Cover Page

Multiple switches between adalimumab-fkjp and reference adalimumab in moderate-to-severe chronic plaque psoriasis:

A multicentre, double-blind, parallel group, randomized clinical trial for interchangeability

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Short Title: Interchangeability study between adalimumab-fkjp and reference adalimumab in chronic plaque psoriasis

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Supplementary Online Content

Deodhar S, Loganathan S, KS R et al. Multiple switches between adalimumab-fkjp and reference adalimumab in chronic plaque psoriasis. A multicentre, double-blind, parallel group randomized clinical trial.

Methods-S1

Inclusion Criteria

A patient was eligible for inclusion in the study if he or she met all the following criteria:

1. Patient was able to understand and voluntarily provide written informed consent to participate in the study.
2. Patient was aged 18 to 75 years inclusive, at the time of Screening.
3. Had moderate to severe chronic plaque psoriasis for at least 6 months prior to screening and that has involved body surface area (BSA) ≥10%, PASI ≥12, and static Physicians Global Assessment (sPGA) ≥3 (moderate) at Screening and at Baseline
4. Had stable disease for at least 2 months (i.e., without significant changes as defined by the principal investigator [PI] or designee)
5. Patient was a candidate for systemic therapy or phototherapy.
6. Had a previous failure, inadequate response, intolerance, or contraindication to at least one conventional anti-psoriatic systemic therapy, including methotrexate, cyclosporine, psoralen plus ultraviolet light A (PUVA), and ultraviolet light B (UVB)
7. Patient was willing to follow the contraception requirement, based on the childbearing potential, as defined in the protocol.

Exclusion Criteria

1. A patient who met any of the following criteria was excluded from the study:
2. Was diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (e.g., eczema), or other systemic autoimmune disorder/ inflammatory disease at the time of the Screening visit that would interfere with evaluations of the effect of the study treatment of psoriasis.
3. Prior and concomitant medications: Had prior use of any of the following medications within specified time periods or required to use during the study:
    a. Topical medications within 2 weeks of baseline (Week 1)
    b. PUVA phototherapy and/or UVB phototherapy within 4 weeks prior to Baseline visit
    c. Nonbiologic psoriasis systemic therapies (eg, cyclosporine, methotrexate, and acitretin) within 4 weeks prior to Baseline visit

d. Any prior or concomitant adalimumab therapy, either approved or investigational
e. Any systemic steroid in the 4 weeks prior to Baseline Visit

4. Specified washout periods were as follows:
    i. Investigational agent(s) within 90 days or 5 half-lives (whichever is longer) before Baseline (Week 1)

Refer to **Table-S1** for approved/marketed products washed out as prior immunosuppressant medications, including biologics, in the run-in period population.

5. Had received live or attenuated vaccines during the 4 weeks prior to Screening or had the intention of receiving a live or attenuated vaccine at any time during the study.
6. Other medical conditions: Known chronic or relevant acute TB; IGRA TB test or PPD skin test was performed according to Reference adalimumab label. If the result was positive, patients may have participated in the trial if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active TB. If latent TB was confirmed, then treatment must have been initiated before treatment in the study and continued according to local country guidelines.
7. Had an underlying condition (including, but not limited to, metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal) which, in the opinion of the PI or designee, significantly immunocompromised the patient and/or placed the patient at unacceptable risk for receiving immunomodulatory therapy.
8. Had a planned surgical intervention during the duration of the study and which, in the opinion of the PI or designee, would have put the patient at further risk or hindered the patient's ability to maintain compliance with study treatment and the visit schedule.
9. Had any active and serious infection or history of infections as follows:
10. Any active infection
11. For which non-systemic anti-infectives were used within 4 weeks prior to enrollment. Note: Patients receiving topical antibiotics for facial acne were not needed to be excluded.
12. Which required hospitalization or systemic anti-infectives within 8 weeks prior to enrollment.
13. Recurrent or chronic infections or other active infections that, in the opinion of the PI or designee, would have caused the study to be detrimental to the patient.
14. Invasive fungal infection or mycobacterial infection
15. Opportunistic infections, such as listeriosis, legionellosis, or pneumocystis Is positive for human immunodeficiency virus (HIV), hepatitis C virus antibody, or hepatitis B surface antigen (HbsAg) or is positive for hepatitis B core antibody (HbcAb) at Screening
16. Had laboratory abnormalities, including but not limited to clinically significant hematological abnormalities, that, in the opinion of the PI or designee, could have caused the study to be detrimental to the patient. The patients were excluded if they had the following laboratory abnormalities.
17. Hemoglobin <9 g/dL
18. Platelet count <100 000/mm3
19. White blood cell count <3000 cells/mm3
20. Aspartate aminotransferase and/or alanine aminotransferase that was persistently ≥2.5X the upper limit of normal. (Persistently indicates elevated transaminases, at least on two separate occasions)
21. Creatinine clearance <50 mL/min (Cockcroft-Gault formula)
22. Had severe progressive or uncontrolled, clinically significant disease that in the judgment of the PI or designee rendered the patient unsuitable for the study.
23. Had a history of malignancy within 5 years except for adequately treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
24. Had an active neurological disease, such as multiple sclerosis, Guillain-Barré syndrome, optic neuritis, and transverse myelitis, or a history of neurologic symptoms suggestive of central nervous system demyelinating disease.
25. Had moderate to severe heart failure (New York Heart Association [NYHA] Class III/IV).
26. Had a history of hypersensitivity to the active substance or to any of the excipients of Reference adalimumab or Adalimumab-fkjp.
27. Was pregnant or nursing (lactating) woman.
28. Had evidence (as assessed by the PI or designee using good clinical judgment) of alcohol or drug abuse or dependency up to 5 years prior to Screening.
29. Was unable to follow study instructions and comply with the protocol in the opinion of the PI or designee.

Table-S1: Use of prior immunosuppressant medications, including biologics, in the run-in period population

	Run-in Period	Randomized Interchangeable Treatment Period		
ATC Code 3rd Level Preferred Term	Reference Adalimumab (N=386) n (%)	Non-switch Arm (N=193) n (%)	Switch arm (N=181) n (%)	Total (N=374) n (%)
IMMUNOSUPPRESANTS	249 (64.5)	126 (65.3)	113 (62.4)	239 (63.9)
METHOTREXATE	186 (48.2)	97 (50.3)	82 (45.3)	179 (47.9)
USTEKINUMAB	49 (12.7)	23 (11.9)	22 (12.2)	45 (12.0)
METHOTREXATE SODIUM	33 (8.5)	19 (9.8)	14 (7.7)	33 (8.8)
CYCLOSPORIN	28 (7.3)	14 (7.3)	14 (7.7)	28 (7.5)
BIMEKIZUMAB	9 (2.3)	6 (3.1)	3 (1.7)	9 (2.4)
IXEKIZUMAB	8 (2.1)	4 (2.1)	3 (1.7)	7 (1.9)
ETANERCEPT	4 (1.0)	2 (1.0)	2 (1.1)	4 (1.1)
CERTOLIZUMAB	3 (0.8)	2 (1.0)	1 (0.6)	3 (0.8)
APREMILAST	2 (0.5)	0	2 (1.1)	2 (0.5)
MIRIKIZUMAB	2 (0.5)	0	0	0
NAMILUMAB	2 (.5)	1 (0.5)	0	1 (0.5)
SECUKINUMAB	2 (0.5)	1 (0.5)	1 (0.6)	2 (0.5)
CERTOLIZUMAB PEGOL	1 (0.3)	0	1 (0.6)	1 (0.3)
DEUCRAVACITINIB	1 (0.3)	0	1 (0.6)	1 (0.3)
GOLIMUMAB	1 (0.3)	0	1 (0.6)	1 (0.3)
LEFLUNOMIDE	1 (0.3)	0	1 (0.6)	1 (0.3)
RISANKIZUMAB	1 (0.3)	0	1 (0.6)	1 (0.3)

Note: 1. N = Number of patients within the analysis population and treatment group, n = number of patients within each respective category. Note 2. Non-switch arm: Patients received Reference Adalimumab (40 mg every other week) until Week 26 /Visit 14. Switch arm: Patients underwent repeated switches until Week 26 /Visit 14: Adalimumab-fkjp (40 mg every other week) for 4 weeks, Reference Adalimumab (40 mg every other week) for 4 weeks, and Adalimumab-fkjp (40 mg every other week) for 8 weeks. Note 3. Percentages are based on the total number of patients in the analysis population and treatment group. Note 4. Prior medications are medications which started and stopped prior to the first dose of study medication. Note 5. WHO Drug dictionary Version WHOGLOBAL_202303_B3 is used. Note 6. Patients experiencing multiple events within the same anatomical therapeutic chemical (ATC) or preferred term are counted only once under those categories. Note 7. Wash-out period: For the biologic therapies the wash-out period was 12 weeks before baseline (Week 1); for methotrexate, cyclosporine, PUVA-UVA-UVB it was 4 weeks. 8. Biologic immunosuppressants are in italics.

Table-S2: Demographics and Other Baseline Characteristics by Treatment Groups

		Run-in Period	Randomized Interchangeable Treatment Period		
Characteristics	**Statistic**	**Reference Adalimumab (N=386) n (%)**	**Non-switch arm (N=193) n (%)**	**Switch arm (N=181) n (%)**	**Total (N=374) n (%)**
Age (Years)	n	386	193	181	374
	Mean (SD)	46.1 (13.08)	46.4 (12.86)	45.7 (13.40)	46.0 (13.11)
	Median	46.0	46.0	46.0	46.0
	Min, Max	18, 76	21, 76	18, 74	18, 76
Male	n (%)	252 (65.3)	132 (68.4)	112 (61.9)	244 (65.2)
Female	n (%)	134 (34.7)	61 (31.6)	69 (38.1)	130 (34.8)
Ethnicity					
Hispanic or Latino	n (%)	3 (0.8)	1 (0.5)	2 (1.1)	3 (0.8)
Not Hispanic or Latino	n (%)	383 (99.2)	192 (99.5)	179 (98.9)	371 (99.2)
Race					
White	n (%)	384 (99.5)	191 (99.0)	181 (100.0)	372 (99.5)
Other	n (%)	2 (0.5)	2 (1.0)	0	2 (0.5)
Baseline PASI Score	n	386	193	181	374
	Mean (SD)	21.12 (8.118)	21.31 (7.908)	21.23 (8.506)	21.27 (8.192)
	Median	18.35	19.00	18.00	18.60
	Min, Max	12.0, 63.2	12.0, 55.8	12.0, 63.2	12.0, 63.2
Baseline sPGA Total Average Score	n	386	193	181	374
	Mean (SD)	3.4 (0.58)	3.5 (0.63)	3.4 (0.53)	3.4 (0.59)
	Median	3.0	3.0	3.0	3.0
	Min, Max	3, 5	3, 5	3, 5	3, 5
Baseline sPGA Severity Score					
0	n (%)	0	0	0	0
1	n (%)	0	0	0	0
2	n (%)	0	0	0	0
3	n (%)	240 (62.2)	113 (58.5)	118 (65.2)	231 (61.8)
4	n (%)	128 (33.2)	66 (34.2)	59 (32.6)	125 (33.4)
5	n (%)	18 (4.7)	14 (7.3)	4 (2.2)	18 (4.8)

Max = Maximum, Min = Minimum, SD = Standard Deviation, PASI = Psoriasis Area and Severity Index, sPGA = Static Physician's Global Assessment, N = Number of patients within the analysis population and treatment group, n = number of patients within each respective category. Note 1: BMI (kg/m^2): Weight (kg)/Height (m^2). Note 2: Percentages are based on the total number of patients in the analysis population and treatment group.

Table-S3: Summary of PASI Total Score (observed) by Visit and Treatment Group

	Randomized Interchangeable Treatment Period	
Visit **Statistic**	**Non-switch Arm (N=189) n (%)**	**Switch Arm (N=175) n (%)**
Baseline (Week1/ Visit 1) (n)	189	175
Mean (SD)	21.39 (7.9)	21.22 (8.5)
Week 12 (Visit 7) (n)	189	175
Mean (SD)	2.86 (2.9)	2.56 (2.6)
Change from Baseline (n)	189	175
Mean (SD)	-18.54 (7.7)	-18.66 (8.0)
Percent Improvement from Baseline (n)	189	175
Mean (SD)	86.3 (12.7)	88.1 (11.3)
Week 16 (Visit 9) (n)	188	173
Mean (SD)	2.27 (2.6)	2.20 (2.6)
Change from Baseline (n)	188	173
Mean (SD)	-19.15 (8.1)	-19.06 (8.2)
Percent Improvement from Baseline (n)	188	173
Mean (SD)	88.7 (13.0)	89.6 (11.3)
Week 20 (Visit 11) (n)	183	171
Mean (SD)	2.01 (3.5)	2.03 (2.6)
Change from Baseline (n)	183	171
Mean (SD)	-19.48 (8.6)	-19.18 (8.5)
Percent Improvement from Baseline (n)	183	171
Mean (SD)	90.1 (16.0)	90.1 (14.1)
Week 28 (Visit 15) (n)	171	162
Mean (SD)	1.64 (2.6)	1.64 (2.5)
Change from Baseline (n)	171	162
Mean (SD)	-19.86 (8.5)	-19.59 (8.8)
Percent Improvement from Baseline (n)	171	162
Mean (SD)	91.7 (13.8)	91.8 (14.2)

N = Number of patients within the analysis population and treatment group, n = number of patients, Max = Maximum, Min =Minimum, SD = Standard Deviation, PASI = Psoriasis Area and Severity Index. Note 1: Baseline is the last non-missing measurement taken prior to the first dose of reference adalimumab in the run-in period (Week 1/ Visit 1). Note 2: Percent improvement from baseline at Visit X = (Test Value at Visit X - Baseline Value) / Baseline Value × 100.

Table-S4: TEAEs (≥3 subjects, in either Group) by SOC and PT during Randomized Interchangeable Treatment Period - Safety Population

	Randomized Interchangeable Treatment Period					
	Non-switch arm (N=193)		Switch arm (N=181)		Total (N=374)	
System Organ Class Preferred Term	n (%)	E	n (%)	E	n (%)	E
Subjects with at least one TEAE	66 (34.2)	139	54 (29.8)	102	120 (32.1)	241
Infections and infestations	35 (18.1)	43	24 (13.3)	28	59 (15.8)	71
Nasopharyngitis	11 (5.7)	11	4 (2.2)	4	15 (4.0)	15
Upper respiratory tract infection	4 (2.1)	4	4 (2.2)	4	8 (2.1)	8
Pharyngitis	4 (2.1)	4	2 (1.1)	2	6 (1.6)	6
Rhinitis	3 (1.6)	3	1 (0.6)	1	4 (1.1)	4
Tonsillitis	2 (1.0)	2	2 (1.1)	2	4 (1.1)	4
Urinary tract infection	2 (1.0)	2	2 (1.1)	2	4 (1.1)	4
Influenza	1 (0.5)	1	2 (1.1)	2	3 (0.8)	3
Sinusitis	2 (1.0)	2	1 (0.6)	1	3 (0.8)	3
General disorders and administration site conditions	7 (3.6)	34	7 (3.9)	16	14 (3.7)	50
Injection site erythema	3 (1.6)	10	3 (1.7)	4	6 (1.6)	14
Injection site pain	4 (2.1)	6	1 (0.6)	1	5 (1.3)	7
Injection site pruritus	2 (1.0)	6	2 (1.1)	4	4 (1.1)	10
Injection site swelling	2 (1.0)	7	2 (1.1)	2	4 (1.1)	9
Musculoskeletal and connective tissue disorders	3 (1.6)	4	10 (5.5)	13	13 (3.5)	17
Arthralgia	2 (1.0)	2	3 (1.7)	5	5 (1.3)	7
Back pain	1 (0.5)	1	2 (1.1)	2	3 (0.8)	3
Psoriatic arthropathy	0	0	3 (1.7)	3	3 (0.8)	3
Nervous system disorders	6 (3.1)	8	6 (3.3)	8	12 (3.2)	16
Headache	6 (3.1)	8	4 (2.2)	6	10 (2.7)	14
Skin and subcutaneous tissue disorders	6 (3.1)	7	6 (3.3)	6	12 (3.2)	13
Psoriasis	3 (1.6)	3	2 (1.1)	2	5 (1.3)	5
Investigations	7 (3.6)	18	4 (2.2)	10	11 (2.9)	28
> Alanine aminotransferase	5 (2.6)	5	3 (1.7)	4	8 (2.1)	9

	Randomized Interchangeable Treatment Period					
	Non-switch arm (N=193)		Switch arm (N=181)		Total (N=374)	
System Organ Class Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
> Gamma-glutamyl transferase	3 (1.6)	3	3 (1.7)	4	6 (1.6)	7
> Aspartate aminotransferase	3 (1.6)	4	2 (1.1)	2	5 (1.3)	6
Gastrointestinal disorders	3 (1.6)	3	3 (1.7)	3	6 (1.6)	6
Diarrhoea	2 (1.0)	2	2 (1.1)	2	4 (1.1)	4
Vascular disorders	5 (2.6)	6	1 (0.6)	1	6 (1.6)	7
Hypertension	4 (2.1)	4	1 (0.6)	1	5 (1.3)	5

N = Number of subjects within the analysis population and treatment group, n = number of subjects within each respective category, TEAE = Treatment Emergent Adverse Events, E = Number of events.
Note: 1. Non-switch arm: Subjects continue to receive Reference Adalimumab (40 mg every other week) until Week 26 /Visit 14. Switch arm: Subjects undergo repeated switches until Week 26 /Visit 14: Adalimumab-fkjp (40 mg every other week) for 4 weeks, Reference Adalimumab (40 mg every other week) for 4 weeks, and Adalimumab-fkjp (40 mg every other week) for 8 weeks. Note 2: Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the date/time of first dose of study medication. Note 3: MedDRA dictionary version 26.0 is used. Note 4: Percentages are based on the total number of subjects in the analysis population and treatment group. Note 5: Subjects with more than one event within a System Organ Class (SOC) or Preferred Term (PT) are counted only once for that SOC or PT.

Table-S5: Treatment-Emergent AESI by SOC and PT during Randomized Interchangeable Treatment Period - Safety Population

	Randomized Interchangeable Treatment Period					
System Organ Class Preferred Term	**Non-switch arm (N=193)**		**Switch arm (N=181)**		**Total (N=374)**	
	n (%)	**E**	**n (%)**	**E**	**n (%)**	**E**
Patients with at least one TEAE of Special Interest	0	0	1 (0.6)	1	1 (0.3)	1
Infections and infestations	0	0	1 (0.6)	1	1 (0.3)	1
COVID-19 pneumonia	0	0	1 (0.6)	1	1 (0.3)	1

Note 1: Non-switch arm: Patients continue to receive Reference Adalimumab (40 mg every other week) until Week 26 /Visit 14. Switch arm: Patients undergo repeated switches until Week 26 /Visit 14: Adalimumab-fkjp (40 mg every other week) for 4 weeks, Reference Adalimumab (40 mg every other week) for 4 weeks, and Adalimumab-fkjp (40 mg every other week) for 8 weeks. N = Number of patients within the analysis population and treatment group, n = number of patients within each respective category, TEAE = Treatment-Emergent Adverse Event, E = Number of events. Note 2: Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the date/time of first dose of study medication. Note 3: MedDRA dictionary version 26.0 is used. Note 4: Percentages are based on the total number of patients in the analysis population and treatment group. Note 5: Patients with more than one event within a System Organ Class (SOC) or Preferred Term (PT) are counted only once for that SOC or PT.

Table-S6: Injection-site reactions (Observed by Investigator or Designee) during randomized interchangeable treatment period.

	Randomized Interchangeable Treatment Period					
System Organ Class	**Non-switch arm (N=193)**		**Switch arm (N=181)**		**Total (N=374)**	
Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
General disorders and administration site conditions	7 (3.6)	30	7 (3.9)	15	14 (3.7)	45
Injection-site erythema	3 (1.6)	10	3 (1.7)	4	6 (1.6)	14
Injection-site pain	4 (2.1)	6	1 (0.6)	1	5 (1.3)	7
Injection-site pruritus	2 (1.0)	6	2 (1.1)	4	4 (1.1)	10
Injection-site swelling	2 (1.0)	7	2 (1.1)	2	4 (1.1)	9
Injection-site hypersensitivity	0	0	2 (1.1)	2	2 (0.5)	2
Administration-site erythema	0	0	1 (0.6)	1	1 (0.3)	1
Administration-site swelling	0	0	1 (0.6)	1	1 (0.3)	1
Injection-site bruising	1 (0.5)	1	0	0	1 (0.3)	1

E: Number of events; N: Total number of patients; n: Number of patients per group.

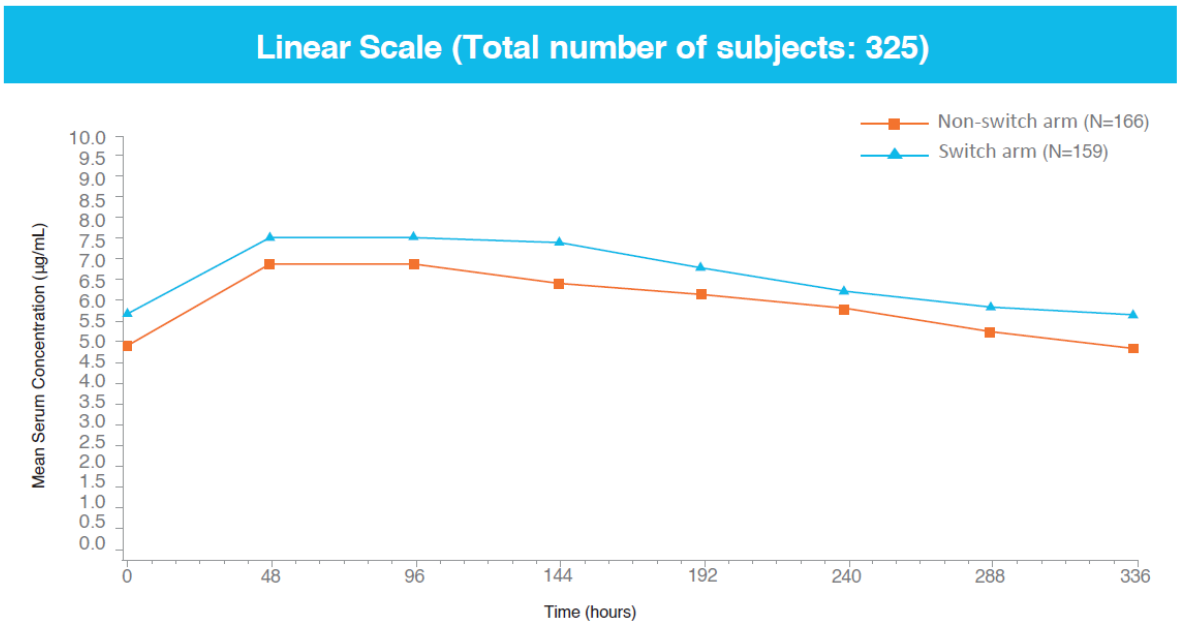
Table-S7: Summary of ADA and Nab response by visit.

Visit Response	Non-switch Arm (N=193) n (%)	Switch Arm (N=181) n (%)	Total (N=374) n (%)
Baseline (Week1/Visit 1)			
ADA Negative	168 (87.0)	165 (91.2)	333 (89.0)
ADA Positive	25 (13.0)	16 (8.8)	41 (11.0)
Nab positive	*4 (2.1)*	*5 (2.8)*	*9 (2.4)*
Nab negative	*189 (97.9)*	*176 (97.2)*	*365 (97.6)*
Week 12/Visit 7			
ADA Negative	5 (2.6)	2 (1.1)	7 (1.9)
ADA Positive	188 (97.4)	179 (98.9)	367 (98.1)
Nab positive	*159 (82.4)*	*139 (76.8)*	*298 (79.7)*
Nab negative	*34 (17.6)*	*42 (23.2)*	*76 (20.3)*
Week 16/Visit 9			
ADA Negative	4 (2.1)	3 (1.7)	7 (1.9)
ADA Positive	186 (97.9)	171 (98.3)	357 (98.1)
Nab positive	*166 (87.4)*	*142 (81.6)*	*308 (84.6)*
Nab negative	*24 (12.6)*	*32 (18.4)*	*56 (15.4)*
Week 20/Visit 11			
ADA Negative	5 (2.7)	2 (1.2)	7 (2.0)
ADA Positive	177 (97.3)	169 (98.8)	346 (98.0)
Nab positive	*162 (89.0)*	*149 (87.1)*	*311 (88.1)*
Nab negative	*20 (11.0)*	*22 (12.9)*	*42 (11.9)*
Week 28/Visit 15			
ADA Negative	5 (2.8)	4 (2.4)	9 (2.6)
ADA Positive	174 (97.2)	164 (97.6)	338 (97.4)
Nab positive	*158 (88.3)*	*144 (85.7)*	*302 (87.0)*
Nab negative	*21 (11.7)*	*24 (4.3)*	*45 (13.0)*

N: Total number of patients; n: Number of patients per group.

Figure-S1: Mean adalimumab serum concentration vs. time plot, pre-dose Week 26 to Week 28 in (a) linear and (b) semi-log scale.

(a)



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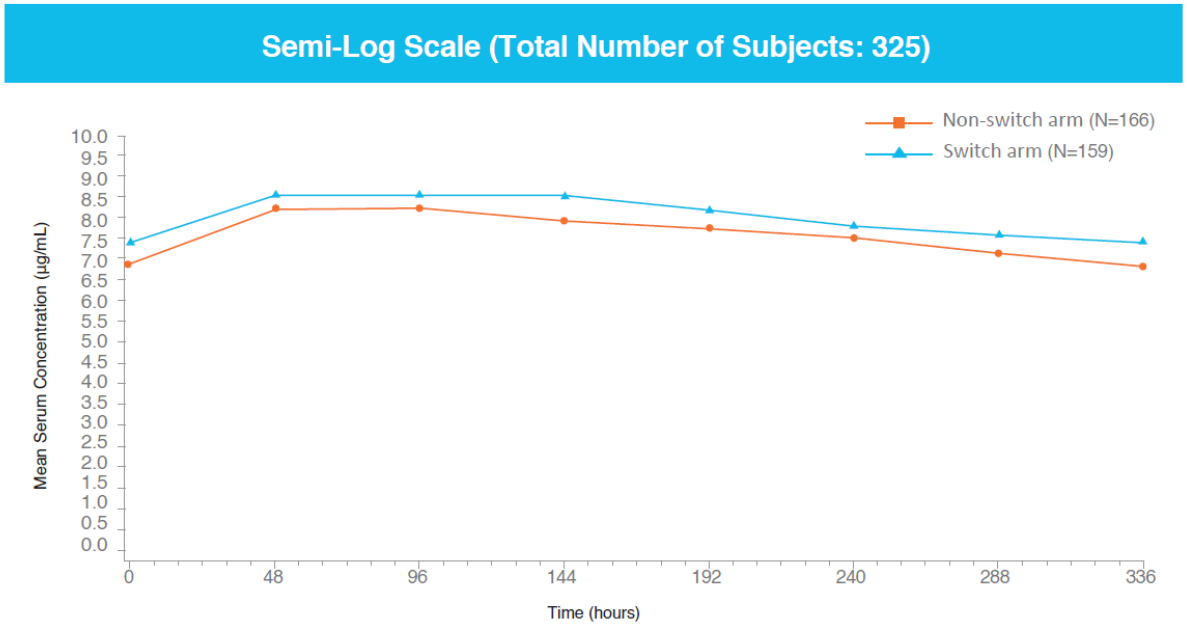

Figure-S2: Box Plot of ADA Titers by Visit – Safety Population