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COMPOUND NUMBER: PF-05212374

PROTOCOL NO.: 3206K1-2203 (B2051001)

PROTOCOL TITLE: A Randomized, Parallel, Double-Blind, Placebo-Controlled Dose Regimen Finding Study to Evaluate the Safety and Efficacy of TRU-015 in Subjects With Active Seropositive Rheumatoid Arthritis on a Stable Background of Methotrexate

Study Centers: This study was a multicenter trial: 51 centers in 9 countries took part in the study and randomized subjects; 22 in the United States, 7 in Mexico, 5 in Romania, 4 each in Canada and Hungary, 3 each in Germany and Serbia, 2 in Belgium, and 1 in France.

Study Initiation and Final Completion Dates: 20 March 2008 to 28 June 2010. The study was terminated prematurely; the last subject received study medication on 28 June 2010.

Phase of Development: Phase 2

Study Objectives: Primary Objective - The primary objective was to evaluate the clinical efficacy of 2 dosing regimens of TRU-015 (PF-05212374) in active seropositive rheumatoid arthritis (RA) subjects compared with placebo at 24 weeks.

Secondary Objective - The secondary objectives included evaluation of safety; patient reported outcomes, pharmacokinetic (PK), pharmacodynamic (PD), magnetic resonance imaging, and additional efficacy data up to 52 weeks.

METHODS:

This was a Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group, outpatient study to evaluate the safety and efficacy of TRU-015 in seropositive subjects with active RA on a stable background of methotrexate (MTX). Subjects were randomized to 1 of 6 arms at Baseline, stratified by prior anti-tumor necrosis factor (TNF) use and geographic region. Subjects who received TRU-015 placebo at Baseline and Week 12 received TRU-015 at Week 24. The study consisted of 2 parts: Part A was from Baseline to Week 24 (Table 1) and Part B was from Week 24 to Week 52 (Table 2).

Table 1. Study Design Part A

	Baseline			Week 12		
	IV TA (Infusion)	**IV TA**	**Oral TA**	**IV TA (Infusion)**	**IV TA**	**Oral TA**
1-A	800 mg TRU-015	100 mg MP	20 mg Prednisone	Placebo	100 mg MP	20 mg Prednisone
1-B	800 mg TRU-015	100 mg MP	20 mg Prednisone	Placebo	Placebo	Placebo
2-A	800 mg TRU-015	100 mg MP	20 mg Prednisone	800 mg TRU-015	100 mg MP	20 mg Prednisone
2-B	800 mg TRU-015	100 mg MP	20 mg Prednisone	800 mg TRU-015	100 mg MP	Placebo
3-A	Placebo	100 mg MP	20 mg Prednisone	Placebo	100 mg MP	20 mg Prednisone
3-B	Placebo	100 mg MP	20 mg Prednisone	Placebo	Placebo	Placebo

IV TA (Infusion) = 800 mg TRU-015 or placebo.
IV TA = 100 mg MP or placebo.
Oral TA = 20 mg prednisone or placebo x 2 days prior and on the morning of the infusion of IV TA (TRU-015 or placebo).
IV = intravenous; MP = methylprednisolone; TA = test article.

Table 2. Study Design Part B

	Week 24			Week 36		
	IV TA (Infusion)	**IV TA**	**Oral TA**	**IV TA (Infusion)**	**IV TA**	**Oral TA**
1-A	800 mg TRU-015	100 mg MP	20 mg Prednisone	Placebo	Placebo	Placebo
1-B	800 mg TRU-015	100 mg MP	20 mg Prednisone	Placebo	Placebo	Placebo
2-A	Placebo	Placebo	Placebo	800 mg TRU-015	100 mg MP	20 mg Prednisone
2-B	Placebo	Placebo	Placebo	800 mg TRU-015	100 mg MP	20 mg Prednisone
3-A	800 mg TRU-015	100 mg MP	20 mg Prednisone	800 mg TRU-015	100 mg MP	20 mg Prednisone
3-B	800 mg TRU-015	100 mg MP	20 mg Prednisone	Placebo	Placebo	Placebo

IV TA (Infusion) = 800 mg TRU-015 or placebo.
IV TA = 100 mg MP or placebo.
Oral TA = 20 mg prednisone or placebo x 2 days prior and on the morning of the infusion of IV TA (TRU-015 or placebo).
IV = intravenous; MP = methylprednisolone; TA = test article.

Subjects who withdrew early for any reason as well as those who completed the Week 52 visit entered the Follow-up period. These subjects remained blinded and in Follow-up until Part A data had been unblinded. During Follow-up, subjects returned for visits once every 8 weeks for safety monitoring and B cell counts. This blinded period of Follow-up may have lasted 24 weeks or longer. When Part A was unblinded, subjects remained in Follow-up until either of the following conditions was met: B cells returned to normal ranges or B cells returned to within 70% of baseline values.

The primary analysis was based on 3 combined treatment arms in Part A defined as:

- TRU-015 single dose (TRU-SD) arm, which was composed of subjects in Arms 1A and 1B

- TRU-015 induction dose (TRU-ID) arm, which was composed of subjects in Arms 2A and 2B

- Placebo arm, which was composed of subjects in Arms 3A and 3B

Since subjects in the Placebo arm received TRU-015 during Part B, the analysis of data for Part B was consequently presented in 4 groups: TRU-SD (Arms 1A/1B), TRU-ID (Arms 2A/2B), Placebo/TRU-SD (Arm 3B), and Placebo/TRU-ID (Arm 3A).

The clinical development of TRU-015 was discontinued in June 2010 after review of the efficacy and safety data from this study, and the study was terminated prematurely. The subjects who were in the active treatment phase at the time the project was terminated were requested to terminate treatment and to proceed to the Follow-up phase until their B-cells either returned to normal limits or to within 70% of their baseline value. The subjects who were already in the Follow-up phase were asked to continue as planned.

The schedule of procedures is presented in Table 3 for Part A and Table 4 for Part B.

Table 3. Study Flowchart Part A

Study Period	**Screening**	**Part A**									
Study Visit	**Screening**	**Baseline**	**Week 0 Infusion Visit**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 12 Infusion Visit**	**Week 16**	**Week 20**	**Week 24**
Study Week[a]	**-4**	**0 Day 1**	**0 Day 4**	**2**	**4**	**8**	**12 Day 1**	**12 Day 4**	**16**	**20**	**24 Day 1**
Visit Number[b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Informed consent	X										
Review eligibility criteria	X	X									
Medical history	X										
Alcohol/tobacco history	X										
Physical examination	X	X		X	X	X	X		X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X
Joint assessment (28-joint count)	X	X		X	X	X	X		X	X	X
Wrist and MCP MRI[d]		X					X				X
Chest radiograph (PA and lateral)[e]	X										
ECG (12-lead)	X										
Prior medications/treatments	X	X									
Concomitant medications/treatments			X	X	X	X	X	X	X	X	X
Randomization		X									
Urine pregnancy[f]	X	X	X					X			
Clinical lab evaluations[g]	X	X		X	X	X	X		X	X	X
Review lab evaluations[h]							X				X
B cell subset and cytokine panel[i]		X					X				X
PD lab evaluations[j]	X	X					X				X
HBsAg, HBcAb & HepCAb (with RIBA confirmation)	X										
HIV screening test (Germany only)	X										
PPD skin test (Germany only)	X										
Pneumococcal and tetanus antibodies		X									X

Table 3. Study Flowchart Part A

Study Period	Screening	Part A									
Study Visit	Screening	Baseline	Week 0 Infusion Visit	Week 2	Week 4	Week 8	Week 12	Week 12 Infusion Visit	Week 16	Week 20	Week 24
Study Week[a]	-4	0 Day 1	0 Day 4	2	4	8	12 Day 1	12 Day 4	16	20	24 Day 1
Visit Number[b]	1	2	3	4	5	6	7	8	9	10	11
PK blood sample collection[k]			X	X	X	X		X	X	X	
Anti-TRU-015 antibody		X					X		X		X
PG blood sample collection[l]		X					X				X
Pain VAS		X		X	X	X	X		X	X	X
Physician and patient global assessment		X		X	X	X	X		X	X	X
Morning stiffness duration		X		X	X	X	X		X	X	X
General Health VAS		X		X	X	X	X		X	X	X
HAQ-DI		X		X	X	X	X		X	X	X
Health outcome assessment[m]		X					X				X
Dispense blinded oral test article		X					X				X
Test article infusion[n]			X					X			
AE recording	X	X	X	X	X	X	X	X	X	X	X
Conclusion of phase											X

AE = adverse event; BAFF = B cell activating factor; CCP = cyclic citrullinated protein; CD-19 = cluster of differentiation 19; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EQ-5D = European Quality of Life (EuroQol) 5 Dimension Scale; ECG = electrocardiogram; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI = Health Assessment Questionnaire - Disability Index; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IV = intravenous; MCP = metacarpophalangeal; MRI = magnetic resonance imaging; PA = posterior anterior; PG = pharmacogenomics; PD = pharmacodynamics; PK = pharmacokinetics; PPD = purified protein derivative; RF = rheumatoid factor; RIBA = radio-immuno blot assay; SAA = serum amyloid A; SF-36 = Short Form 36; VAS = visual analog scale; WPAI-RA = Work Productivity and Activity Impairment Questionnaire – Rheumatoid Arthritis; WR = Wyeth Research.

a. Baseline visit to the Week 24 visit occurred within a window of ±3 days, except for infusion visits. Infusion visits were performed 3 to 5 days after the Baseline and Week 12 visits and infusion visits were separated from the Baseline and Week 12 visits by a minimum of 3 days.

b. For internal use only.

c. Height at Screening; body weight at Screening, Week 24, Week 52, or Early Withdrawal Visit. Vital signs: blood pressure and pulse rate, after sitting for 5 minutes, and oral or tympanic temperature (°F or °C). At the infusion visits, vital signs collected every 30 minutes prior to the infusion, during

Table 3. Study Flowchart Part A

Study Period	Screening	Part A									
Study Visit	Screening	Baseline	Week 0 Infusion Visit	Week 2	Week 4	Week 8	Week 12	Week 12 Infusion Visit	Week 16	Week 20	Week 24
Study Week[a]	-4	0 Day 1	0 Day 4	2	4	8	12 Day 1	12 Day 4	16	20	24 Day 1
Visit Number[b]	1	2	3	4	5	6	7	8	9	10	11

the infusion and for 2 hours post infusion.

d. MRIs were completed within a window of 7 days prior to or including Study Day 1 Baseline, Week 12 Day 1, or Week 24 Day 1 visits. MRIs performed at select sites only.

e. Chest x-ray performed during Screening period, unless a report of a radiograph was performed within the 24 weeks prior to Screening.

f. For women of childbearing potential only. Analysis performed by site with test kits provided by the central laboratory. If a urine pregnancy test was positive, subject was discontinued from study.

g. CD19 + B cells and fasting lab evaluations included hematology, chemistry, urinalysis, ESR, CRP, serum IgA, IgG, IgM (subjects did not have to fast at screening and CD19 + B cells were not collected at Screening). Laboratory tests were repeated only once during Screening period.

h. A safety assessment was performed before each study medication administration.

i. For subjects participating in the cytokines and B cell subsets substudy, Baseline, Week 12, and Week 24 visits occurred between Monday and Thursday in order to maintain sample stability. Cytokines and B cell subsets were drawn at select sites only.

j. If a documented history of anti-CCP and/or RF criteria was not available at Screening, anti-CCP and total RF were collected at Screening. PD lab evaluations collected at Baseline, Week 12, and Week 24 included: BAFF, total RF, RF (IgA, IgG, IgM), SAA, CRP and Anti-CCP.

k. Serum PK samples were collected on day of infusion pre-infusion and 30 minutes post infusion. Subjects did not have to fast on infusion days.

l. Subjects signed and dated a separate informed consent form for pharmacogenomic testing before any pharmacogenomic blood samples were drawn.

m. Health Outcome Assessments included the EQ-5D, SF-36, FACIT-F, WPAI-RA, and Tiredness Scale.

n. All subjects received oral and IV premedication.

Table 4. Study Flowchart Part B

Study Period	**Part B**										
Study Visit	**Week 24 Infusion Visit**	**Week 28**	**Week 32**	**Week 36**	**Week 36 Infusion Visit**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Early Withdrawal**	**Follow-Up[a]**
Study Week[b]	**24 Day 4**	**28**	**32**	**36**	**36 Day 4**	**40**	**44**	**48**	**52**		**Every 8 Weeks[a]**
Visit Numbers[c]	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**98**	**21**
Alcohol/tobacco usage									X		
Physical examination		X	X	X		X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	
Joint assessment (28-joint count)		X	X	X		X	X	X	X	X	
Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy[e]	X				X				X	X	X
Clinical lab evaluations[f]		X	X	X		X	X	X	X	X	X
Review lab evaluations[g]				X							
B cell subset and cytokine panel[h]				X					X		
PD lab evaluations[i]				X					X	X	
Pneumococcal and tetanus antibodies									X		
PK blood sample collection[j]	X	X	X		X	X	X				
Anti-TRU-015 antibody		X		X		X		X	X		
PG blood sample collection[k]				X					X		
Pain VAS		X	X	X		X	X	X	X	X	
Physician and patient global assessment		X	X	X		X	X	X	X	X	
Morning stiffness duration		X	X	X		X	X	X	X	X	
General health VAS		X	X	X		X	X	X	X	X	
HAQ-DI		X	X	X		X	X	X	X	X	
Health outcome assessment[l]				X					X	X	

Table 4. Study Flowchart Part B

Study Period	**Part B**										
Study Visit	**Week 24 Infusion Visit**	**Week 28**	**Week 32**	**Week 36**	**Week 36 Infusion Visit**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Early Withdrawal**	**Follow-Up[a]**
Study Week[b]	**24 Day 4**	**28**	**32**	**36**	**36 Day 4**	**40**	**44**	**48**	**52**		**Every 8 Weeks[a]**
Visit Numbers[c]	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**98**	**21**
Dispense blinded oral test article				X							
Test article infusion[m]	X				X						
AE recording	X	X	X	X	X	X	X	X	X	X	X
Conclusion of phase									X	X	X[n]
Conclusion of subject participation											X[n]

AE = adverse event; BAFF = B cell activating factor; CCP = cyclic citrullinated protein; CD-19 = cluster of differentiation 19; CRP = C-reactive protein; EQ-5D = European Quality of Life (EuroQol) 5 Dimension Scale; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; PD = pharmacodynamic; PG = pharmacogenomics; PK = pharmacokinetics; RF = rheumatoid factor; SAA = serum amyloid A; SF-36 = Short Form 36; VAS = visual analog scale; WPAI-RA = Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis; WR = Wyeth Research.

a. Subjects who withdrew early for any reason as well as those who completed the Week 52 visit entered the Follow-up period. These subjects remained blinded and in follow up until Part A data had been unblended. During follow up, subjects returned for visits once every 8 weeks for safety monitoring and B cell counts. When Part A was unblinded, subjects remained in follow up until either of the following conditions were met: B cells returned to normal ranges or B cells returned to within 70% of their baseline values.

b. Week 24 to Week 52 visits occurred within a window of ±3 days, except for infusion visits. Infusion visits were performed 3 to 5 days after the Week 24 and Week 36 visits and infusion visits were separated from the Week 24 and Week 36 visits by a minimum of 3 days.

c. For internal use only.

d. Height at Screening; body weight at Screening, Week 24, Week 52, or Early Withdrawal Visit. Vital signs: blood pressure and pulse rate, after sitting for 5 minutes, and oral or tympanic temperature (°F or °C). At the infusion visits, vital signs collected every 30 minutes prior to the infusion, during the infusion and for 2 hours post infusion.

e. For women of childbearing potential only. Analysis performed by site with test kits provided by the central laboratory. If a urine pregnancy test was positive, subject was discontinued from study.

f. CD19 + B cells and fasting lab evaluations included hematology, chemistry, urinalysis, ESR, CRP, serum IgA, IgG, IgM.

g. A safety assessment was performed before each test article administration.

Table 4. Study Flowchart Part B

Study Period	Part B										
Study Visit	**Week 24 Infusion Visit**	**Week 28**	**Week 32**	**Week 36**	**Week 36 Infusion Visit**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Early Withdrawal**	**Follow-Up[a]**
Study Week[b]	**24 Day 4**	**28**	**32**	**36**	**36 Day 4**	**40**	**44**	**48**	**52**		**Every 8 Weeks[a]**
Visit Numbers[c]	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**98**	**21**

h. For subjects participating in the cytokines and B cell subsets substudy, Weeks 36 and 52 visits occurred between Monday and Thursday in order to maintain sample stability. Cytokines and B cell subsets were drawn at select sites only.
i. PD laboratory evaluations collected at Weeks 36 and 52 included: BAFF, total RF, RF (IgA, IgG, IgM), SAA, CRP and Anti-CCP.
j. Serum PK samples were collected on day of infusion pre-infusion and 30 minutes post infusion. Subjects did not have to fast on infusion days.
k. Subjects signed and dated a separate informed consent form for testing.
l. Health Outcome Assessments included the EQ-5D, SF-36, FACIT-F, WPAI-RA, and Tiredness Scale.
m. All subjects received oral and IV premedication.
n. To be completed at the last Follow-up visit.

Number of Subjects (Planned and Analyzed): For the primary efficacy endpoint, a sample size of 72 subjects per combined arm was planned to provide 80% power to detect a 20% difference in American College of Rheumatology response with 50% improvement (ACR50) between each combined TRU-015 arm and combined placebo at Week 24 using a two-sided test, with a significance level of 0.05, assuming a lowest response rate of 30% in the TRU-015 arms and 10% in combined placebo arm. A total of 222 subjects entered Part A of the study, 175 of whom (78.8%) completed Part A and 174 of whom entered Part B. A total of 122 subjects (70.1%) entering Part B completed this portion of the study.

Diagnosis and Main Criteria for Inclusion: The study included male and female subjects who were ≥18 years of age with a clinical diagnosis of active seropositive rheumatoid arthritis (RA) on a stable dose of methotrexate (7.5 to 25 mg weekly) for at least 12 weeks with or without a history of anti-TNF use.

Exclusion Criteria**:** Subjects with any prior use of rituximab or other B-cell depleting agents or with any significant health problem other than RA, or clinically significant laboratory abnormalities were excluded from study.

Study Treatment: Study medications included 800 mg intravenous (IV) TRU-015 and placebo, 20 mg oral prednisone and placebo, and 100 mg IV methylprednisolone (MP) and placebo. To reduce the incidence of possible infusion reactions, subjects were pre-treated within 1 hour prior to the infusion of TRU-015 or placebo with 1000 mg of oral acetaminophen/paracetamol, and 25 mg of oral diphenhydramine (or equivalent antihistamine).

Efficacy Endpoints: The primary efficacy endpoint was the ACR50 at Week 24 for the modified intent-to-treat (mITT) population. ACR50 response was defined as ≥50% improvement in the total number of tender joints and ≥50% improvement in the total number of swollen joints plus ≥50% improvement in 3 of the following 5 assessments: Pain visual analog scale (VAS), Physician Global Assessment, Patient Global Assessment, Health Assessment Questionnaire Disability Index (HAQ-DI), or C-reactive protein (CRP).

Secondary efficacy evaluations included the American College of Rheumatology response with 20% improvement (ACR20), ACR50 (except Week 24), and American College of Rheumatology response with 70% improvement (ACR70) at all-time points, a standardized joint assessment, duration of morning stiffness, pain VAS, Physician and Patient Global Assessments of disease activity, General Health VAS, Health Assessment Questionnaire-Disability Index (HAQ-DI), Disease Activity Score (DAS)28, Short Form-36 (SF-36), European Quality of Life (EuroQol) 5 Dimension Scale (EQ-5D), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Productivity and Disease Burden Questionnaire, and European League Against Rheumatism (EULAR) response as derived from DAS28.

Safety Evaluations: Safety was evaluated based on adverse events (AEs), clinical laboratory measurements, physical examinations, and vital signs.

Statistical Methods: The primary population for efficacy analysis in Part A was the mITT population, which was defined as all randomized subjects who received any portion of study medication in Part A. Major efficacy parameters were also analyzed for the valid-for-efficacy (VFE) population, which was a subset of the mITT population that excluded subjects who had major protocol deviations. All safety analyses were based on mITT population.

The primary efficacy endpoint was the ACR50 response at Week 24. The comparison of TRU-015 versus placebo was performed on the 3 combined arms using a 2-sided Cochran-Mantel Haenszel test, stratified by prior anti-TNF use and geographic region. The primary analysis was performed when all subjects completed 24 weeks (Part A) of the study.

The statistical methods used for the primary efficacy endpoint (ACR50 at Week 24) were also used for the ACR50 at Weeks 2, 4, 8, 12, 16, and 20 and for the ACR20, ACR70, and EULAR responses at Weeks 2, 4, 8, 12, 16, 20, and 24. For continuous variables and ordinal variables, the change from Baseline at Weeks 2, 4, 8, 12, 16, 20, and 24 was analyzed using analysis of covariance, with treatment, prior anti-TNF use, and geographic region as factors and baseline as a covariate.

For all efficacy analyses, missing data were imputed using the method of last-observation-carried-forward (LOCF) as the primary analysis. Observed case analysis was performed for all variables. For ACR responses, nonresponder data (defined as a subject with data missing at any given time point) was used for sensitivity analyses. For continuous endpoints, a baseline-carried-forward and mixed model repeated measures analysis were used.

Subject Disposition and Demography: Subject disposition and subjects analyzed are summarized for Part A in Table 5. Subject disposition is summarized for Part B in Table 6; efficacy analyses were not performed for Part B.

RESULTS

Table 5. Subject Disposition and Subjects Analyzed: Part A

	Number (%) of Subjects			
	Placebo	**TRU-SD**	**TRU-ID**	**Total**
Randomized	74	75	73	222
Completed Part A	63 (85.1)	57 (76.0)	55 (75.3)	175 (78.8)
Discontinued Part A[a]	11 (14.9)	18 (24.0)	18 (24.7)	47 (21.2)
Adverse event	4 (5.4)	4 (5.3)	8 (11.0)	16 (7.2)
Death	1 (1.4)	0	0	1 (0.5)
Failed to return	1 (1.4)	0	0	1 (0.5)
Investigator request	1 (1.4)	1 (1.3)	1 (1.4)	3 (1.4)
Lost to follow-up	0	1 (1.3)	1 (1.4)	2 (0.9)
Other	1 (1.4)	8 (10.7)	5 (6.8)	14 (6.3)
Subject request	0	3 (4.0)	3 (4.1)	6 (2.7)
Unsatisfactory response -efficacy	3 (4.1)	1 (1.3)	0	4 (1.8)
mITT population	74	75	73	222
VFE population	70	71	69	210
Safety population	74	75	73	222

Treatment Arms:
Placebo = placebo at Baseline and placebo at Week 12 (Arms 3A/3B).
TRU-SD = TRU-015 at Baseline and placebo at Week 12 (Arms 1A/1B) – single dose.
TRU-ID = TRU-015 at Baseline and at Week 12 (Arms 2A/2B) – induction dose.
mITT = modified intent-to treat; VFE = valid for efficacy.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 6. Subject Disposition: Part B

	Number (%) of Subjects				
	TRU-SD	**TRU-ID**	**Placebo/ TRU-SD**	**Placebo/ TRU-ID**	**Total**
Entered Part B	56	55	31	32	174
Completed Part B	42 (75.0)	33 (60.0)	25 (80.6)	22 (68.8)	122 (70.1)
Discontinued Part B	14 (25.0)	22 (40.0)	6 (19.4)	10 (31.3)	52 (29.9)
Adverse event	1 (1.8)	1 (1.8)	1 (3.2)	0	3 (1.7)
Discontinuation of study by Sponsor	11 (19.6)	14 (25.5)	3 (9.7)	7 (21.9)	35 (20.1)
Investigator request	1 (1.8)	1 (1.8)	0	0	2 (1.1)
Other	0	5 (9.1)	0	1 (3.1)	6 (3.4)
Protocol violation	0	0	0	1 (3.1)	1 (0.6)
Subject request	0	0	2 (6.5)	1 (3.1)	3 (1.7)
Unsatisfactory response - efficacy	1 (1.8)	1 (1.8)	0	0	2 (1.1)

Treatment Arms:
TRU-SD = TRU-015 at Baseline, placebo at Week 12, TRU-015 at Week 24, placebo at Week 36 (Arms 1A/1B) – single dose.
TRU-ID = TRU-015 at Baseline and Week 12, placebo at Week 24, and TRU-015 at Week 36 (Arms 2A/2B – induction dose.
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm 3B) – single dose.
Placebo/TRU-ID = placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.

The mean age of the 222 subjects treated in Part A was 52.1 years. The majority of subjects were female (83.3%), white (61.3%), and non-Hispanic/non-Latino (64.9%). The mean baseline height was 162.9 cm and mean baseline weight was 74.2 kg. All subjects had a primary diagnosis of RA, with a mean duration of 8.7 years. The most frequently used prior medications were nonsteroidal antiinflammatory drugs (85.1% of subjects). Prior anti-TNF therapy was reported by 21.6% of subjects and prior disease-modifying antirheumatic drug (DMARD) use was reported by 55.9% of subjects with the majority of these subjects having received only 1 DMARD; a total of 8 subjects reported ≥4 DMARDs as prior medications. No statistically significant differences were observed across treatment arms. A detailed summary of demographic and baseline characteristics for Part A is presented in Table 7. The demographic and baseline characteristics for the subset of 174 subjects who entered Part B were similar to those of the subjects who entered Part A.

Table 7. Summary of Demographics and Baseline Characteristics: Part A (Safety Population)

Characteristic	Number (%) of Subjects				
	p-Value	Placebo (N=74)	TRU-SD (N=75)	TRU-ID (N=73)	Total (N=222)
Age (years)					
Mean (SD)	4.33[a]	50.6 (11.1)	53.0 (11.3)	52.6 (13.0)	52.1 (11.8)
Minimum, maximum		18.0, 75.0	25.0, 74.0	26.0, 84.0	18.0, 84.0
Sex [n (%)]	0.656[b]				
Female		64 (86.5)	62 (82.7)	59 (80.8)	185 (83.3)
Male		10 (13.5)	13 (17.3)	14 (19.2)	37 (16.7)
Race [n (%)]	0.783[b]				
Asian		0	1 (1.3)	0	1 (0.5)
Black or African American		1 (1.4)	3 (4.0)	2 (2.7)	6 (2.7)
Other		24 (32.4)	27 (36.0)	28 (38.4)	79 (35.6)
White		49 (66.2)	44 (58.7)	43 (58.9)	136 (61.3)
Ethnicity [n (%)]	0.837[b]				
Hispanic or Latino		24 (32.4)	27 (36.0)	27 (37.0)	78 (35.1)
Non-Hispanic or non-Latino		50 (67.6)	48 (64.0)	46 (63.0)	144 (64.9)
Baseline Height (cm)					
Mean (SD)	0.801[a]	163.3 (8.2)	163.0 (8.4)	162.4 (9.4)	162.9 (8.6)
Minimum, maximum		147.0, 182.9	145.0, 188.0	148.0, 185.4	145.0, 188.0
Baseline weight (kg)					
Mean (SD)	0.750[a]	75.5 (18.7)	73.3 (16.8)	73.8 (18.8)	74.2 (18.0)
Minimum, maximum		43.0, 152.0	44.0, 115.0	46.0, 135.9	43.0, 152.0
Duration of disease (yr)					
n		74	74	73	221
Mean (SD)	0.294[a]	7.6 (7.1)	8.9 (8.5)	9.7 (9.5)	8.7 (8.4)
Minimum, maximum		0.42, 33.1	0.41, 42.1	0.22, 45.1	0.22, 45.1
Prior medication use = yes [n (%)]					
Corticosteroids	0.536[b]	42 (56.8)	41 (54.7)	35 (48.0)	118 (53.2)
NSAID	0.841[b]	63 (85.1)	65 (86.7)	61 (83.6)	189 (85.1)
Anti-TNF	0.958[b]	17 (23.0)	16 (21.3)	15 (20.6)	48 (21.6)
DMARD	0.452[b]	38 (51.4)	46 (61.3)	40 (54.8)	124 (55.9)
Number of prior DMARDs	0.169[b]				
0		36 (48.7)	29 (38.7)	33 (45.2)	98 (44.1)
1		18 (24.3)	26 (34.7)	29 (40.0)	73 (32.9)
2		12 (16.2)	11 (14.7)	8 (11.0)	31 (14.0)
3		4 (5.4)	7 (9.3)	1 (1.4)	12 (5.4)
4		0	1 (1.3)	2 (2.7)	3 (1.4)
5		1 (1.4)	1 (1.3)	0	2 (0.9)
6		2 (2.7)	0	0	2 (0.9)
7		1 (1.4)	0	0	1 (0.5)

Treatment Arms:
Placebo = placebo at Baseline and placebo at Week 12 (Arms 3A/3B).
TRU-SD = TRU-015 at Baseline and placebo at Week 12 (Arms 1A/1B) - single dose.
TRU-ID = TRU-015 at Baseline and at Week 12 (Arms 2A/2B) – induction dose.
DMARD = disease-modifying antirheumatic drug; N = total number of subjects; n = number of subjects meeting prespecified criteria; NSAID = nonsteroidal antiinflammatory drug; SD = standard deviation; TNF = tumor necrosis factor.
a. One-way analysis of variance with treatment as factor.
b. Fisher's exact test, 2-tailed.

Efficacy Results:

ACR20, ACR50, and ACR70 Efficacy Endpoints:

Primary Endpoint: In the mITT population with LOCF imputation, the percentages of ACR50 responders at Week 24 were numerically higher for subjects in the TRU-SD (29.3%) and TRU-ID (27.4%) treatment arms compared with placebo (16.2%; Table 8). However, these differences in ACR50 response were not statistically significant ($p>0.05$).

Secondary Endpoints: The analysis of ACR20 response showed that the percentage of responders was higher in the TRU-SD and TRU-ID treatment arms compared with placebo at all-time points. This difference was statistically significant at all-time points from Week 12 to Week 24 for the TRU-ID arm and at Week 12, Week 16, and Week 24 for the TRU-SD arm compared to placebo (Table 8).

The analysis of ACR50 at time points prior to Week 24 showed that the percentage of responders was statistically significantly higher for subjects in both the TRU-SD and TRU-ID treatment arms compared with placebo at Week 2 and Week 16 (Table 8).

No statistically significant differences were observed among treatment arms for ACR70 at any time point (Table 8).

Table 8. Analysis of ACR Response by 3 Combined Arms: Part A (mITT Population, LOCF)

					p-Value		Confidence Interval (20% Percentile, 90% Percentile)[a]	
ACR Response	**Time Point**	**Placebo n/N (%)**	**TRU-SD n/N (%)**	**TRU-ID n/N (%)**	**TRU-SD vs Placebo**	**TRU-ID vs Placebo**	**TRU-SD - Placebo**	**TRU-ID - Placebo**
ACR20	Week 2	13/74 (17.6)	16/75 (21.3)	19/73 (26.0)	0.570	0.200	(-1.7, 11.8)	(3.2, 17.1)
	Week 4	23/74 (31.1)	26/75 (34.7)	25/73 (34.2)	0.616	0.671	(-2.5, 13.5)	(-3.0, 12.9)
	Week 8	23/74 (31.1)	33/75 (44.0)	31/73 (42.5)	0.108	0.174	(6.3, 22.7)	(4.3, 20.9)
	Week 12	23/74 (31.1)	39/75 (52.0)	36/73 (49.3)	0.010	0.029	(14.2, 30.5)	(11.1, 27.8)
	Week 16	31/74 (41.9)	48/75 (64.0)	45/73 (61.6)	0.006	0.021	(15.4, 31.8)	(12.4, 29.4)
	Week 20	35/74 (47.3)	47/75 (62.7)	47/73 (64.4)	0.062	0.049	(8.5, 25.0)	(9.3, 25.9)
	Week 24	32/74 (43.2)	46/75 (61.3)	49/73 (67.1)	0.030	0.005	(11.0, 27.7)	(16.5, 33.0)
ACR50	Week 2	0/74 (0.0)	6/75 (8.0)	5/73 (6.8)	0.014	0.025	(5.4, 11.8)	(4.3, 10.5)
	Week 4	5/74 (6.8)	6/75 (8.0)	5/73 (6.8)	0.794	0.966	(-2.4, 6.6)	(-3.3, 5.4)
	Week 8	9/74 (12.2)	8/75 (10.7)	6/73 (8.2)	0.770	0.456	(-5.8, 5.0)	(-7.9, 2.5)
	Week 12	11/74 (14.9)	12/75 (16.0)	10/73 (13.7)	0.880	0.814	(-4.0, 8.3)	(-6.1, 5.9)
	Week 16	12/74 (16.2)	23/75 (30.7)	23/73 (31.5)	0.042	0.035	(8.6, 22.8)	(9.2, 23.7)
	Week 20	12/74 (16.2)	21/75 (28.0)	21/73 (28.8)	0.086	0.082	(6.1, 19.9)	(6.4, 20.7)
	Week 24	12/74 (16.2)	22/75 (29.3)	20/73 (27.4)	0.061	0.120	(7.2, 21.2)	(5.0, 19.3)
ACR70	Week 2	0/74 (0.0)	1/75 (1.3)	1/73 (1.4)	0.325	0.338	(0.2, 3.0)	(0.2, 3.0)
	Week 4	1/74 (1.4)	1/75 (1.3)	0/73 (0.0)	0.983	0.296	(-1.6, 2.4)	(-2.6, 0.4)
	Week 8	1/74 (1.4)	2/75 (2.7)	1/73 (1.4)	0.575	1.000	(-0.6, 4.2)	(-1.7, 2.5)
	Week 12	1/74 (1.4)	2/75 (2.7)	2/73 (2.7)	0.573	0.563	(-0.6, 4.2)	(-0.6, 4.3)
	Week 16	5/74 (6.8)	6/75 (8.0)	5/73 (6.8)	0.768	0.977	(-2.3, 6.7)	(-3.6, 5.2)
	Week 20	2/74 (2.7)	5/75 (6.7)	5/73 (6.8)	0.249	0.268	(1.2, 8.4)	(1.0, 8.4)
	Week 24	2/74 (2.7)	7/75 (9.3)	7/73 (9.6)	0.089	0.079	(3.5, 11.2)	(3.7, 12.1)

Treatment Arms:
Placebo = placebo at Baseline and placebo at Week 12 (Arms 3A/3B).
TRU-SD = TRU-015 at Baseline and placebo at Week 12 (Arms 1A/1B) - single dose.
TRU-ID = TRU-015 at Baseline and at Week 12 (Arms 2A/2B) - induction dose.
ACR 20 = American College of Rheumatology response with 20% improvement; ACR 50 = American College of Rheumatology response with 50% improvement; ACR 70 = American College of Rheumatology response with 70% improvement; LOCF = last-observation-carried-forward; mITT = modified-intent-to-treat; N = number of subjects, n = number of subjects with prespecified criteria; vs = versus.
a. The confidence interval of 20% percentile and 90% percentile was used for internal decision making.

Secondary Efficacy Endpoints: The ACR is comprised of 7 individual components which were also analyzed separately as secondary efficacy endpoints; the results of these analyses at Week 24 are presented in Table 9. A statistically significant difference in change from Baseline CRP was observed for both the TRU-SD and TRU-ID treatment arms compared with placebo ($p<0.001$). Statistically significant differences were also observed for swollen joints and HAQ-DI in the TRU-ID arm compared with placebo, and for pain VAS in the TRU-SD arm compared with placebo.

Table 9. ANCOVA Model Analysis for Improvement From Baseline in Individual ACR Response Components (mITT Population, LOCF Data, Part A)

Week on Therapy	Treatment	N	Raw Mean	Raw Mean Change (%) From Baseline	Adjusted Mean Change (SE)	Difference of Adjusted Mean Change (95% CI) TRU-015 vs Placebo	p-Value TRU-015 vs Placebo
Tender Joints							
Baseline	Placebo	74	17.0	-	-	-	-
	TRU-SD	75	16.8	-	-	-	-
	TRU-ID	73	17.7	-	-	-	-
Week 24	Placebo	74	9.4	7.6 (42.4)	7.2 (0.9)	-	-
	TRU-SD	75	8.1	8.7 (50.5)	8.4 (0.9)	1.2 (-1.1, 3.5)	0.297
	TRU-ID	73	7.6	10.1 (57.9)	9.2 (0.9)	2.0 (-0.3, 4.3)	0.088
Swollen Joints							
Baseline	Placebo	74	12.2	-	-	-	-
	TRU-SD	75	12.3	-	-	-	-
	TRU-ID	73	13.9	-	-	-	-
Week 24	Placebo	74	6.2	6.0 (46.9)	5.7 (0.6)	-	-
	TRU-SD	75	4.7	7.6 (57.5)	7.2 (0.6)	1.5 (-0.1, 3.0)	0.059
	TRU-ID	73	5.0	8.9 (61.5)	7.3 (0.6)	1.6 (0.1, 3.2)	0.040
Pain VAS							
Baseline	Placebo	74	65.4	-	-	-	-
	TRU-SD	75	62.5	-	-	-	-
	TRU-ID	73	61.6	-	-	-	-
Week 24	Placebo	74	49.2	16.1 (22.0)	12.0 (2.9)	-	-
	TRU-SD	75	39.2	23.2 (33.9)	20.5 (2.9)	8.5 (1.0, 15.9)	0.027
	TRU-ID	73	43.9	17.7 (23.8)	15.2 (3.0)	3,2 (-4.3, 10.8)	0.403
Physician Global Assessment							
Baseline	Placebo	74	6.8	-	-	-	-
	TRU-SD	75	6.4	-	-	-	-
	TRU-ID	73	6.6	-	-	-	-
Week 24	Placebo	74	4.3	2.5 (36.8)	2.2 (0.3)	-	-
	TRU-SD	75	3.7	2.7 (40.5)	2.6 (0.3)	0.4 (-0.3, 1.1)	0.260
	TRU-ID	73	3.6	3.1 (43.9)	2.8 (0.3)	0.6 (-0.1, 1.3)	0.075
Patient Global Assessment							
Baseline	Placebo	74	7.3	-	-	-	-
	TRU-SD	75	6.9	-	-	-	-
	TRU-ID	73	7.0	-	-	-	-

Table 9. ANCOVA Model Analysis for Improvement From Baseline in Individual ACR Response Components (mITT Population, LOCF Data, Part A)

Week on Therapy	Treatment	N	Raw Mean	Raw Mean Change (%) From Baseline	Adjusted Mean Change (SE)	Difference of Adjusted Mean Change (95% CI) TRU-015 vs Placebo	p-Value TRU-015 vs Placebo
Week 24	Placebo	74	5.3	2.0 (24.0)	1.6 (0.3)	-	-
	TRU-SD	75	4.6	2.3 (31.8)	2.2 (0.3)	0.6 (-0.1, 1.4)	0.095
	TRU-ID	73	4.7	2.4 (28.1)	2.2 (0.3)	0.5 (-0.2, 1.3)	0.148
HAQ-DI							
Baseline	Placebo	74	1.8	-	-	-	-
	TRU-SD	75	1.7	-	-	-	-
	TRU-ID	73	1.6	-	-	-	-
Week 24	Placebo	74	1.4	0.4 (21.1)	0.3 (0.1)	-	-
	TRU-SD	75	1.2	0.5 (28.7)	0.4 (0.1)	0.1 (-0.0, 0.3)	0.154
	TRU-ID	73	1.0	0.6 (38.5)	0.5 (0.1)	0.2 (0.1, 0.4)	0.007
CRP							
Baseline	Placebo	74	21.2	-	-	-	-
	TRU-SD	75	12.8	-	-	-	-
	TRU-ID	73	21.9	-	-	-	-
Week 24	Placebo	74	18.1	3.2 (-39.2)	1.3 (1.7)	-	-
	TRU-SD	75	7.1	5.7 (5.9)	10.2 (1.7)	8.9 (4.5, 13.2)	<0.001
	TRU-ID	73	10.7	11.2 (16.8)	8.8 (1.7)	7.5 (3.2, 11.8)	<0.001

Treatment Arms:
Placebo = placebo at Baseline and placebo at Week 12 (Arms 3A/3B).
TRU-SD = TRU-015 at Baseline and placebo at Week 12 (Arms 1A/1B) – single dose.
TRU-ID = TRU-015 at Baseline and at Week 12 (Arms 2A/2B) – induction dose.
ACR = American College of Rheumatology; ANCOVA = analysis of covariance; CI = confidence interval; CRP = C reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; LOCF = last-observation-carried-forward; mITT = modified-intent-to-treat; N = number of subjects; SE = standard error; vs = versus.

The results for the secondary efficacy parameters at other time points showed no statistically significant differences between the treatment arms, at almost all time points, for tender joints and swollen joints. The exceptions were TRU-SD at Week 12 and TRU-ID at Week 24, where the values for swollen joints were statistically significantly different compared with Placebo (p=0.048 and p=0.040, respectively). There was a statistically significant difference in pain VAS for both TRU-015 treatment arms compared with Placebo from Week 8 to Week 20 and at Week 24 for TRU-SD compared with Placebo. The analysis of Physician and Patient Global Assessments showed improvement in scores, with statistically significant differences achieved at some time points for both TRU-SD and TRU-ID treatment arms compared with Placebo. A decrease in HAQ-DI scores was noted, especially in the TRU-ID treatment arm, where the difference from Baseline was statistically significant compared with Placebo at all time points from Week 8 to Week 24. A clear decrease in CRP values compared with Baseline was also seen and the decrease was statistically significant for both TRU-015 treatments arms compared with Placebo from Week 12 to Week 24. Similarly, statistically significant differences in change from Baseline DAS28 score were noted in both TRU-SD and TRU-ID treatment arms compared with Placebo from Week 12 to Week 24. A statistically significantly higher proportion of EULAR responders was observed in both TRU-015 arms compared with Placebo beginning at Week 12, with the exception of the TRU-ID arm at Week 16 (p=0.113). Statistically significant differences in ESR were observed for both TRU-015 arms compared with Placebo beginning at Week 12, with the exception of the TRU-ID arm at Week 24 (p=0.110).

Health outcomes data were not analyzed since the clinical development of TRU-015 has been discontinued.

Safety Results: Treatment-emergent non serious AEs occurring in ≥5% of subjects in any treatment group in Part A are presented in Table 10.

Table 10. Number (%) of Subjects Reporting Percentages ≥5% Treatment Emergent Adverse Events Excluding Serious Adverse Events (Safety Population): Part A

System Organ Class[a] Preferred Term	Treatment			
	Placebo N=74 N(F)=64	TRU-SD N=75 N(F)=62	TRU-ID N=73 N(F)=59	Total N=222 N(F)=185
Any adverse event	50 (67.6)	50 (66.7)	47 (64.4)	147 (66.2)
Blood and lymphatic system disorders	6 (8.1)	1 (1.3)	2 (2.7)	9 (4.1)
Anaemia	4 (5.4)	1 (1.3)	0	5 (2.3)
Gastrointestinal disorders	13 (17.6)	10 (13.3)	15 (20.5)	38 (17.1)
Diarrhoea	2 (2.7)	3 (4.0)	4 (5.5)	9 (4.1)
Nausea	4 (5.4)	0	4 (5.5)	8 (3.6)
Infections and infestations	19 (25.7)	22 (29.3)	21 (28.8)	62 (27.9)
Bronchitis	4 (5.4)	2 (2.7)	0	6 (2.7)
Pharyngitis	0	4 (5.3)	2 (2.7)	6 (2.7)
Urinary tract infection	5 (6.8)	6 (8.0)	5 (6.8)	16 (7.2)
Nervous system disorders	7 (9.5)	8 (10.7)	9 (12.3)	24 (10.8)
Headache	7 (9.5)	4 (5.3)	6 (8.2)	17 (7.7)
Respiratory, thoracic and mediastinal disorders	8 (10.8)	13 (17.3)	9 (12.3)	30 (13.5)
Cough	4 (5.4)	5 (6.7)	0	9 (4.1)
Skin and subcutaneous tissue disorders	10 (13.5)	17 (22.7)	18 (24.7)	45 (20.3)
Pruritus	2 (2.7)	7 (9.3)	5 (6.8)	14 (6.3)
Rash	0	4 (5.3)	10 (13.7)	14 (6.3)
Urticaria	1 (1.4)	1 (1.3)	5 (6.8)	7 (3.2)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm_3B) – single dose.
Placebo/TRU-ID = Placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
AEs = adverse events; F = female; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Infections were reported for 32% of subjects including 28.4% in the Placebo arm, 33.3% in the TRU-SD arm and 34.2% in the TRU-ID arm. Urinary tract infection was the most common infection and was reported in 10.4% of subjects overall.

Infusion reactions were observed in 18.9% of subjects and were more frequent in the TRU-SD (24%) and TRU-ID (27.4%) treatment arms compared with the Placebo arm (5.4%). A statistically significant difference was observed in particular for rash and urticarial.

Treatment-emergent, treatment-related non serious AEs in Part A are presented in Table 11.

Table 11. Number (%) of Subjects Reporting Treatment-Related Treatment Emergent Adverse Events (Excluding Infections and Infusion Reactions): Safety Population, Part A

System Organ Class[a] Preferred Term	Treatment			
	Placebo N=74	TRU-SD N=75	TRU-ID N=73	Total N=222
Any adverse event	13 (17.6)	11 (14.7)	8 (11.0)	32 (14.4)
Blood and lymphatic system disorders	2 (2.7)	0	2 (2.7)	4 (1.8)
Anaemia	1 (1.4)	0	0	1 (0.5)
Leukopenia	0	0	1 (1.4)	1 (0.5)
Lymphadenopathy	0	0	1 (1.4)	1 (0.5)
Thrombocytopenia	1 (1.4)	0	0	1 (0.5)
Cardiac disorders	0	2 (2.7)	0	2 (0.9)
Cardiac failure congestive	0	1 (1.3)	0	1 (0.5)
Tachycardia	0	1 (1.3)	0	1 (0.5)
Gastrointestinal disorders	2 (2.7)	2 (2.7)	2 (2.7)	6 (2.7)
Abdominal pain	0	0	1 (1.4)	1 (0.5)
Abdominal tenderness	0	0	1 (1.4)	1 (0.5)
Diarrhoea	1 (1.4)	0	1 (1.4)	2 (0.9)
Gastrooesophageal reflux disease	1 (1.4)	0	0	1 (0.5)
Irritable bowel syndrome	0	1 (1.3)	1 (1.4)	2 (0.9)
Nausea	1 (1.4)	0	0	1 (0.5)
Tongue ulceration	0	1 (1.3)	0	1 (0.5)
General disorders and administration site conditions	1 (1.4)	0	3 (4.1)	4 (1.8)
Infusion related reaction	0	0	1 (1.4)	1 (0.5)
Oedema peripheral	1 (1.4)	0	0	1 (0.5)
Pyrexia	0	0	2 (2.7)	2 (0.9)
Investigations	0	2 (2.7)	0	2 (0.9)
Alanine aminotransferase increased	0	2 (2.7)	0	2 (0.9)
Aspartate aminotransferase increased	0	2 (2.7)	0	2 (0.9)
Blood alkaline phosphatase increased	0	1 (1.3)	0	1 (0.5)
Metabolism and nutrition disorders	1 (1.4)	0	0	1 (0.5)
Hypertriglyceridaemia	1 (1.4)	0	0	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (1.4)	0	1 (1.4)	2 (0.9)
Myalgia	0	0	1 (1.4)	1 (0.5)
Pain in extremity	1 (1.4)	0	0	1 (0.5)
Nervous system disorders	1 (1.4)	4 (5.3)	2 (2.7)	7 (3.2)
Dizziness	0	2 (2.7)	0	2 (0.9)
Headache	1 (1.4)	2 (2.7)	2 (2.7)	5 (2.3)
Psychiatric disorders	1 (1.4)	1 (1.3)	0	2 (0.9)
Insomnia	1 (1.4)	1 (1.3)	0	2 (0.9)
Renal and urinary disorders	1 (1.4)	0	0	1 (0.5)
Haematuria	1 (1.4)	0	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	2 (2.7)	2 (2.7)	5 (2.3)
Dyspnoea	0	1 (1.3)	0	1 (0.5)
Pharyngeal oedema	0	0	1 (1.4)	1 (0.5)
Pharyngeal ulceration	0	1(1.3)	0	1(0.5)
Pulmonary fibrosis	1 (1.4)	0	0	1 (0.5)

Table 11. Number (%) of Subjects Reporting Treatment-Related Treatment Emergent Adverse Events (Excluding Infections and Infusion Reactions): Safety Population, Part A

System Organ Class[a] Preferred Term	Treatment			
	Placebo N=74	TRU-SD N=75	TRU-ID N=73	Total N=222
Sinus congestion	0	0	1 (1.4)	1 (0.5)
Skin and subcutaneous tissue disorders	7 (9.5)	3 (4.0)	3 (4.1)	13 (5.9)
Alopecia	0	0	1 (1.4)	1 (0.5)
Dermatitis	1 (1.4)	0	0	1 (0.5)
Dyshidrosis	1 (1.4)	0	0	1 (0.5)
Pruritus	2 (2.7)	1 (1.3)	1 (1.4)	4 (1.8)
Pruritus generalised	1 (1.4)	0	0	1 (0.5)
Rash	0	1 (1.3)	0	1 (0.5)
Rash papular	1 (1.4)	0	0	1 (0.5)
Skin burning sensation	0	1 (1.3)	0	1 (0.5)
Skin hyperpigmentation	0	0	1 (1.4)	1 (0.5)
Skin nodule	1 (1.4)	0	0	1 (0.5)
Urticaria	0	1 (1.3)	0	1 (0.5)
Vascular disorders	1 (1.4)	0	0	1 (0.5)
Flushing	1 (1.4)	0	0	1 (0.5)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm_3B) – single dose.
Placebo/TRU-ID = Placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
Classifications of AEs are based on the MedDRA.
AEs and SAEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SAEs = serious adverse events.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Treatment-emergent non serious AEs occurring in ≥5% of subjects in any treatment group in Part B are presented in Table 12.

Table 12. Number (%) of Subjects Reporting Percentages ≥5% Treatment Emergent Adverse Events Excluding Serious Adverse Events (Safety Population): Part B

System Organ Class[a] MedDRA Preferred Term	Treatment				
	TRU-SD N=56 N(F)=49	TRU-ID N=55 N(F)=42	Placebo/TRU-SD N=31 N(F)=29	Placebo/TRU-IDN =32 N(F)=28	Total N=174 N(F)=148
Any adverse event	38 (67.9)	27 (49.1)	24 (77.4)	20 (62.5)	109 (62.6)
Blood and lymphatic system disorders	0	1 (1.8)	1 (3.2)	2 (6.3)	4 (2.3)
Anaemia	0	0	1 (3.2)	2 (6.3)	3 (1.7)
General disorders and administration site conditions	4 (7.1)	3 (5.5)	5 (16.1)	3 (9.4)	15 (8.6)
Infusion related reaction	0	1 (1.8)	2 (6.5)	0	3 (1.7)
Oedema peripheral	1 (1.8)	1 (1.8)	1 (3.2)	2 (6.3)	5 (2.9)
Infections and infestations	21 (37.5)	13 (23.6)	13 (41.9)	9 (28.1)	56 (32.2)
Bronchitis	1 (1.8)	1 (1.8)	2 (6.5)	0	4 (2.3)
Gastroenteritis	0	0	2 (6.5)	0	2 (1.1)
Nasopharyngitis	3 (5.4)	3 (5.5)	1 (3.2)	1 (3.1)	8 (4.6)
Upper respiratory tract infection	4 (7.1)	1 (1.8)	2 (6.5)	3 (9.4)	10 (5.7)
Urinary tract infection	8 (14.3)	3 (5.5)	6 (19.4)	4 (12.5)	21 (12.1)
Musculoskeletal and connective tissue disorders	10 (17.9)	5 (9.1)	4 (12.9)	6 (18.8)	25 (14.4)
Arthralgia	4 (7.1)	0	3 (9.7)	1 (3.1)	8 (4.6)
Back pain	2 (3.6)	3 (5.5)	1 (3.2)	0	6 (3.4)
Pain in extremity	0	0	0	2 (6.3)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	4 (7.1)	4 (7.3)	2 (6.5)	5 (15.6)	15 (8.6)
Cough	2 (3.6)	1 (1.8)	1 (3.2)	3 (9.4)	7 (4.0)
Skin and subcutaneous tissue disorders	4 (7.1)	4 (7.3)	8 (25.8)	6 (18.8)	22 (12.6)
Pruritus	1 (1.8)	0	1 (3.2)	3 (9.4)	5 (2.9)
Rash	3 (5.4)	2 (3.6)	3 (9.7)	2 (6.3)	10 (5.7)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm 3B) – single dose.
Placebo/TRU-ID = placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
AE = adverse events; F = female; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Infections were reported for 34.5% of subjects during Part B, including 39.3% in the TRU-SD arm, 25.5% in TRU-ID arm, 48.4% in Placebo/TRU-SD arm, and 28.1% in Placebo/TRU-ID arm. The most frequent infection was urinary tract infection, which was reported in 12.6% of the subjects overall during Part B.

Infusion reactions were observed for 12.1% of subjects including 10.7% in TRU-SD, 5.5% in TRU-ID, 29.0% in Placebo/TRU-SD, and 9.4% in Placebo/TRU-ID arms.

Treatment-emergent, treatment-related non serious AEs in Part A are presented in Table 13.

Table 13. Number (%) of Subjects Reporting Treatment-Related Treatment Emergent Adverse Events (Excluding Infections and Infusion Reactions): Safety Population, Part B

System Organ Class[a] Preferred Term	Treatment				
	TRU-SD N=56	TRU-ID N=55	Placebo/TRU-SD N=31	Placebo/TRU-ID N=32	Total N=174
Any adverse event	8 (14.3)	6 (10.9)	1 (3.2)	2 (6.3)	17 (9.8)
Blood and lymphatic system disorders	0	1 (1.8)	0	1 (3.1)	2 (1.1)
Anaemia	0	0	0	1 (3.1)	1 (0.6)
Thrombocytopenia	0	1 (1.8)	0	0	1 (0.6)
Eye disorders	0	1 (1.8)	0	0	1 (0.6)
Conjunctival hyperaemia	0	1 (1.8)	0	0	1 (0.6)
Gastrointestinal disorders	2 (3.6)	0	0	0	2 (1.1)
Tongue ulceration	1 (1.8)	0	0	0	1 (0.6)
Vomiting	1 (1.8)	0	0	0	1 (0.6)
Investigations	3 (5.4)	3 (5.5)	0	0	6 (3.4)
Blood triglycerides increased	1 (1.8)	1 (1.8)	0	0	2 (1.1)
Body temperature	0	1 (1.8)	0	0	1 (0.6)
Liver function test abnormal	0	1 (1.8)	0	0	1 (0.6)
Transaminases increased	1 (1.8)	0	0	0	1 (0.6)
White blood cell count decreased	1 (1.8)	0	0	0	1 (0.6)
Metabolism and nutrition disorders	1 (1.8)	1 (1.8)	0	0	2 (1.1)
Hypercholesterolaemia	0	1 (1.8)	0	0	1 (0.6)
Hypocalcaemia	1 (1.8)	0	0	0	1 (0.6)
Musculoskeletal and connective tissue disorders	2 (3.6)	0	0	0	2 (1.1)
Back pain	1 (1.8)	0	0	0	1 (0.6)
Musculoskeletal chest pain	1 (1.8)	0	0	0	1 (0.6)
Nervous system disorders	1 (1.8)	0	1 (3.2)	0	2 (1.1)
Headache	1 (1.8)	0	0	0	1 (0.6)
Tremor	0	0	1 (3.2)	0	1 (0.6)
Renal and urinary disorders	1 (1.8)	0	0	0	1 (0.6)
Nephrolithiasis	1 (1.8)	0	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	0	1 (1.8)	0	0	1 (0.6)
Rhinorrhoea	0	1 (1.8)	0	0	1 (0.6)
Skin and subcutaneous tissue disorders	1 (1.8)	1 (1.8)	0	2 (6.3)	4 (2.3)
Pruritus	1 (1.8)	0	0	2 (6.3)	3 (1.7)
Urticaria	0	1 (1.8)	0	1 (3.1)	2 (1.1)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm 3B) – single dose.
Placebo/TRU-ID = placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
Classifications of AEs are based on the MedDRA.
AEs and SAEs are not separated out in this table.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects;
SAEs = serious adverse events.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Serious Adverse Event (SAE): During Part A, SAEs were reported for 18 subjects (8.1%), including 9.5% in the Placebo arm, 5.3% in the TRU-SD arm, and 9.6% in the TRU-ID arm. Serious infections were reported for 5 subjects (2.3%) during Part A: 2 in the Placebo arm

(1 influenza and 1 pneumonia), 1 in the TRU-SD arm (acute cholecystitis), and 2 in the TRU-ID arm (2 bronchitis; Table 14).

Table 14. Number (%) of Subjects Reporting Serious Adverse Events: Safety Population, Part A

System Organ Class[a] Preferred Term	Treatment			
	Placebo N=74 N(F)=64	TRU-SD N=75 N(F)=62	TRU-ID N=73 N(F)=59	Total N=222 N(F)=185
Any adverse event	7 (9.5)	4 (5.3)	7 (9.6)	18 (8.1)
Blood and lymphatic system disorders	1 (1.4)	0	0	1 (0.5)
Anaemia	1 (1.4)	0	0	1 (0.5)
Cardiac disorders	1 (1.4)	1 (1.3)	1 (1.4)	3 (1.4)
Atrial fibrillation	0	0	1 (1.4)	1 (0.5)
Cardiac failure congestive	0	1 (1.3)	0	1 (0.5)
Tachycardia	1 (1.4)	0	0	1 (0.5)
Gastrointestinal disorders	0	1 (1.3)	0	1 (0.5)
Oesophageal ulcer	0	1 (1.3)	0	1 (0.5)
Hepatobiliary disorders	2 (2.7)	1 (1.3)	0	3 (1.4)
Cholecystitis acute	0	1 (1.3)	0	1 (0.5)
Cholecystitis chronic	2 (2.7)	0	0	2 (0.9)
Cholelithiasis	0	1 (1.3)	0	1 (0.5)
Infections and infestations	2 (2.7)	0	2 (2.7)	4 (1.8)
Bronchitis	0	0	2 (2.7)	2 (0.9)
Influenza	1 (1.4)	0	0	1 (0.5)
Pneumonia	1 (1.4)	0	0	1 (0.5)
Injury, poisoning and procedural complications	0	0	1 (1.4)	1 (0.5)
Hip fracture	0	0	1 (1.4)	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (1.4)	0	1 (1.4)	2 (0.9)
Bursitis	0	0	1 (1.4)	1 (0.5)
Rheumatoid arthritis	1 (1.4)	0	0	1 (0.5)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	1 (1.4)	0	0	1 (0.5)
Bronchial carcinoma	1 (1.4)	0	0	1 (0.5)
Nervous system disorders	1 (1.4)	0	0	1 (0.5)
Intercostal neuralgia	1 (1.4)	0	0	1 (0.5)
Pregnancy, puerperium and perinatal conditions	0	1 (1.3)	1 (1.4)	2 (0.9)
Pregnancy	0	1 (1.6)	1 (1.7)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	2 (2.7)	0	0	2 (0.9)
Haemoptysis	1 (1.4)	0	0	1 (0.5)
Pulmonary fibrosis	1 (1.4)	0	0	1 (0.5)
Skin and subcutaneous tissue disorders	0	0	1 (1.4)	1 (0.5)
Angioedema	0	0	1 (1.4)	1 (0.5)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm 3B) – single dose.
Placebo/TRU-ID = Placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
Classifications of AEs are based on the MedDRA. .
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

During Part B, SAEs were reported for 4 subjects (2.3%), including 3.6% in both the TRU-SD and TRU-ID arms. Two of these SAEs were serious infections: 1 in the TRU-SD

arm (appendicitis) and 1 in the TRU-ID arm (H1N1 influenza). One subject in the TRU-SD group reported a serious joint sprain and 1 subject in the TRU-ID group had serious osteoarthritis. No SAEs or serious infections were reported in the Placebo/TRU-SD or Placebo/TRU-ID arms during Part B (Table 15).

Table 15. Number (%) of Subjects Reporting Serious Adverse Events, Safety Population, Part B

System Organ Class[a] Preferred Term	TRU-SD N=56	TRU-ID N=55	Placebo/TRU-SD N=31	Placebo/TRU-ID N=32	Total N=174
Any Adverse Event	2 (3.6)	2 (3.6)	0	0	4 (2.3)
Infections and infestations	1 (1.8)	1 (1.8)	0	0	2 (1.1)
Appendicitis	1 (1.8)	0	0	0	1 (0.6)
H1N1 influenza	0	1 (1.8)	0	0	1 (0.6)
Injury, poisoning and procedural complications	1 (1.8)	0	0	0	1 (0.6)
Joint sprain	1 (1.8)	0	0	0	1 (0.6)
Musculoskeletal and connective tissue disorders	0	1 (1.8)	0	0	1 (0.6)
Osteoarthritis	0	1 (1.8)	0	0	1 (0.6)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm 3B) – single dose.
Placebo/TRU-ID = placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
Classifications of AEs are based on the MedDRA.
AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Discontinuations Due to AEs: During Part A, a total of 16 subjects (7.2%) were discontinued from the study due to AEs including 4 subjects in the Placebo arm (5.4%), 4 subjects in the TRU-SD arm (5.3%) and 8 subjects in the TRU-ID arm (11.0%). Two of these subjects, both from the Placebo arm, were discontinued due to infections (1 influenza and 1 pneumonia; Table 16).

Table 16. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal from the Study Safety Population, Part A

System Organ Class[a] Preferred Term	Treatment			
	Placebo N=74 N(F)=64	TRU-SD N=75 N(F)=62	TRU-ID N=73 N(F)=59	Total N=222 N(F)=185
Any Adverse events	4 (5.4)	4 (5.3)	8 (11.0)	16 (7.2)
Blood and lymphatic system disorders	0	0	1 (1.4)	1 (0.5)
Leukopenia	0	0	1 (1.4)	1 (0.5)
Cardiac disorders	0	1 (1.3)	0	1 (0.5)
Cardiac failure congestive	0	1 (1.3)	0	1 (0.5)
General disorders and administration site conditions	0	0	1 (1.4)	1 (0.5)
Infusion related reaction	0	0	1 (1.4)	1 (0.5)
Immune system disorders	0	1 (1.3)	1 (1.4)	2 (0.9)
Drug hypersensitivity	0	1 (1.3)	1 (1.4)	2 (0.9)
Infections and infestations	2 (2.7)	0	0	2 (0.9)
Influenza	1 (1.4)	0	0	1 (0.5)
Pneumonia	1 (1.4)	0	0	1 (0.5)
Investigations	1 (1.4)	0	0	1 (0.5)
Aspartate aminotransferase increased	1 (1.4)	0	0	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (1.4)	1 (1.3)	0	2 (0.9)
Rheumatoid arthritis	1 (1.4)	1 (1.3)	0	2 (0.9)
Pregnancy, puerperium and perinatal conditions	0	1 (1.3)	1 (1.4)	2 (0.9)
Pregnancy	0	1 (1.6)	1 (1.7)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	0	1 (1.4)	2 (0.9)
Laryngeal oedema	0	0	1 (1.4)	1 (0.5)
Pulmonary fibrosis	1 (1.4)	0	0	1 (0.5)
Skin and subcutaneous tissue disorders	0	0	4 (5.5)	4 (1.8)
Angioedema	0	0	1 (1.4)	1 (0.5)
Erythema	0	0	1 (1.4)	1 (0.5)
Urticaria	0	0	2 (2.7)	2 (0.9)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm_3B) – single dose.
Placebo/TRU-ID = Placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
Classifications of AEs are based on the MedDRA.
AE = adverse events; F = female; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category

During Part B, 3 subjects discontinued due to AEs: 1 subject in the TRU-SD arm (paraesthesia oral/rash pruritic), 1 subject in the TRU-ID arm (thrombocytopenia), and 1 subject in the Placebo/TRU-SD arm (urticaria; Table 17).

Table 17. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Study Safety Population, Part B

System Organ Class[a] Preferred Term	TRU-SD N=56	TRU-ID N=55	Placebo/TRU-SD N=31	Placebo/TRU-ID N=32	Total N=174
Any Adverse Event	1 (1.8)	1 (1.8)	1 (3.2)	0	3 (1.7)
Blood and lymphatic system disorders	0	1 (1.8)	0	0	1 (0.6)
Thrombocytopenia	0	1 (1.8)	0	0	1 (0.6)
Gastrointestinal disorders	1 (1.8)	0	0	0	1 (0.6)
Paraesthesia oral	1 (1.8)	0	0	0	1 (0.6)
Skin and subcutaneous tissue disorders	1 (1.8)	0	1 (3.2)	0	2 (1.1)
Rash pruritic	1 (1.8)	0	0	0	1 (0.6)
Urticaria	0	0	1 (3.2)	0	1 (0.6)

Treatment Arms:
Placebo/TRU-SD = placebo at Baseline and Week 12, TRU-015 at Week 24, and placebo at Week 36 (Arm 3B) – single dose.
Placebo/TRU-ID = placebo at Baseline and Week 12, TRU-015 at Weeks 24 and 36 (Arm 3A) – induction dose.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Death: One death occurred during Part A for a subject in the Placebo arm. The death occurred on Study Day 93 and was due to hemoptysis and bronchial cancer. No deaths were reported during Part B.

There were no apparent patterns observed across treatment arms for clinical laboratory data. No clinically important changes for any of the vital signs parameters measured in the study were detected within treatment arms for either Part A or Part B.

CONCLUSIONS:

- TRU-015 appeared to provide improvement in disease activity in subjects with RA in this study; however no statistically significant differences were observed between treatments arms for the primary endpoint (ACR50) at Week 24 in either the mITT or VFE populations.

- TRU-015 was generally well tolerated when administered to subjects with RA in this study.