treatment-Related Adverse Events

The incidence of treatment-related TEAEs is summarized in Table 20. The most frequently reported AEs were in the MedDRA SOCs of Gastrointestinal Disorders (4 subjects [5.8%] for adalimumab-Pfizer; 7 subjects [9.9%] for adalimumab-US; 9 subjects [12.9%] for adalimumab-EU) and Nervous System Disorders (4 subjects [5.8%] for adalimumab-Pfizer; 10 subjects [14.1%] for adalimumab-US; 6 subjects [8.6%] for adalimumab-EU). In the Gastrointestinal Disorders SOC, the most common treatment-related AEs were nausea (6 subjects, 2.9%), constipation (4 subjects, 1.9%), and diarrhea (3 subjects, 1.4%); in the Nervous System Disorders SOC, the most common treatment-related AEs were headache (14 subjects, 6.7%) and somnolence (2 subjects, 1.0%) (Table 14.3.1.3.2.1).

Table 20. Incidence of Treatment-Emergent Adverse Events, Treatment-Related

Number (%) of Subjects with AEs by MedDRA (version 16.1) SOC	Adalimumab			Total
	Pfizer N=69	US N=71	EU N=70	N=210
Any AEs	**15 (21.7%)**	**24 (33.8%)**	**24 (34.3%)**	**63 (30.0%)**
Ear and Labyrinth Disorders	1 (1.4%)	0	0	1 (0.5%)
Gastrointestinal Disorders	4 (5.8%)	7 (9.9%)	9 (12.9%)	20 (9.5%)
General Disorders and Administration Site Conditions	2 (2.9%)	8 (11.3%)	3 (4.3%)	13 (6.2%)
Infections and Infestations	4 (5.8%)	5 (7.0%)	8 (11.4%)	17 (8.1%)
Musculoskeletal and Connective Tissue Disorders	2 (2.9%)	1 (1.4%)	4 (5.7%)	7 (3.3%)
Nervous System Disorders	4 (5.8%)	10 (14.1%)	6 (8.6%)	20 (9.5%)
Renal and Urinary Disorders	0	0	1 (1.4%)	1 (0.5%)
Reproductive System and Breast Disorders	1 (1.4%)	0	0	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders	1 (1.4%)	0	1 (1.4%)	2 (1.0%)
Skin and Subcutaneous Tissue Disorders	0	2 (2.8%)	2 (2.9%)	4 (1.9%)

Source: Table 14.3.1.3.2.1
For each of any AEs by SOC, each subject was only counted once under the highest grade.
Abbreviations: AE=adverse event; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of evaluable subjects; SOC=system organ class; US=United States.

The only treatment-related AE in ≥5% of subjects by study arm was headache (4 subjects [5.8%] for adalimumab-Pfizer; 5 subjects [7.0%] for adalimumab-US; 5 subjects [7.1%] for adalimumab-EU) (Table 14.3.1.3.3).

12.2.2.3. All-Causality Adverse Events by Grade Severity

There was no all-causality AE of Grade 4 or Grade 5 in any treatment group (Table 21).

Three (3) subjects reported Grade 3 (severe) AEs; gastroenteritis in 1 subject who received adalimumab-US, subcutaneous abscess and increased ALT in 2 subjects who received adalimumab-EU. Forty-three (43) subjects (20.5%) reported Grade 2 (moderate) AEs (Table 14.3.1.2.2.1, see ERRATA); 10 subjects for adalimumab-Pfizer, 15 subjects for adalimumab-US, and 18 subjects for adalimumab-EU. Sixty-eight (68) subjects (32.4%) experienced Grade 1 (mild) AEs; 22 subjects for adalimumab-Pfizer, 22 subjects for adalimumab-US, and 24 subjects for adalimumab-EU (Table 14.3.1.2.2.1).

Table 21. Summary of Treatment-Emergent Adverse Events by Grade, All-Causality

Number (%) of Subjects with AEs	Adalimumab			Total
	Pfizer N=69	US N=71	EU N=70	N=210
Grade 1	22 (31.9%)	22 (31.0%)	24 (34.3%)	68 (32.4%)
Grade 2	10 (14.5%)	15 (21.1%)	18 (25.7%)	43 (20.5%)
Grade 3	0	1 (1.4%)	2 (2.9%)	3 (1.4%)
Grade 4 or higher	0	0	0	0

Source: Table 14.3.1.2.2.1, see ERRATA
Subjects [redacted] and [redacted] had 2 laboratory abnormalities that were reported as Grade 2 AEs, however, the abnormalities were actually Grade 3; numbers and percentages affected by these 2 subjects are not corrected in this table and relevant text.
For each of any AEs, each subject was only counted once under the highest grade.
Abbreviations: AE=adverse event; EU=European Union; N=number of evaluable subjects; US=United States.

12.2.2.4. Treatment-Related Adverse Events by Grade Severity

There were no Grade 4 or higher treatment-related AEs in any treatment group (Table 22).

Two (2) subjects reported treatment-related Grade 3 (severe) AEs; gastroenteritis in 1 subject who received adalimumab-US, subcutaneous abscess in 1 subject who received adalimumab-EU (Table 14.3.1.3.2.1). Eleven (11) subjects (5.2%) reported Grade 2 (moderate) AEs; 3 subjects (4.3%) for adalimumab-Pfizer, 2 subjects (2.8%) for adalimumab-US, and 6 subjects (8.6%) for adalimumab-EU. Fifty (50) subjects (23.8%) experienced Grade 1 (mild) AEs; 12 subjects (17.4%) for adalimumab-Pfizer, 21 subjects (29.6%) for adalimumab-US, and 17 subjects (24.3%) for adalimumab-EU.

Table 22. Summary of Treatment-Emergent Adverse Events by Grade, Treatment-Related

Number (%) of Subjects with AEs	Adalimumab			Total
	Pfizer N=69	US N=71	EU N=70	N=210
Grade 1	12 (17.4%)	21 (29.6)	17 (24.3%)	50 (23.8%)
Grade 2	3 (4.3%)	2 (2.8)	6 (8.6%)	11 (5.2%)
Grade 3	0	1 (1.4%)	1 (1.4%)	2 (1.0%)
Grade 4 or higher	0	0	0	0

Source: Table 14.3.1.3.2.1
For each of any AEs, each subject was only counted once under the highest grade.
Abbreviations: AE=adverse event; EU=European Union; N=number of evaluable subjects; US=United States.

12.2.2.5. Treatment-Emergent Injection Site Reactions

A summary of treatment-emergent TEAEs for injection site is provided in Table 14.3.1.2.2.2 (all causality) and Table 23 (treatment-related). Six (6) subjects (2.9%) experienced injection site reactions (ISR), with severity of ISRs provided in Table 24. One (1) subject experienced Grade 2 injection site erythema after receiving adalimumab-US and 5 subjects experienced Grade 1 ISRs (rash in 1 subject after receiving adalimumab-Pfizer; pain, erythema and/or haematoma in 4 subjects after receiving adalimumab-US). All injection site reactions were

considered to be treatment-related (Tables 14.3.1.3.2.2 and 16.2.7.1). No ISR subject tested positive for ADA prior to dosing, and all ISR subjects tested positive at least once in the post-dose period (Tables 16.2.7.1 and 16.2.8.5.1).

Table 23. Incidence of Treatment-Emergent Adverse Events for Injection Site, Treatment-Related

Number (%) of Subjects with AEs by SOC and MedDRA v16.1 Preferred Term	Adalimumab			Total
	Pfizer N=69	US N=71	EU N=70	N=210
Any AEs	**1 (1.4%)**	**5 (7.0%)**	**0**	**6 (2.9%)**
General Disorders and Administration Site Conditions	1(1.4%)	5 (7.0%)	0	6 (2.9%)
Injection site erythema	0	3 (4.2%)	0	3 (1.4%)
Injection site haematoma	0	1 (1.4%)	0	1 (0.5%)
Injection site pain	0	2 (2.8%)	0	2 (1.0%)
Injection site reaction	1 (1.4%)	0	0	1 (0.5%)

Source: Table 14.3.1.3.2.2
For each of any AEs, SOC or Preferred Term, each subject was only counted once under the highest grade.
Abbreviations: AE=adverse event; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of evaluable subjects; SOC=system organ class; US=United States; v=version.

Table 24. Summary of Injection Site Treatment-Emergent Adverse Events by Grade, All Causality

Number (%) of Subjects with AEs	Adalimumab			Total
	Pfizer N=69	US N=71	EU N=70	N=210
Grade 1	1 (1.4%)	4 (5.6%)	0	5 (2.4%)
Grade 2	0	1 (1.4%)	0	1 (0.5%)
Grade 3	0	0	0	0
Grade 4 or higher	0	0	0	0

Source: Table 14.3.1.2.2.2
For each of any AEs, each subject was only counted once under the highest grade.
Abbreviations: AE=adverse event; EU=European Union; N=number of evaluable subjects; US=United States.

12.2.3. Analysis of Adverse Events

Individual subjects were only counted once in each treatment group.

12.2.3.1. Permanent Discontinuations Due to Adverse Events (Not Applicable)

There were no permanent discontinuations due to AEs.

12.2.3.2. Dose Reductions or Temporary Discontinuations Due to Adverse Events (Not Applicable)

There were no dose reductions or temporary discontinuations due to AEs.

12.2.4. Listing of Adverse Events by Subject

A listing of AEs by subject is provided in Table 16.2.7.1 (see ERRATA).

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths (None Reported)

There were no deaths in this study.

12.3.1.2. Other Serious Adverse Events

There was 1 reported SAE of upper abdominal pain (Subject [redacted] in the adalimumab-EU study arm (Table 14.3.2.2).

Refer to Section 12.3.2.2 for more details.

12.3.1.3. Other Significant Adverse Events (None Reported)

There were no other significant AEs in this study.

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

12.3.2.1. Death Narratives (Not Applicable)

12.3.2.2. Other Serious Adverse Event Narratives

Subject [redacted] a [redacted] year-old [redacted] male from [redacted] who received a single dose of adalimumab-EU 40 mg SC injection on Study Day 1, was hospitalized for epigastric pain on Study Day 38. [redacted] Concomitant medications included paracetamol as needed for headaches.

Two (2) days prior to the hospitalization, the subject woke up with intense headaches lasting approximately 1 hour that was not relieved by paracetamol, followed by onsets of nausea, vomiting, diarrhea, and abdominal pain with heartburn sensation. The following day, there was increased pain and the subject spent the day in bed. Upon admission to the emergency room, the subject was afebrile with an unremarkable physical examination with the exception of sensitivity to deep palpitation to the epigastric region. Work-up procedures (including laboratory tests, computed tomography [CT] scan, ultrasound of the abdomen, and endoscopy of the upper gastrointestinal track) were also unremarkable. Cytology of the gastric antrum and fundus showed numerous H. pylori. During the hospital stay, the subject was administered paracetamol for headache and tramadol (Contramal®) for the epigastric pain.

The SAE of upper abdominal pain was moderate in severity and considered to be resolved on Study Day 44 (AE lasted approximately 6 days). As a result of the SAE, the subject withdrew from the study during the double-blind treatment period. In the opinion of the investigator, the epigastric pain was unrelated to the study drug, concomitant drugs, or clinical trial procedures; instead, it was likely due to a viral infection.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There was only 1 subject who experienced 1 SAE, which was determined by the investigator as unrelated to treatment.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Values

Individual laboratory test data are listed in Table 16.2.8.1.1.1 and Table 16.2.8.1.1.3 (by NCI-CTCAE grade). Laboratory data listings for unplanned readings are presented by subject in Table 16.2.8.1.1.1.1 and by test in Table 16.2.8.1.1.1.2. Laboratory test abnormalities are listed by subject in Table 16.2.8.1.2 and by test in Table 16.2.8.1.3.

12.4.2. Evaluation of Each Laboratory Parameter

Laboratory data are summarized in Table 14.3.4.1.2.1 (absolute values) and Table 14.3.4.1.2.2 (mean baseline and change from baseline).

A total of 158 subjects (75.2%) had laboratory abnormalities without regard to baseline values, including 46 subjects (66.7%) in the adalimumab-Pfizer group, 57 subjects (80.3%) in the adalimumab-US group, and 55 subjects (78.6%) in the adalimumab-EU group (Table 14.3.4.1.1). The most frequently reported abnormal laboratory parameters were increased mean platelet volume >1.1 × ULN (MPV; 77 subjects, 36.7%), decreased MPV <0.9 × lower limit of normal (LLN) (24 subjects, 11.4%) and increased eosinophils/leukocytes >1.2 × ULN (22 subjects, 10.5%).

For evaluation of drug-induced serious hepatotoxicity (eDISH), all subjects who received study drug were assessed for occurrence of elevations in total bilirubin, ALT and AST (Table 14.3.4.1.3). One subject ([redacted]) in the adalimumab-EU group had elevated ALT/AST ≥3× ULN with normal bilirubin on Study Day 29 (Table 16.2.8.1.4). The causality was attributed to alcohol use and not to the study drug. By Study Day 71, the AST/ALT values returned to normal limits and the AE was considered resolved (Table 16.2.7.1). This case did not qualify as a Hy's Law case.

The majority of hematologic and chemistry abnormalities were of Grade 1 severity (Table 14.3.4.1.5.1 and Table 14.3.4.1.6.1). The most prominent Grade 1 hematological disorder was decreased white blood cells (WBC) (23 subjects, 11.0%). The most prominent Grade 1 chemistry abnormality was increased creatinine (135 subjects, 64.3%). Shift summary results by maximum CTCAE grade are presented in Table 14.3.4.1.5.2 (hematology) and Table 14.3.4.1.6.2 (chemistry).

12.4.2.1. Individual Clinically Significant Laboratory Abnormalities

Subjects with laboratory abnormalities of Grades ≥3 are listed in Table 25.

One (1) subject [redacted] adalimumab-US) experienced Grade 3 neutrophil count decreased on Study Days 4, 5 and 7. Six (6) subjects experienced clinical chemistry abnormalities (1 [redacted] and [redacted] [adalimumab-US]; [redacted] [redacted] [redacted] and [redacted] [adalimumab-EU]). Three (3) subjects ([redacted] [adalimumab-US]; [redacted] and 1 [redacted] [adalimumab-EU]) experienced Grade 3 ALT and/or AST abnormalities.

A total of 4 subjects (1.9%) experienced Grade 3 or 4 elevated creatine phosphokinase levels post study drug administration. Two (2) subjects ([redacted] and [redacted]) were in the adalimumab-US group and 2 subjects ([redacted] and [redacted] were in the adalimumab-EU group. The creatine phosphokinase elevation for Subject [redacted] in the adalimumab-EU group only occurred pre-dose. No subjects in the adalimumab-Pfizer group experienced laboratory abnormalities of Grades ≥3.

Table 25. Laboratory Abnormalities with NCI-CTCAE Grades ≥3

Subject ID	Test	Study Day	CTCAE Grade	Laboratory Result (unit)	Reference Range
Adalimumab-US					
[redacted]	Creatine phosphokinase increased	42	3	4787 (U/L)	50-600
	Neutrophil count decreased	4	3	0.9 (10^3/mm^3)	1.4-7.5
		5	3	0.9 (10^3/mm^3)	1.4-7.5
		7	3	0.9 (10^3/mm^3)	1.4-7.5
[redacted]	Creatine phosphokinase increased	15	4	24549 (U/L)	20-200
		17	4	5114 (U/L)	20-200
	Alanine aminotransferase increased	15	3	297 (U/L)	0-49
	Aspartate aminotransferase increased	15	3	740 (U/L)	0-40
		17	3	267 (U/L)	0-40
Adalimumab-EU					
[redacted]	Creatine phosphokinase increased	29	3	4426 (U/L)	50-600
	Alanine aminotransferase increased	29	3	215 (U/L)	0-41
	Creatine phosphokinase increased	-6	3	4274 (U/L)	50-600
	Creatine phosphokinase increased	71	4	13577 (U/L)	20-200
		74	4	3191 (U/L)	20-200
	Aspartate aminotransferase increased	71	3	214 (U/L)	0-40

Source: Table 16.2.8.1.1.2
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; EU=European Union; ID=identification number; NCI=National Cancer Institute; US=United States.

12.5. Vital Signs, Electrocardiogram, Physical Findings, and Other Observations Related to Safety

12.5.1. Vital Signs

A summary of vital signs data is provided in Table 14.3.4.2.1.1 (absolute values) and Table 14.3.4.2.1.2 (mean baseline and change from baseline).

Categorical summaries of vital signs absolute values are provided in Table 14.3.4.2.2.1.

Maximum increases from baseline in systolic BP of ≥30 mmHg were reported by 2 subjects (1 subject in the adalimumab-Pfizer group and 1 subject in the adalimumab-US group). Maximum increases from baseline in diastolic BP of ≥20 mmHg were reported by 7 subjects (2 subjects in the adalimumab-Pfizer group, 4 subjects in the adalimumab-US group, and 1 subject in the adalimumab-EU group) (Table 14.3.4.2.2.2). There were no subjects with decreases from baseline in systolic BP of ≥30 mmHg or in diastolic BP of ≥20 mmHg (Table 14.3.4.2.2.3).

No vital signs abnormalities were considered to be clinically significant and none were reported as AEs.

12.5.2. Electrocardiogram

A summary of ECG data is provided in Table 14.3.4.3.1.1 (absolute values). Mean baseline and change from baseline for ECG data are provided in Table 14.3.4.3.1.2. Categorical summaries of ECG data are provided in Table 14.3.4.3.2.1 (absolute values) and Table 14.3.4.3.2.2 (increases from baseline).

There were 5 subjects with post-dose ECG values meeting categorical summarization criteria: Subject [redacted] (adalimumab-Pfizer) had a 32-msec increase in QT corrected for heart rate using Fridericia's formula (QTcF) from baseline on Study Day 71; Subject [redacted] (adalimumab-Pfizer) had a QTcF interval absolute value of 453 msec on Study Day 71; Subject [redacted] (adalimumab-US) had a 34-msec change from baseline in QTcF interval on Study Day 71; Subject [redacted] (adalimumab-US) had a QT interval of 500 msec on Study Day 70; Subject [redacted] (adalimumab-EU) had a QT interval value of 508 msec on Study Day 71 (Table 16.2.8.3.3).

No ECG abnormalities were considered to be clinically significant, and no subjects had ECG abnormalities that were reported as AEs.

12.5.3. Physical Findings

Physical examination findings are listed by subject in Table 16.2.8.4.1.

Subject [redacted] (adalimumab-Pfizer) was found to have mild redness of the throat on Study Day 29 and enlarged submandibular nodes on Study Days 29 and 36. Subject [redacted] (adalimumab-EU) had some abnormal skin findings on Study Day 22 and enlarged tonsils on Study Day 29.

None of these abnormalities were considered to be clinically significant and none were reported as AEs.

12.6. Safety Conclusion

A single dose of study treatment (adalimumab-Pfizer, adalimumab-US, or adalimumab-EU) was generally safe and well-tolerated when administered to the healthy subjects in this study.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

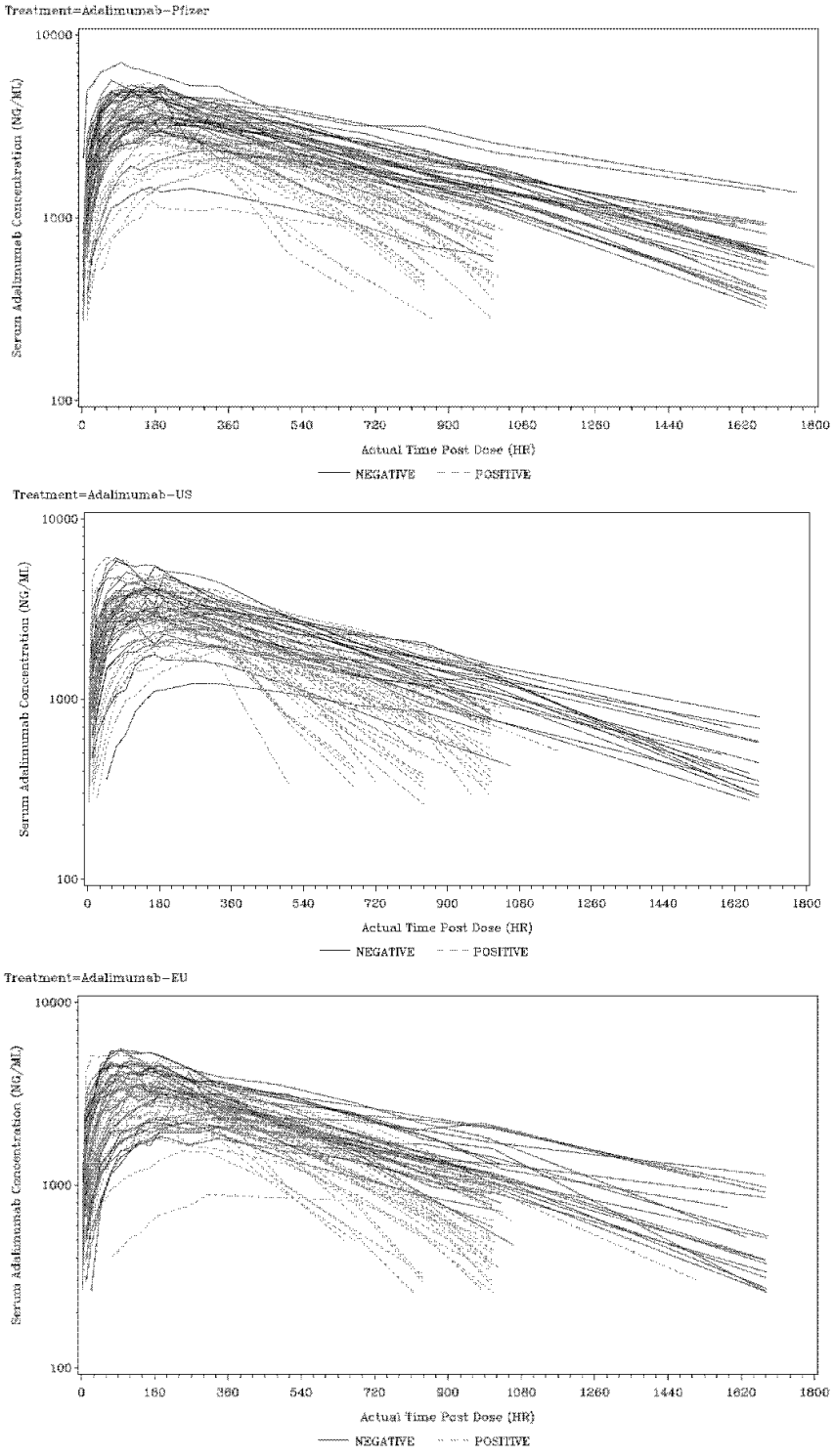
Impact of Immunogenicity on PK

The study showed that there was a high rate of ADA response following a single SC dose of adalimumab-Pfizer, adalimumab-US, and adalimumab-EU in healthy subjects. This was expected as adalimumab was known to be highly immunogenic in healthy subjects, especially at low adalimumab concentrations, such as those observed at 10 weeks in this study. Therefore, the ADA responses observed in this study may not represent the adalimumab patient population with autoimmune disease in clinical settings, who may be receiving background immunosuppressive therapy such as methotrexate and corticosteroids, and have adalimumab concentrations maintained at therapeutic levels.

The majority of ADA positive subjects also tested positive for NAb. The impact of the development of NAb can be seen in Figure 4 (Day 1-71), where the individual serum concentrations versus time profiles are plotted by treatment and NAb status. NAb positive subjects in all treatment groups showed an accelerated terminal disposition phase and a decreased $t_{½}$.

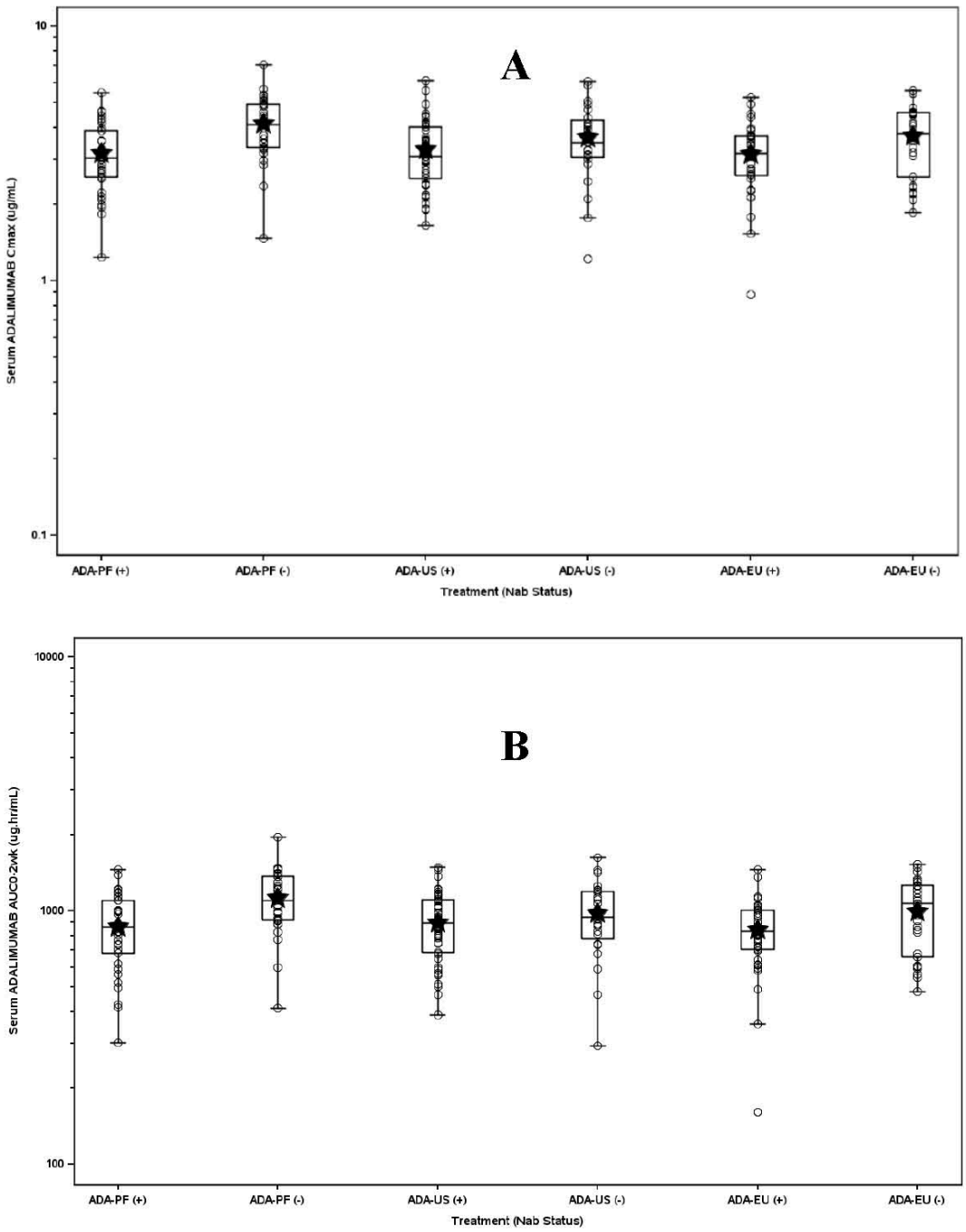
The impact of NAb on each of the PK parameters (Day 1-43) is shown in Figure 5 and Figure 6 for each treatment group. The formation of ADA/NAb appeared to have minimal effect on C_{max} and $AUC_{0\text{-}2wk}$, and a profound effect on AUC_t and AUC_{inf}.

Figure 4. Serum Drug Concentration-Time Plot by Treatment and NAb Status (Day 1-71, PP Analysis Set)



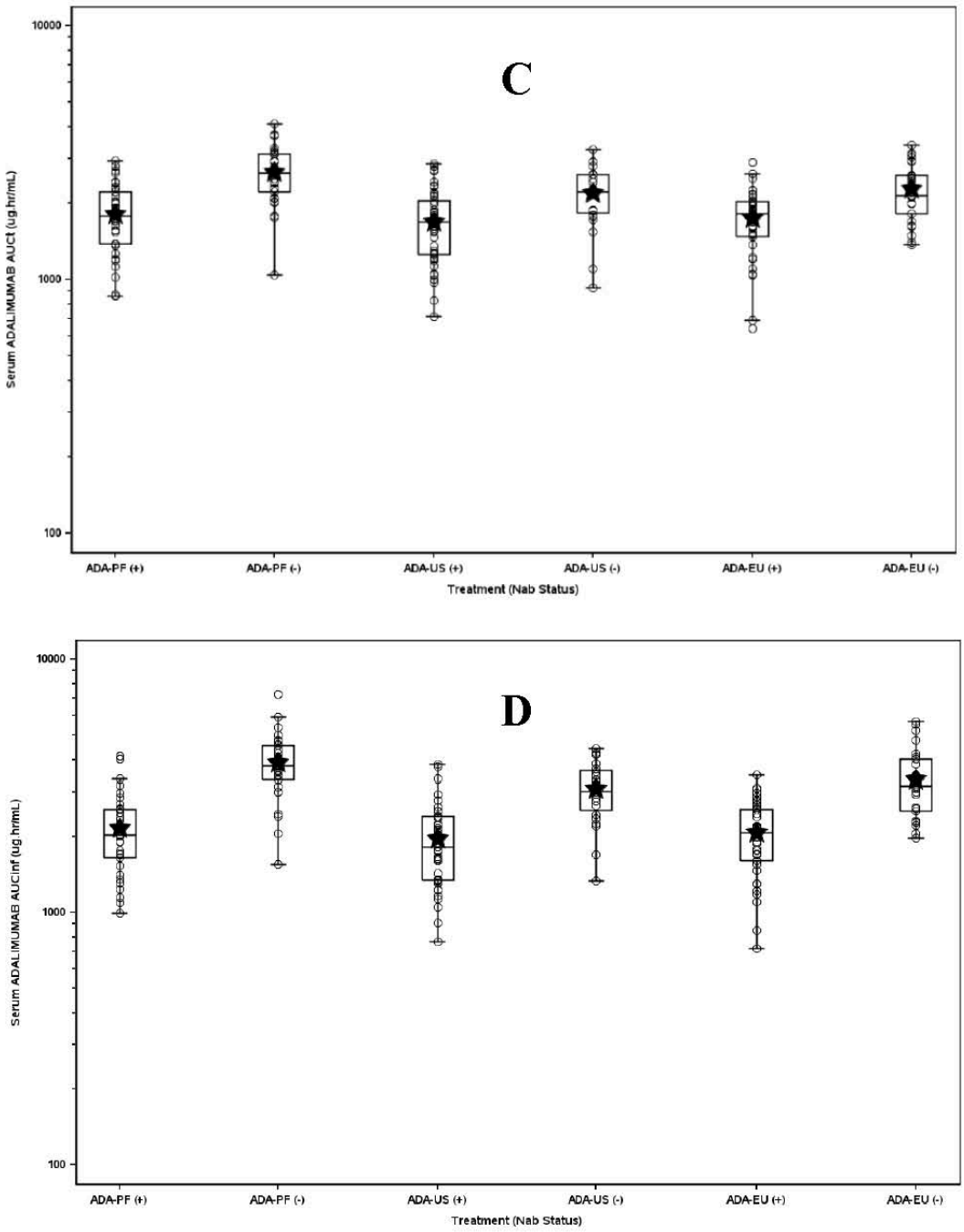
Source: Figure 16.2.5.4.2.5
Abbreviations: EU=European Union; HR=hour; ML=milliliter; NAb=neutralizing antibodies; NG=nanogram; PP=per-protocol; US=United States.

Figure 5. Box and Whisker Plots by Treatment and NAb Status for C_{max} (Panel A) and AUC_{0-2wk} (Panel B) (Day 1-43, PP Analysis Set)



Source: Figure 14.4.3.2.3.2 and Figure 14.4.3.2.4.2
Pharmacokinetic parameters are defined in Table 3.
Stars represent geometric mean and circles represent individual subject values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times inter-quartile range.
All not tested subjects have been classified as NAb negative.
Abbreviations: ADA=adalimumab; EU=European Union; hr=hour; mL=milliliter; NAb=neutralizing antibodies; µg=microgram; PF=Pfizer; PP=per-protocol; US=United States.

Figure 6. Box and Whisker Plots by Treatment and NAb Status for AUC_t (Panel C) and AUC_{inf} (Panel D) (Day 1-43, PP Analysis Set)



Source: Figure 14.4.3.2.1.2 and Figure 14.4.3.2.2.2
Pharmacokinetic parameters are defined in Table 3.
Stars represent geometric mean and circles represent individual subject values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times inter-quartile range.
All not tested subjects have been classified as NAb negative.
Abbreviations: ADA=adalimumab; EU=European Union; hr=hour; mL=milliliter; NAb=neutralizing antibodies; µg=microgram; PF=Pfizer; PP=per-protocol; US=United States.

In addition, there appeared to be an imbalance in immunogenicity between treatment groups: the adalimumab-US group showed a trend toward somewhat higher incidence of both ADA and NAb compared to the other 2 groups. After dosing, 94.4% of the subjects in the adalimumab-US group tested positive for ADA at 1 or more time points, compared to 85.5% for the adalimumab-Pfizer treatment group and 90.0% for the adalimumab-EU group. Similarly, 66.2% of the subjects in the adalimumab-US group tested positive for NAb at 1 or more time point post-dose, compared to 53.6% in the adalimumab-Pfizer group and 61.4% in the adalimumab-EU group. Furthermore, the adalimumab-US group had a trend towards higher titers in both the ADA and NAb assays, compared to adalimumab-Pfizer and adalimumab-EU groups. This imbalance in the immunogenicity appears to be accompanied by an imbalanced impact on the terminal disposition phase.

Estimation of AUC_{inf}

To determine bioequivalence after a single dose, the parameters to be analyzed are AUC_t and C_{max}, as described in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) bioequivalence guidance.[2,3] For these parameters, the 90% CI for the ratio of the test and reference products should be contained within the acceptance interval of 80.00% to 125.00%. AUC_{inf}, along with other PK parameters such as T_{max}, residual area, and $t_{½}$, may be calculated and reported. In the EMA guideline on similar biological medicinal products, AUC_{inf} and C_{max} are recommended as the parameters to be analyzed. In addition, if no data are provided for the intravenous (IV) route, partial AUC was to be assessed to ensure comparability of both absorption and elimination.[4]

An estimate of AUC_{inf} after a single dose is often desired, as the ratio of the administered dose to AUC_{inf} yields the drug clearance estimate, or when the single-dose PK (AUC_{inf}) is compared to the multiple-dose PK (AUC_t) at steady state. The drawback of an AUC_{inf} estimate is that the estimate is not completely verifiable, as it is calculated as AUC_t plus residual area that is not based on observable drug concentrations and instead is approximated using C_t/λ_z, where C_t is the last observable concentration at time t and λ_z is the slope of the terminal disposition phase, or $\lambda_z=\ln 2/t_{½}$. This approximation assumes that λ_z is a constant, even beyond the C_t, independent of time and concentration. For most drugs that have linear PK and for which the profiles can be characterized by a multi-exponential function, the approximation is reasonable, provided that the terminal disposition phase of the concentration-time profile can be adequately defined by the last exponential term with the smallest rate constant (λ_z).

However, estimation of λ_z for adalimumab can be extremely challenging for the following reasons. Firstly, NAb responses to a single-dose administration of adalimumab were excessive during PK profiling at the label recommended dose, resulting in apparent acceleration of the terminal phase with a drastic increase in λ_z for approximately 2/3 of subjects. Secondly, individual subject's NAb responses were unpredictable in terms of the time to onset and titer. The time to the first appearance of NAb varied from 336 to 1680 hours among subjects, and the titers varied from 0.75 to 2.52 (on a log scale), which added considerable variability to estimations of λ_z and AUC_{inf}. Due to the relatively small sample size, these factors also increased the likelihood of introducing a sizable bias between

the treatment groups, since the propensity for NAb responses from a subject characteristics point of view, and therefore the impact on estimations of λ_z and AUC_{inf}, was not evenly distributed between the treatment groups. Consequently, AUC_{inf} may not be a reliable PK endpoint for adalimumab PK similarity determination.

13.2. Conclusions

- Overall, there appeared to be minimal differences in drug product characteristics, as indicated by similar C_{max} and $AUC_{0\text{-}2wk}$; the PK similarity of adalimumab-Pfizer to both adalimumab-EU and adalimumab-US, and of adalimumab-EU to adalimumab-US, has been demonstrated for these parameters.

- The development of ADA/NAb had profound effects on the estimates of AUC_t and AUC_{inf}. For AUC_t, the 80.00% to 125.00% acceptance criterion was met for the comparisons of adalimumab-Pfizer to adalimumab-EU and adalimumab-EU to adalimumab-US, but not for the comparison of adalimumab-Pfizer to adalimumab-US; the upper limit of the 90% CI for the latter comparison was slightly outside of the acceptance criterion, which was attributed largely to the trend toward higher observed immunogenicity response in subjects from the adalimumab-US group. The AUC_{inf} estimation was not reliable due to the formation of ADA/NAb.

- There was a high incidence of immunogenicity following a single 40-mg SC dose of adalimumab-Pfizer, adalimumab-US, and adalimumab-EU in the healthy subjects evaluated in this study.

- All 3 treatments were generally well-tolerated by study subjects, with no clinically significant imbalances in abnormal laboratory parameters or in the incidence, type, severity, timing, seriousness and relatedness of TEAEs.

- PK similarity of adalimumab-EU to adalimumab-US has been demonstrated, supporting the use of only 1 of the 2 innovator products as the reference comparator in future clinical trials.

14. TABLES AND FIGURES REFERRED TO BUT NOT INCLUDED IN THE TEXT

Table 14.1.1.1
PF-06410293 Protocol B5381001
Subject Evaluation Groups

	Adalimumab-Pfizer	Adalimumab-US	Adalimumab-EU	Total
	n (%)	n (%)	n (%)	n (%)
Assigned to Treatment	69 (100.0)	71 (100.0)	70 (100.0)	210 (100.0)
Treated	69 (100.0)	71 (100.0)	70 (100.0)	210 (100.0)
Not Treated	0	0	0	0
Full Analysis Set	69 (100.0)	71 (100.0)	70 (100.0)	210 (100.0)
Per Protocol Analysis Set	66 (95.7)	67 (94.4)	66 (94.3)	199 (94.8)
Safety Analysis Set	69 (100.0)	71 (100.0)	70 (100.0)	210 (100.0)

Table 14.1.1.2
PF-06410293 Protocol B5381001
Disposition Events Summary - Safety Analysis Set

	Adalimumab-Pfizer (N=69)	Adalimumab-US (N=71)	Adalimumab-EU (N=70)	Total (N=210)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Discontinued	1 (1.4)	0	1 (1.4)	2 (1.0)
Withdrawal By Subject	1 (1.4)	0	1 (1.4)	2 (1.0)
Completed	68 (98.6)	71 (100.0)	69 (98.6)	208 (99.0)

Table 14.1.2.1
PF-06410293 Protocol B5381001
Demographic Characteristics - Safety Analysis Set

	Adalimumab-Pfizer			Adalimumab-US		
	Male (N=69)	Female (N=0)	Total (N=69)	Male (N=71)	Female (N=0)	Total (N=71)
Age (Years):						
<18	0	0	0	0	0	0
18-44	57 (82.6)	0	57 (82.6)	55 (77.5)	0	55 (77.5)
45-64	12 (17.4)	0	12 (17.4)	16 (22.5)	0	16 (22.5)
>=65	0	0	0	0	0	0
Mean	34.3	-	34.3	35.3	-	35.3
SD	9.9	-	9.9	9.2	-	9.2
Range	(19- 54)	-	(19- 54)	(18- 54)	-	(18- 54)
Race						
WHITE	43 (62.3)	0	43 (62.3)	44 (62.0)	0	44 (62.0)
BLACK	19 (27.5)	0	19 (27.5)	17 (23.9)	0	17 (23.9)
ASIAN	0	0	0	4 (5.6)	0	4 (5.6)
OTHER	7 (10.1)	0	7 (10.1)	6 (8.5)	0	6 (8.5)

Table 14.1.2.1
PF-06410293 Protocol B5381001
Demographic Characteristics - Safety Analysis Set

	Adalimumab-EU			Total		
	Male (N=69)	**Female (N=1)**	**Total (N=70)**	**Male (N=209)**	**Female (N=1)**	**Total (N=210)**
Age (Years):						
<18	0	0	0	0	0	0
18-44	56 (81.2)	0	56 (80.0)	168 (80.4)	0	168 (80.0)
45-64	13 (18.8)	1 (100.0)	14 (20.0)	41 (19.6)	1 (100.0)	42 (20.0)
>=65	0	0	0	0	0	0
Mean	35.0	54.0	35.2	34.9	54.0	35.0
SD	8.9	-	9.1	9.3	-	9.4
Range	(20- 51)	(54- 54)	(20- 54)	(18- 54)	(54- 54)	(18- 54)
Race						
WHITE	44 (63.8)	0	44 (62.9)	131 (62.7)	0	131 (62.4)
BLACK	17 (24.6)	1 (100.0)	18 (25.7)	53 (25.4)	1 (100.0)	54 (25.7)
ASIAN	0	0	0	4 (1.9)	0	4 (1.9)
OTHER	8 (11.6)	0	8 (11.4)	21 (10.0)	0	21 (10.0)

Table 14.1.2.1.1
PF-06410293 Protocol B5381001
Physical Measurements - Safety Analysis Set

		Adalimumab-Pfizer (N=69)			Adalimumab-US (N=71)		
		Male	Female	Total	Male	Female	Total
Parameter	Summary Statistics						
HEIGHT (CM)	n	69	0	69	71	0	71
	Mean	177.7	-	177.7	176.6	-	176.6
	SD	7.4	-	7.4	6.7	-	6.7
	Range	(159.0- 194.0)	-	(159.0- 194.0)	(161.0- 197.0)	-	(161.0- 197.0)
WEIGHT (KG)	n	69	0	69	71	0	71
	Mean	80.5	-	80.5	80.6	-	80.6
	SD	12.1	-	12.1	10.6	-	10.6
	Range	(50.8- 107.7)	-	(50.8- 107.7)	(59.8- 101.6)	-	(59.8- 101.6)
BODY MASS INDEX (KG/M**2)	n	69	0	69	71	0	71
	Mean	25.5	-	25.5	25.9	-	25.9
	SD	3.2	-	3.2	2.9	-	2.9
	Range	(17.7- 30.5)	-	(17.7- 30.5)	(19.7- 30.4)	-	(19.7- 30.4)

Body Mass Index is calculated as wt/(ht*.01)**2.

		Adalimumab-EU (N=70)			Total (N=210)		
		Male	Female	Total	Male	Female	Total
Parameter	Summary Statistics						
HEIGHT (CM)	n	69	1	70	209	1	210
	Mean	178.1	163.0	177.8	177.4	163.0	177.4
	SD	6.3	-	6.5	6.8	-	6.9
	Range	(165.0- 192.0)	(163.0- 163.0)	(163.0- 192.0)	(159.0- 197.0)	(163.0- 163.0)	(159.0- 197.0)
WEIGHT (KG)	n	69	1	70	209	1	210
	Mean	82.3	70.3	82.1	81.1	70.3	81.1
	SD	11.6	-	11.6	11.4	-	11.4
	Range	(58.7- 105.6)	(70.3- 70.3)	(58.7- 105.6)	(50.8- 107.7)	(70.3- 70.3)	(50.8- 107.7)
BODY MASS INDEX (KG/M**2)	n	69	1	70	209	1	210
	Mean	25.9	26.5	25.9	25.8	26.5	25.8
	SD	3.0	-	3.0	3.0	-	3.0
	Range	(19.8- 30.4)	(26.5- 26.5)	(19.8- 30.4)	(17.7- 30.5)	(26.5- 26.5)	(17.7- 30.5)

Body Mass Index is calculated as wt/(ht*.01)**2.

Table 14.1.2.2
PF-06410293 Protocol B5381001
Demographic Characteristics - Full Analysis Set

	Adalimumab-Pfizer			Adalimumab-US		
	Male (N=69)	Female (N=0)	Total (N=69)	Male (N=71)	Female (N=0)	Total (N=71)
Age (Years):						
<18	0	0	0	0	0	0
18-44	57 (82.6)	0	57 (82.6)	55 (77.5)	0	55 (77.5)
45-64	12 (17.4)	0	12 (17.4)	16 (22.5)	0	16 (22.5)
>=65	0	0	0	0	0	0
Mean	34.3	-	34.3	35.3	-	35.3
SD	9.9	-	9.9	9.2	-	9.2
Range	(19- 54)	-	(19- 54)	(18- 54)	-	(18- 54)
Race						
WHITE	43 (62.3)	0	43 (62.3)	44 (62.0)	0	44 (62.0)
BLACK	19 (27.5)	0	19 (27.5)	17 (23.9)	0	17 (23.9)
ASIAN	0	0	0	4 (5.6)	0	4 (5.6)
OTHER	7 (10.1)	0	7 (10.1)	6 (8.5)	0	6 (8.5)

Table 14.1.2.2
PF-06410293 Protocol B5381001
Demographic Characteristics - Full Analysis Set

	Adalimumab-EU			Total		
	Male (N=69)	**Female (N=1)**	**Total (N=70)**	**Male (N=209)**	**Female (N=1)**	**Total (N=210)**
Age (Years):						
<18	0	0	0	0	0	0
18-44	56 (81.2)	0	56 (80.0)	168 (80.4)	0	168 (80.0)
45-64	13 (18.8)	1 (100.0)	14 (20.0)	41 (19.6)	1 (100.0)	42 (20.0)
>=65	0	0	0	0	0	0
Mean	35.0	54.0	35.2	34.9	54.0	35.0
SD	8.9	-	9.1	9.3	-	9.4
Range	(20- 51)	(54- 54)	(20- 54)	(18- 54)	(54- 54)	(18- 54)
Race						
WHITE	44 (63.8)	0	44 (62.9)	131 (62.7)	0	131 (62.4)
BLACK	17 (24.6)	1 (100.0)	18 (25.7)	53 (25.4)	1 (100.0)	54 (25.7)
ASIAN	0	0	0	4 (1.9)	0	4 (1.9)
OTHER	8 (11.6)	0	8 (11.4)	21 (10.0)	0	21 (10.0)

Table 14.1.2.2.1
PF-06410293 Protocol B5381001
Physical Measurements - Full Analysis Set

		Adalimumab-Pfizer (N=69)			Adalimumab-US (N=71)		
		Male	Female	Total	Male	Female	Total
Parameter	Summary Statistics						
HEIGHT (CM)	n	69	0	69	71	0	71
	Mean	177.7	-	177.7	176.6	-	176.6
	SD	7.4	-	7.4	6.7	-	6.7
	Range	(159.0- 194.0)	-	(159.0- 194.0)	(161.0- 197.0)	-	(161.0- 197.0)
WEIGHT (KG)	n	69	0	69	71	0	71
	Mean	80.5	-	80.5	80.6	-	80.6
	SD	12.1	-	12.1	10.6	-	10.6
	Range	(50.8- 107.7)	-	(50.8- 107.7)	(59.8- 101.6)	-	(59.8- 101.6)
BODY MASS INDEX (KG/M**2)	n	69	0	69	71	0	71
	Mean	25.5	-	25.5	25.9	-	25.9
	SD	3.2	-	3.2	2.9	-	2.9
	Range	(17.7- 30.5)	-	(17.7- 30.5)	(19.7- 30.4)	-	(19.7- 30.4)

Body Mass Index is calculated as wt/(ht*.01)**2.

		Adalimumab-EU (N=70)			Total (N=210)		
		Male	Female	Total	Male	Female	Total
Parameter	Summary Statistics						
HEIGHT (CM)	n	69	1	70	209	1	210
	Mean	178.1	163.0	177.8	177.4	163.0	177.4
	SD	6.3	-	6.5	6.8	-	6.9
	Range	(165.0- 192.0)	(163.0- 163.0)	(163.0- 192.0)	(159.0- 197.0)	(163.0- 163.0)	(159.0- 197.0)
WEIGHT (KG)	n	69	1	70	209	1	210
	Mean	82.3	70.3	82.1	81.1	70.3	81.1
	SD	11.6	-	11.6	11.4	-	11.4
	Range	(58.7- 105.6)	(70.3- 70.3)	(58.7- 105.6)	(50.8- 107.7)	(70.3- 70.3)	(50.8- 107.7)
BODY MASS INDEX (KG/M**2)	n	69	1	70	209	1	210
	Mean	25.9	26.5	25.9	25.8	26.5	25.8
	SD	3.0	-	3.0	3.0	-	3.0
	Range	(19.8- 30.4)	(26.5- 26.5)	(19.8- 30.4)	(17.7- 30.5)	(26.5- 26.5)	(17.7- 30.5)

Body Mass Index is calculated as wt/(ht*.01)**2.

Table 14.1.2.3
PF-06410293 Protocol B5381001
Demographic Characteristics - Per Protocol Analysis Set

	Adalimumab-Pfizer			Adalimumab-US		
	Male (N=66)	Female (N=0)	Total (N=66)	Male (N=67)	Female (N=0)	Total (N=67)
Age (Years):						
<18	0	0	0	0	0	0
18-44	55 (83.3)	0	55 (83.3)	52 (77.6)	0	52 (77.6)
45-64	11 (16.7)	0	11 (16.7)	15 (22.4)	0	15 (22.4)
>=65	0	0	0	0	0	0
Mean	34.5	-	34.5	35.3	-	35.3
SD	9.8	-	9.8	9.3	-	9.3
Range	(19- 54)	-	(19- 54)	(18- 54)	-	(18- 54)
Race						
WHITE	42 (63.6)	0	42 (63.6)	41 (61.2)	0	41 (61.2)
BLACK	18 (27.3)	0	18 (27.3)	17 (25.4)	0	17 (25.4)
ASIAN	0	0	0	3 (4.5)	0	3 (4.5)
OTHER	6 (9.1)	0	6 (9.1)	6 (9.0)	0	6 (9.0)

Table 14.1.2.3
PF-06410293 Protocol B5381001
Demographic Characteristics - Per Protocol Analysis Set

	Adalimumab-EU			Total		
	Male (N=65)	Female (N=1)	Total (N=66)	Male (N=198)	Female (N=1)	Total (N=199)
Age (Years):						
<18	0	0	0	0	0	0
18-44	53 (81.5)	0	53 (80.3)	160 (80.8)	0	160 (80.4)
45-64	12 (18.5)	1 (100.0)	13 (19.7)	38 (19.2)	1 (100.0)	39 (19.6)
>=65	0	0	0	0	0	0
Mean	34.8	54.0	35.1	34.9	54.0	35.0
SD	8.8	-	9.1	9.3	-	9.4
Range	(20- 51)	(54- 54)	(20- 54)	(18- 54)	(54- 54)	(18- 54)
Race						
WHITE	41 (63.1)	0	41 (62.1)	124 (62.6)	0	124 (62.3)
BLACK	17 (26.2)	1 (100.0)	18 (27.3)	52 (26.3)	1 (100.0)	53 (26.6)
ASIAN	0	0	0	3 (1.5)	0	3 (1.5)
OTHER	7 (10.8)	0	7 (10.6)	19 (9.6)	0	19 (9.5)

Table 14.1.2.3.1
PF-06410293 Protocol B5381001
Physical Measurements - Per Protocol Analysis Set

		Adalimumab-Pfizer (N=66)			Adalimumab-US (N=67)		
		Male	Female	Total	Male	Female	Total
Parameter	Summary Statistics						
HEIGHT (CM)	n	66	0	66	67	0	67
	Mean	177.6	-	177.6	176.4	-	176.4
	SD	7.4	-	7.4	6.8	-	6.8
	Range	(159.0- 194.0)	-	(159.0- 194.0)	(161.0- 197.0)	-	(161.0- 197.0)
WEIGHT (KG)	n	66	0	66	67	0	67
	Mean	80.4	-	80.4	80.2	-	80.2
	SD	12.2	-	12.2	10.4	-	10.4
	Range	(50.8- 107.7)	-	(50.8- 107.7)	(59.8- 101.6)	-	(59.8- 101.6)
BODY MASS INDEX (KG/M**2)	n	66	0	66	67	0	67
	Mean	25.5	-	25.5	25.8	-	25.8
	SD	3.2	-	3.2	2.9	-	2.9
	Range	(17.7- 30.5)	-	(17.7- 30.5)	(19.7- 30.4)	-	(19.7- 30.4)

Body Mass Index is calculated as wt/(ht*.01)**2.

		Adalimumab-EU (N=66)			Total (N=199)		
		Male	Female	Total	Male	Female	Total
Parameter	Summary Statistics						
HEIGHT (CM)	n	65	1	66	198	1	199
	Mean	178.1	163.0	177.9	177.3	163.0	177.3
	SD	6.2	-	6.5	6.9	-	6.9
	Range	(165.0- 192.0)	(163.0- 163.0)	(163.0- 192.0)	(159.0- 197.0)	(163.0- 163.0)	(159.0- 197.0)
WEIGHT (KG)	n	65	1	66	198	1	199
	Mean	82.5	70.3	82.3	81.0	70.3	81.0
	SD	11.6	-	11.6	11.4	-	11.4
	Range	(58.7- 105.6)	(70.3- 70.3)	(58.7- 105.6)	(50.8- 107.7)	(70.3- 70.3)	(50.8- 107.7)
BODY MASS INDEX (KG/M**2)	n	65	1	66	198	1	199
	Mean	26.0	26.5	26.0	25.7	26.5	25.7
	SD	3.0	-	3.0	3.1	-	3.0
	Range	(19.8- 30.4)	(26.5- 26.5)	(19.8- 30.4)	(17.7- 30.5)	(26.5- 26.5)	(17.7- 30.5)

Body Mass Index is calculated as wt/(ht*.01)**2.

Table 14.1.2.4
PF-06410293 Protocol B5381001
Summary of Prior Exposure to Biologics - Full Analysis Set

	Adalimumab-Pfizer (N=69)	Adalimumab-US (N=71)	Adalimumab-EU (N=70)	Total (N=210)
	n (%)	n (%)	n (%)	n (%)
Number of subjects with prior exposure to biologics	10 (14.5%)	8 (11.3%)	9 (12.9%)	27 (12.9%)
Number of subjects with no prior exposure to biologics	59 (85.5%)	63 (88.7%)	61 (87.1%)	183 (87.1%)

Table 14.3.1.2.1
PF-06410293 Protocol B5381001
Treatment-Emergent Adverse Events (All Causalities) - CTC Grade - Safety Analysis Set

	Adalimumab-Pfizer	Adalimumab-US	Adalimumab-EU	Total
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects evaluable for adverse events	69	71	70	210
Number of adverse events	49	77	93	219
Subjects with adverse events	32 (46.4)	38 (53.5)	44 (62.9)	114 (54.3)
Subjects with serious adverse events	0	0	1 (1.4)	1 (0.5)
Subjects with Grade 3 or 4 adverse events	0	1 (1.4)	2 (2.9)	3 (1.4)
Subjects with Grade 5 adverse events	0	0	0	0
Subjects discontinued from study due to adverse events	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	0

Includes all data collected since the first dose of study drug.
Subjects are counted only once per treatment in each row, except for the Number of Adverse Events.
Serious Adverse Events - according to the investigator's assessment.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:36)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-Pfizer (N=69)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	22 (31.9)	10 (14.5)	0	0	0	32 (46.4)
EAR AND LABYRINTH DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Ear pain	1 (1.4)	0	0	0	0	1 (1.4)
GASTROINTESTINAL DISORDERS	7 (10.1)	2 (2.9)	0	0	0	9 (13.0)
Abdominal discomfort	1 (1.4)	0	0	0	0	1 (1.4)
Abdominal pain	2 (2.9)	0	0	0	0	2 (2.9)
Constipation	1 (1.4)	0	0	0	0	1 (1.4)
Diarrhoea	1 (1.4)	1 (1.4)	0	0	0	2 (2.9)
Nausea	1 (1.4)	0	0	0	0	1 (1.4)
Tooth disorder	0	1 (1.4)	0	0	0	1 (1.4)
Toothache	1 (1.4)	0	0	0	0	1 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (4.3)	1 (1.4)	0	0	0	4 (5.8)
Fatigue	2 (2.9)	0	0	0	0	2 (2.9)
Injection site reaction	1 (1.4)	0	0	0	0	1 (1.4)
Vessel puncture site haematoma	0	1 (1.4)	0	0	0	1 (1.4)
INFECTIONS AND INFESTATIONS	10 (14.5)	4 (5.8)	0	0	0	14 (20.3)
Infestation	0	1 (1.4)	0	0	0	1 (1.4)
Influenza	0	1 (1.4)	0	0	0	1 (1.4)
Nasopharyngitis	4 (5.8)	0	0	0	0	4 (5.8)
Oral herpes	3 (4.3)	1 (1.4)	0	0	0	4 (5.8)
Pharyngitis	2 (2.9)	0	0	0	0	2 (2.9)
Rhinitis	1 (1.4)	0	0	0	0	1 (1.4)
Upper respiratory tract infection	0	1 (1.4)	0	0	0	1 (1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.4)	0	0	0	0	1 (1.4)
Laceration	1 (1.4)	0	0	0	0	1 (1.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (7.2)	0	0	0	0	5 (7.2)
Back pain	1 (1.4)	0	0	0	0	1 (1.4)
Musculoskeletal pain	1 (1.4)	0	0	0	0	1 (1.4)
Myalgia	1 (1.4)	0	0	0	0	1 (1.4)
Neck pain	1 (1.4)	0	0	0	0	1 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-Pfizer (N=69)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sensation of heaviness	1 (1.4)	0	0	0	0	1 (1.4)
NERVOUS SYSTEM DISORDERS	4 (5.8)	2 (2.9)	0	0	0	6 (8.7)
Headache	3 (4.3)	2 (2.9)	0	0	0	5 (7.2)
Lethargy	1 (1.4)	0	0	0	0	1 (1.4)
PSYCHIATRIC DISORDERS	2 (2.9)	1 (1.4)	0	0	0	3 (4.3)
Anxiety	0	1 (1.4)	0	0	0	1 (1.4)
Insomnia	2 (2.9)	0	0	0	0	2 (2.9)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Haematospermia	1 (1.4)	0	0	0	0	1 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (5.8)	1 (1.4)	0	0	0	5 (7.2)
Nasal congestion	2 (2.9)	0	0	0	0	2 (2.9)
Oropharyngeal discomfort	1 (1.4)	0	0	0	0	1 (1.4)
Oropharyngeal pain	0	1 (1.4)	0	0	0	1 (1.4)
Sneezing	1 (1.4)	0	0	0	0	1 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-US (N=71)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	22 (31.0)	15 (21.1)	1 (1.4)	0	0	38 (53.5)
EYE DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Blepharitis	1 (1.4)	0	0	0	0	1 (1.4)
GASTROINTESTINAL DISORDERS	11 (15.5)	3 (4.2)	0	0	0	14 (19.7)
Abdominal pain	2 (2.8)	0	0	0	0	2 (2.8)
Abnormal faeces	1 (1.4)	0	0	0	0	1 (1.4)
Change of bowel habit	1 (1.4)	0	0	0	0	1 (1.4)
Constipation	1 (1.4)	0	0	0	0	1 (1.4)
Diarrhoea	1 (1.4)	1 (1.4)	0	0	0	2 (2.8)
Dyspepsia	1 (1.4)	0	0	0	0	1 (1.4)
Flatulence	2 (2.8)	0	0	0	0	2 (2.8)
Nausea	2 (2.8)	0	0	0	0	2 (2.8)
Oral pain	1 (1.4)	0	0	0	0	1 (1.4)
Toothache	0	2 (2.8)	0	0	0	2 (2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (11.3)	1 (1.4)	0	0	0	9 (12.7)
Cyst	1 (1.4)	0	0	0	0	1 (1.4)
Fatigue	1 (1.4)	0	0	0	0	1 (1.4)
Feeling hot	1 (1.4)	0	0	0	0	1 (1.4)
Influenza like illness	0	1 (1.4)	0	0	0	1 (1.4)
Injection site erythema	2 (2.8)	1 (1.4)	0	0	0	3 (4.2)
Injection site haematoma	1 (1.4)	0	0	0	0	1 (1.4)
Injection site pain	2 (2.8)	0	0	0	0	2 (2.8)
Non-cardiac chest pain	2 (2.8)	0	0	0	0	2 (2.8)
Thirst	1 (1.4)	0	0	0	0	1 (1.4)
Vessel puncture site pain	0	1 (1.4)	0	0	0	1 (1.4)
INFECTIONS AND INFESTATIONS	7 (9.9)	5 (7.0)	1 (1.4)	0	0	13 (18.3)
Gastroenteritis	0	1 (1.4)	1 (1.4)	0	0	2 (2.8)
Herpes dermatitis	0	1 (1.4)	0	0	0	1 (1.4)
Influenza	3 (4.2)	2 (2.8)	0	0	0	5 (7.0)
Nasopharyngitis	3 (4.2)	1 (1.4)	0	0	0	4 (5.6)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-US (N=71)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Otitis media	1 (1.4)	0	0	0	0	1 (1.4)
Tracheitis	0	1 (1.4)	0	0	0	1 (1.4)
Upper respiratory tract infection	2 (2.8)	0	0	0	0	2 (2.8)
INVESTIGATIONS	0	1 (1.4)	0	0	0	1 (1.4)
Liver function test abnormal	0	1 (1.4)	0	0	0	1 (1.4)
METABOLISM AND NUTRITION DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Decreased appetite	1 (1.4)	0	0	0	0	1 (1.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6 (8.5)	2 (2.8)	0	0	0	8 (11.3)
Back pain	3 (4.2)	1 (1.4)	0	0	0	4 (5.6)
Muscle spasms	1 (1.4)	0	0	0	0	1 (1.4)
Musculoskeletal pain	1 (1.4)	0	0	0	0	1 (1.4)
Myalgia	1 (1.4)	0	0	0	0	1 (1.4)
Pain in extremity	0	1 (1.4)	0	0	0	1 (1.4)
NERVOUS SYSTEM DISORDERS	10 (14.1)	1 (1.4)	0	0	0	11 (15.5)
Cognitive disorder	1 (1.4)	0	0	0	0	1 (1.4)
Dizziness postural	1 (1.4)	0	0	0	0	1 (1.4)
Head discomfort	1 (1.4)	0	0	0	0	1 (1.4)
Headache	5 (7.0)	1 (1.4)	0	0	0	6 (8.5)
Somnolence	2 (2.8)	0	0	0	0	2 (2.8)
PSYCHIATRIC DISORDERS	2 (2.8)	0	0	0	0	2 (2.8)
Anxiety	1 (1.4)	0	0	0	0	1 (1.4)
Depressed mood	1 (1.4)	0	0	0	0	1 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.8)	2 (2.8)	0	0	0	4 (5.6)
Nasal congestion	2 (2.8)	0	0	0	0	2 (2.8)
Oropharyngeal pain	0	2 (2.8)	0	0	0	2 (2.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (1.4)	1 (1.4)	0	0	0	2 (2.8)
Dry skin	1 (1.4)	0	0	0	0	1 (1.4)
Pruritus	0	1 (1.4)	0	0	0	1 (1.4)
Rash	0	1 (1.4)	0	0	0	1 (1.4)
SURGICAL AND MEDICAL PROCEDURES	0	1 (1.4)	0	0	0	1 (1.4)
Tooth extraction	0	1 (1.4)	0	0	0	1 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-EU (N=70)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	24 (34.3)	18 (25.7)	2 (2.9)	0	0	44 (62.9)
EYE DISORDERS	0	1 (1.4)	0	0	0	1 (1.4)
Conjunctivitis	0	1 (1.4)	0	0	0	1 (1.4)
GASTROINTESTINAL DISORDERS	13 (18.6)	1 (1.4)	0	0	0	14 (20.0)
Abdominal discomfort	1 (1.4)	0	0	0	0	1 (1.4)
Abdominal distension	1 (1.4)	0	0	0	0	1 (1.4)
Abdominal pain	1 (1.4)	0	0	0	0	1 (1.4)
Abdominal pain lower	1 (1.4)	0	0	0	0	1 (1.4)
Abdominal pain upper	0	1 (1.4)	0	0	0	1 (1.4)
Change of bowel habit	1 (1.4)	0	0	0	0	1 (1.4)
Constipation	2 (2.9)	0	0	0	0	2 (2.9)
Diarrhoea	3 (4.3)	0	0	0	0	3 (4.3)
Flatulence	2 (2.9)	0	0	0	0	2 (2.9)
Haemorrhoids	1 (1.4)	0	0	0	0	1 (1.4)
Nausea	3 (4.3)	1 (1.4)	0	0	0	4 (5.7)
Vomiting	0	1 (1.4)	0	0	0	1 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (5.7)	1 (1.4)	0	0	0	5 (7.1)
Fatigue	3 (4.3)	0	0	0	0	3 (4.3)
Feeling hot	1 (1.4)	0	0	0	0	1 (1.4)
Influenza like illness	1 (1.4)	1 (1.4)	0	0	0	2 (2.9)
INFECTIONS AND INFESTATIONS	9 (12.9)	10 (14.3)	1 (1.4)	0	0	20 (28.6)
Folliculitis	2 (2.9)	0	0	0	0	2 (2.9)
Gastroenteritis	3 (4.3)	0	0	0	0	3 (4.3)
Influenza	0	1 (1.4)	0	0	0	1 (1.4)
Nasopharyngitis	4 (5.7)	5 (7.1)	0	0	0	9 (12.9)
Oral herpes	0	2 (2.9)	0	0	0	2 (2.9)
Pharyngitis	0	1 (1.4)	0	0	0	1 (1.4)
Rhinitis	2 (2.9)	0	0	0	0	2 (2.9)
Sinusitis	0	1 (1.4)	0	0	0	1 (1.4)
Subcutaneous abscess	0	0	1 (1.4)	0	0	1 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-EU (N=70)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Upper respiratory tract infection	0	1 (1.4)	0	0	0	1 (1.4)
Viral infection	1 (1.4)	0	0	0	0	1 (1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (2.9)	1 (1.4)	0	0	0	3 (4.3)
Excoriation	1 (1.4)	0	0	0	0	1 (1.4)
Laceration	1 (1.4)	0	0	0	0	1 (1.4)
Limb injury	0	1 (1.4)	0	0	0	1 (1.4)
INVESTIGATIONS	0	2 (2.9)	1 (1.4)	0	0	3 (4.3)
Alanine aminotransferase increased	0	1 (1.4)	1 (1.4)	0	0	2 (2.9)
Aspartate aminotransferase increased	0	2 (2.9)	0	0	0	2 (2.9)
METABOLISM AND NUTRITION DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Hypokalaemia	1 (1.4)	0	0	0	0	1 (1.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (11.4)	0	0	0	0	8 (11.4)
Arthralgia	2 (2.9)	0	0	0	0	2 (2.9)
Back pain	2 (2.9)	0	0	0	0	2 (2.9)
Musculoskeletal chest pain	1 (1.4)	0	0	0	0	1 (1.4)
Musculoskeletal discomfort	1 (1.4)	0	0	0	0	1 (1.4)
Musculoskeletal stiffness	1 (1.4)	0	0	0	0	1 (1.4)
Myalgia	1 (1.4)	0	0	0	0	1 (1.4)
NERVOUS SYSTEM DISORDERS	9 (12.9)	6 (8.6)	0	0	0	15 (21.4)
Dizziness	2 (2.9)	0	0	0	0	2 (2.9)
Headache	6 (8.6)	6 (8.6)	0	0	0	12 (17.1)
Somnolence	1 (1.4)	0	0	0	0	1 (1.4)
PSYCHIATRIC DISORDERS	0	1 (1.4)	0	0	0	1 (1.4)
Anxiety	0	1 (1.4)	0	0	0	1 (1.4)
RENAL AND URINARY DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Urine odour abnormal	1 (1.4)	0	0	0	0	1 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (5.7)	1 (1.4)	0	0	0	5 (7.1)
Cough	1 (1.4)	0	0	0	0	1 (1.4)
Oropharyngeal pain	2 (2.9)	1 (1.4)	0	0	0	3 (4.3)
Sneezing	1 (1.4)	0	0	0	0	1 (1.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (2.9)	1 (1.4)	0	0	0	3 (4.3)
Alopecia	1 (1.4)	0	0	0	0	1 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Adalimumab-EU (N=70)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dermatitis acneiform	0	1 (1.4)	0	0	0	1 (1.4)
Dermatitis contact	1 (1.4)	0	0	0	0	1 (1.4)
Pruritus	0	1 (1.4)	0	0	0	1 (1.4)
VASCULAR DISORDERS	1 (1.4)	0	0	0	0	1 (1.4)
Haematoma	1 (1.4)	0	0	0	0	1 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Table 14.3.1.2.2.1
PF-06410293 Protocol B5381001
Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTC Grade (All Causalities) - Safety Analysis Set

Number of Subjects Evaluable for AEs	Total (N=210)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	68 (32.4)	43 (20.5)	3 (1.4)	0	0	114 (54.3)
EAR AND LABYRINTH DISORDERS	1 (0.5)	0	0	0	0	1 (0.5)
Ear pain	1 (0.5)	0	0	0	0	1 (0.5)
EYE DISORDERS	1 (0.5)	1 (0.5)	0	0	0	2 (1.0)
Blepharitis	1 (0.5)	0	0	0	0	1 (0.5)
Conjunctivitis	0	1 (0.5)	0	0	0	1 (0.5)
GASTROINTESTINAL DISORDERS	31 (14.8)	6 (2.9)	0	0	0	37 (17.6)
Abdominal discomfort	2 (1.0)	0	0	0	0	2 (1.0)
Abdominal distension	1 (0.5)	0	0	0	0	1 (0.5)
Abdominal pain	5 (2.4)	0	0	0	0	5 (2.4)
Abdominal pain lower	1 (0.5)	0	0	0	0	1 (0.5)
Abdominal pain upper	0	1 (0.5)	0	0	0	1 (0.5)
Abnormal faeces	1 (0.5)	0	0	0	0	1 (0.5)
Change of bowel habit	2 (1.0)	0	0	0	0	2 (1.0)
Constipation	4 (1.9)	0	0	0	0	4 (1.9)
Diarrhoea	5 (2.4)	2 (1.0)	0	0	0	7 (3.3)
Dyspepsia	1 (0.5)	0	0	0	0	1 (0.5)
Flatulence	4 (1.9)	0	0	0	0	4 (1.9)
Haemorrhoids	1 (0.5)	0	0	0	0	1 (0.5)
Nausea	6 (2.9)	1 (0.5)	0	0	0	7 (3.3)
Oral pain	1 (0.5)	0	0	0	0	1 (0.5)
Tooth disorder	0	1 (0.5)	0	0	0	1 (0.5)
Toothache	1 (0.5)	2 (1.0)	0	0	0	3 (1.4)
Vomiting	0	1 (0.5)	0	0	0	1 (0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	15 (7.1)	3 (1.4)	0	0	0	18 (8.6)
Cyst	1 (0.5)	0	0	0	0	1 (0.5)
Fatigue	6 (2.9)	0	0	0	0	6 (2.9)
Feeling hot	2 (1.0)	0	0	0	0	2 (1.0)
Influenza like illness	1 (0.5)	2 (1.0)	0	0	0	3 (1.4)
Injection site erythema	2 (1.0)	1 (0.5)	0	0	0	3 (1.4)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Number of Subjects Evaluable for AEs	Total (N=210)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Injection site haematoma	1 (0.5)	0	0	0	0	1 (0.5)
Injection site pain	2 (1.0)	0	0	0	0	2 (1.0)
Injection site reaction	1 (0.5)	0	0	0	0	1 (0.5)
Non-cardiac chest pain	2 (1.0)	0	0	0	0	2 (1.0)
Thirst	1 (0.5)	0	0	0	0	1 (0.5)
Vessel puncture site haematoma	0	1 (0.5)	0	0	0	1 (0.5)
Vessel puncture site pain	0	1 (0.5)	0	0	0	1 (0.5)
INFECTIONS AND INFESTATIONS	26 (12.4)	19 (9.0)	2 (1.0)	0	0	47 (22.4)
Folliculitis	2 (1.0)	0	0	0	0	2 (1.0)
Gastroenteritis	3 (1.4)	1 (0.5)	1 (0.5)	0	0	5 (2.4)
Herpes dermatitis	0	1 (0.5)	0	0	0	1 (0.5)
Infestation	0	1 (0.5)	0	0	0	1 (0.5)
Influenza	3 (1.4)	4 (1.9)	0	0	0	7 (3.3)
Nasopharyngitis	11 (5.2)	6 (2.9)	0	0	0	17 (8.1)
Oral herpes	3 (1.4)	3 (1.4)	0	0	0	6 (2.9)
Otitis media	1 (0.5)	0	0	0	0	1 (0.5)
Pharyngitis	2 (1.0)	1 (0.5)	0	0	0	3 (1.4)
Rhinitis	3 (1.4)	0	0	0	0	3 (1.4)
Sinusitis	0	1 (0.5)	0	0	0	1 (0.5)
Subcutaneous abscess	0	0	1 (0.5)	0	0	1 (0.5)
Tracheitis	0	1 (0.5)	0	0	0	1 (0.5)
Upper respiratory tract infection	2 (1.0)	2 (1.0)	0	0	0	4 (1.9)
Viral infection	1 (0.5)	0	0	0	0	1 (0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (1.4)	1 (0.5)	0	0	0	4 (1.9)
Excoriation	1 (0.5)	0	0	0	0	1 (0.5)
Laceration	2 (1.0)	0	0	0	0	2 (1.0)
Limb injury	0	1 (0.5)	0	0	0	1 (0.5)
INVESTIGATIONS	0	3 (1.4)	1 (0.5)	0	0	4 (1.9)
Alanine aminotransferase increased	0	1 (0.5)	1 (0.5)	0	0	2 (1.0)
Aspartate aminotransferase increased	0	2 (1.0)	0	0	0	2 (1.0)
Liver function test abnormal	0	1 (0.5)	0	0	0	1 (0.5)
METABOLISM AND NUTRITION DISORDERS	2 (1.0)	0	0	0	0	2 (1.0)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Number of Subjects Evaluable for AEs	Total (N=210)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Decreased appetite	1 (0.5)	0	0	0	0	1 (0.5)
Hypokalaemia	1 (0.5)	0	0	0	0	1 (0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	19 (9.0)	2 (1.0)	0	0	0	21 (10.0)
Arthralgia	2 (1.0)	0	0	0	0	2 (1.0)
Back pain	6 (2.9)	1 (0.5)	0	0	0	7 (3.3)
Muscle spasms	1 (0.5)	0	0	0	0	1 (0.5)
Musculoskeletal chest pain	1 (0.5)	0	0	0	0	1 (0.5)
Musculoskeletal discomfort	1 (0.5)	0	0	0	0	1 (0.5)
Musculoskeletal pain	2 (1.0)	0	0	0	0	2 (1.0)
Musculoskeletal stiffness	1 (0.5)	0	0	0	0	1 (0.5)
Myalgia	3 (1.4)	0	0	0	0	3 (1.4)
Neck pain	1 (0.5)	0	0	0	0	1 (0.5)
Pain in extremity	0	1 (0.5)	0	0	0	1 (0.5)
Sensation of heaviness	1 (0.5)	0	0	0	0	1 (0.5)
NERVOUS SYSTEM DISORDERS	23 (11.0)	9 (4.3)	0	0	0	32 (15.2)
Cognitive disorder	1 (0.5)	0	0	0	0	1 (0.5)
Dizziness	2 (1.0)	0	0	0	0	2 (1.0)
Dizziness postural	1 (0.5)	0	0	0	0	1 (0.5)
Head discomfort	1 (0.5)	0	0	0	0	1 (0.5)
Headache	14 (6.7)	9 (4.3)	0	0	0	23 (11.0)
Lethargy	1 (0.5)	0	0	0	0	1 (0.5)
Somnolence	3 (1.4)	0	0	0	0	3 (1.4)
PSYCHIATRIC DISORDERS	4 (1.9)	2 (1.0)	0	0	0	6 (2.9)
Anxiety	1 (0.5)	2 (1.0)	0	0	0	3 (1.4)
Depressed mood	1 (0.5)	0	0	0	0	1 (0.5)
Insomnia	2 (1.0)	0	0	0	0	2 (1.0)
RENAL AND URINARY DISORDERS	1 (0.5)	0	0	0	0	1 (0.5)
Urine odour abnormal	1 (0.5)	0	0	0	0	1 (0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.5)	0	0	0	0	1 (0.5)
Haematospermia	1 (0.5)	0	0	0	0	1 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	10 (4.8)	4 (1.9)	0	0	0	14 (6.7)
Cough	1 (0.5)	0	0	0	0	1 (0.5)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)

Number of Subjects Evaluable for AEs	Total (N=210)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Nasal congestion	4 (1.9)	0	0	0	0	4 (1.9)
Oropharyngeal discomfort	1 (0.5)	0	0	0	0	1 (0.5)
Oropharyngeal pain	2 (1.0)	4 (1.9)	0	0	0	6 (2.9)
Sneezing	2 (1.0)	0	0	0	0	2 (1.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1.4)	2 (1.0)	0	0	0	5 (2.4)
Alopecia	1 (0.5)	0	0	0	0	1 (0.5)
Dermatitis acneiform	0	1 (0.5)	0	0	0	1 (0.5)
Dermatitis contact	1 (0.5)	0	0	0	0	1 (0.5)
Dry skin	1 (0.5)	0	0	0	0	1 (0.5)
Pruritus	0	2 (1.0)	0	0	0	2 (1.0)
Rash	0	1 (0.5)	0	0	0	1 (0.5)
SURGICAL AND MEDICAL PROCEDURES	0	1 (0.5)	0	0	0	1 (0.5)
Tooth extraction	0	1 (0.5)	0	0	0	1 (0.5)
VASCULAR DISORDERS	1 (0.5)	0	0	0	0	1 (0.5)
Haematoma	1 (0.5)	0	0	0	0	1 (0.5)

For each of Any AEs, SOC or Preferred Term, each subject is only counted once under the highest grade.
MedDRA v16.1 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7.1 Date of SDTM Dataset Creation: 11APR2018 Date of Table Generation: 16MAY2018 (02:43)