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GENERIC DRUG NAME and COMPOUND NUMBER: Tofacitinib / CP-690,550

PROTOCOL NO.: A3921029

PROTOCOL TITLE: A Prospective Observational Study to Evaluate Long-Term Safety and Functional Status of Subjects With Rheumatoid Arthritis Previously Enrolled in Studies of CP-690,550

Study Centers: Sixty-eight centers took part in the study and enrolled subjects from 20 countries which included 18 centers in the United States (US); 6 centers in Republic of Korea; 5 centers each in Czech Republic and Poland; 4 centers each in Brazil and Japan; 3 centers each in Chile, Hungary, India, and Slovakia; 2 centers each in Argentina, Mexico, Greece, and Italy; 1 center each in Spain, Bulgaria, Canada, Dominican Republic, Finland, and Ukraine.

Study Initiation and Completion Dates: 12 April 2007 to 27 February 2012

Phase of Development: Phase 2

Study Objectives:

- To estimate the incidences of lymphoproliferative disorder (LPD), lymphoma and important infections over 2 years in subjects with rheumatoid arthritis (RA) who completed or discontinued a qualifying tofacitinib clinical trial (randomized clinical trial with or without an open-label extension).
- To compare the incidences of LPD, lymphoma and important infections in these subjects stratified by prior exposure to tofacitinib.
- To describe the use of immunosuppressive and immunomodulatory therapies by all subjects during the follow-up period.
- To describe the functional status of all subjects during the follow-up period.

METHODS

Study Design: This was a prospective, observational study that enrolled subjects who had received at least 1 dose of study drug (tofacitinib or placebo or adalimumab) and had ceased participation in any Phase 2b or 3 randomized, controlled or open-label (qualifying) study of tofacitinib for the treatment of RA. Consent was sought for participation at the time of the last randomized trial or open-label study visit or up to 7 days later. Subjects who gave consent were contacted and queried at 6, 12, 18, and 24 months after the date of their last tofacitinib study visit through questionnaires and interviews using standard follow-up

methods for observational studies about the possible occurrence of LPD, lymphoma, and important infections; immunosuppressive and immunomodulatory medications taken; diagnosis of diabetes (an independent risk factor); and their functional status (assessed by the Stanford Health Assessment Questionnaire-Disability Index [HAQ-DI]). Any subject reporting the possible occurrence of LPD, lymphoma, or important infections was asked to provide contact information and a release to contact the diagnosing and/or treating physician and health facility, in order to allow written confirmation of the reported event. Medical records and other documentation, where applicable, were obtained to verify safety outcomes. The Schedule of Activities is presented in Table 1.

Table 1. Schedule of Activities

Schedule of Events	Screening Baseline	6 Month[a]	12 Month[a]	18 Month[a]	24 Month[a]
Informed consent	X				
Contact information	X				
Medical history and current medication	X				
Diabetes diagnosis and medications	X	X	X	X	X
RA medications	X	X	X	X	X
Serious infections, LPD/lymphoma assessment (endpoint assessments)[b]		X	X	X	X
HAQ-DI	X[c]	X	X	X	X

HAQ-DI = Health Assessment Questionnaire-Disability Index; LPD = lymphoproliferative disorder; RA = rheumatoid arthritis.

a. The Screening Baseline visit was the only clinic visit. The remaining visits were contacts by questionnaire and interview. Mailings were sent 2 weeks prior to the target visit date.

b. If possible occurrence of these events was reported, the subject was to follow-up with treating physician for confirmation and documentation.

c. Baseline HAQ-DI score was obtained (as part of the final visit of the subjects coming from the "qualifying studies").

Number of Subjects (Planned and Analyzed): This was an observational study where any subject could enroll from the previous qualifying studies; there was no pre-planned time point or sample size for performing the final analysis. It was estimated that 300 subjects from the currently completed and planned studies would participate in the study. A total of 162 subjects were randomized: 35 from the US, 18 each from Poland and Chile; 13 each from Hungary and Czech Republic; 12 from Republic of Korea; 11 from Brazil; 7 each from Mexico and Japan; 6 each from India and Slovakia; 4 from Argentina; 2 each from Bulgaria, Greece, Dominican Republic and Italy; 1 each from Canada, Finland, Spain and Ukraine.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in the study had received at least 1 dose of study drug and had discontinued participation in any Phase 2b or 3 randomized, controlled, or open-label (qualifying) study of tofacitinib for the treatment of RA.

Study Treatment: No study medication was administered as this was an observational study.

Safety Endpoints: Primary endpoints included long-term safety evaluations comprising of:

- Incident LPD as confirmed by a local pathologist.
- Incident lymphoma as confirmed by a local pathologist.
- Incident LPD as confirmed by a central pathologist.
- Incident lymphoma as confirmed by a central pathologist.
- Incident important infections, defined as serious or opportunistic infections.
- Functional status as assessed by the HAQ-DI score. HAQ-DI was collected as a potential predictor of infection events (and death) and not as an efficacy endpoint in the study.

Safety Evaluations: Safety evaluations were as defined above. Adverse events (AEs) (except those that qualified as outcomes), safety laboratory tests, vital signs, and electrocardiograms were not collected in this study.

Statistical Methods: Safety analyses were descriptive in nature; there was no formal hypothesis testing, although 95% 2-sided confidence intervals (CIs) could have been calculated. P-values, if any, were considered descriptive.

Primary Endpoint Analysis: The incidence rates for each of the outcomes of interest (important infection, and pathologically confirmed LPD or lymphoma) were calculated per 100 subject years and their 95% CIs were calculated. For important infections, LPD and lymphoma, the incidence rates were calculated for the period of study.

Time to-First-Event Analysis: Kaplan-Meier cumulative probabilities of developing a first event of interest were calculated. In the Kaplan-Meier analysis the interval of time to experiencing a first event constituted the period of exposure (and subjects were censored after their first event). A separate analysis was conducted for important infections, LPD and lymphoma.

Secondary Analyses: Secondary analyses included exposures in the qualifying study and exposure during this study, as well as exposure estimates and incidence rates for important infections and herpes zoster.

For calculating the exposure to different types of immunosuppressive and immunomodulatory medications, 2 sets of variables were used. Variables, for both the follow-up period and for the period prior to and during tofacitinib studies, were created from data available to classify subjects with regard to their exposure to the immunosuppressive and immunomodulatory medications, where available. These medications included methotrexate, tumor necrosis factor (TNF)-alpha inhibitors, other immunosuppressive small molecules, other disease-modifying anti-rheumatic drugs (DMARDs), and other biologics.

RESULTS

In this section, subjects who received tofacitinib doses ≥10 mg twice daily in the previous studies are included in the 'CP ≥10 mg group', subjects who received tofacitinib doses <10 mg twice daily in the previous studies are included in the 'All Other CP' group, and both these groups together are referred to as the 'All CP' group.

Subject Disposition and Demography: A total of 162 subjects who had been treated in the qualifying studies and were screened, a majority of subjects 54.9% (89/162) had received the previous treatment with all other CP doses, and 29.6% (48/162) had received previous treatment with CP ≥10 mg. Additionally, 13.6% (22/162) of subjects had received placebo and 1.8% (3/162) of subjects had received adalimumab as the previous study treatment. In total, 70.8% of the subjects in the CP ≥10 mg group and 84.3% of subjects in the All Other CP group completed the study as shown in the Table 2.

Table 2. Subject Evaluation Groups by Previous Study Treatment

Number (%) of Subjects		CP ≥10 mg	All Other CP	Placebo	Adalimumab
Screened	162				
Assigned to study treatment		48	89	22	3
Treated		48	89	22	3
Completed		34 (70.8)	75 (84.3)	20 (90.9)	0
Discontinued		14 (29.2)	14 (15.7)	2 (9.1)	3 (100.0)
Subject died		2 (4.2)	5 (5.6)	0	0
Not related to study drug		12 (25.0)	9 (10.1)	2 (9.1)	3 (100.0)
Lost to follow-up		1 (2.1)	4 (4.5)	0	1 (33.3)
No longer willing to participate in study		5 (10.4)	2 (2.2)	2 (9.1)	2 (66.7)
Other		6 (12.5)	3 (3.4)	0	0
Full analysis set[a]		48 (100.0)	89 (100.0)	22 (100.0)	3 (100.0)
Safety analysis set		48 (100.0)	89 (100.0)	21 (95.5)[b]	3 (100.0)

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.
The last dose previously taken refers to what subject was last administered prior to enrolling in this study, ie, during the qualifying study.
AE = adverse event; CP = CP-690,550 (tofacitinib); HAQ-DI= Health Assessment Questionnaire-Disability Index.

a. Analyzed for HAQ-DI.
b. One subject was not in the AE data. The site was closed in 2009 and the AE log pages were not completed. This was recorded in the data management issues log.

A majority of the subjects were female (81.5%). The mean ± standard deviation (SD) age of the study population was 55±11.7 years (overall age range 24 to 82 years). Table 3 summarizes the demographic characteristics of the subjects in the study.

Table 3. Demographic Characteristics by Previous Study Treatment

	CP ≥10 mg			All Other CP			Placebo			Adalimumab			Total		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Number of subjects	8	40	48	17	72	89	5	17	22	0	3	3	30	132	162
Age (years)															
<18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-44	0	5 (12.5)	5 (10.4)	2 (11.8)	12 (16.7)	14 (15.7)	1 (20.0)	5 (29.4)	6 (27.3)	0	1 (33.3)	1 (33.3)	3 (10.0)	23 (17.4)	26 (16.0)
45-64	6 (75.0)	25 (62.5)	31 (64.6)	10 (58.8)	49 (68.1)	59 (66.3)	4 (80.0)	9 (52.9)	13 (59.1)	0	1 (33.3)	1 (33.3)	20 (66.7)	84 (63.6)	104 (64.2)
≥65	2 (25.0)	10 (25.0)	12 (25.0)	5 (29.4)	11 (15.3)	16 (18.0)	0	3 (17.6)	3 (13.6)	0	1 (33.3)	1 (33.3)	7 (23.3)	25 (18.9)	32 (19.8)
Mean	58.3	57.0	57.2	58.4	53.9	54.7	51.2	52.0	51.8	0.0	52.3	52.3	57.1	54.5	55.0
Standard deviation	8.6	11.3	10.8	10.7	11.7	11.6	15.3	13.4	13.5	0.0	16.0	16.0	11.0	11.9	11.7
Range	45-70	27-79	27-79	37-75	24-82	24-82	25-64	29-75	25-75	0-0	37-69	37-69	25-75	24-82	24-82

The last dose previously taken refers to what subject was last administered prior to enrolling in this study, ie, during the qualifying study.
CP = CP-690,550 (tofacitinib).

Safety Results:

LPD and Lymphoma: No subject reported LPD or lymphoma at any time during the study.

HAQ-DI Status: Both the CP ≥10 mg and the All Other CP group showed a significant decrease in HAQ-DI score from Baseline to Month 6, which stabilized thereafter. The placebo group showed continuous decrease over the 24 months, with a significant reduction from Baseline to Month 6. Table 4 summarizes the HAQ-DI values in the study.

Table 4. Descriptive Statistics of HAQ Disability Index Values at Baseline and Months 6, 12, 18 and 24 by Previous Study Treatment (Full Analysis Set)

Visit	Treatment	N	Mean	Standard Deviation	Minimum	Q1	Median	Q3	Maximum
Baseline	CP≥10 mg	48	1.32	0.67	0.00	0.75	1.50	1.88	2.38
	All other CP	88	1.42	0.67	0.00	0.88	1.50	1.94	2.88
	Placebo	22	1.63	0.76	0.00	1.13	1.88	2.00	3.00
	Adalimumab	3	1.13	0.13	1.00	1.00	1.13	1.25	1.25
Month 6	CP≥10 mg	37	1.08	0.61	0.00	0.50	1.25	1.50	2.00
	All other CP	81	1.23	0.69	0.00	0.75	1.38	1.75	2.63
	Placebo	21	1.21	0.82	0.00	0.75	1.00	1.88	2.88
	Adalimumab	2	0.19	0.27	0.00	0.00	0.19	0.38	0.38
Month 12	CP≥10 mg	39	1.16	0.63	0.00	0.50	1.38	1.63	2.75
	All other CP	79	1.12	0.76	0.00	0.38	1.13	1.75	2.88
	Placebo	21	1.15	0.81	0.00	0.63	1.25	1.75	2.75
	Adalimumab	1	0.88	-	0.88	0.88	0.88	0.88	0.88
Month 18	CP≥10 mg	35	1.15	0.59	0.00	0.63	1.38	1.63	2.00
	All other CP	76	1.07	0.77	0.00	0.33	1.13	1.63	2.63
	Placebo	20	1.12	0.86	0.00	0.25	1.25	1.75	2.75
Month 24	CP≥10 mg	31	1.15	0.69	0.00	0.50	1.38	1.63	2.63
	All other CP	68	1.14	0.78	0.00	0.50	1.19	1.75	2.75
	Placebo	20	1.07	0.87	0.00	0.00	1.31	1.88	2.25

The last dose previously taken refers to what subject was last administered prior to enrolling in the study, ie, during the qualifying study.
CP = CP-690,550 (tofacitinib); HAQ = Health Assessment Questionnaire; N = number of subjects; Q = quartile.

Important Infections: Table 5 summarizes the exposure estimates and incidence rates for important infections in subjects grouped by previous study treatment. For the All CP group, the exposure for important infections was 245.94 subject years (81.31 subject years for the CP ≥10 mg group and 164.63 subject years for the All Other CP group). A single important infection AE (tuberculosis in a subject who received the CP 5 mg dose in the qualifying study, diagnosed on Day 58) was reported in the All Other CP group. The crude incidence rate for important infections was 0.407/100 subject years for the All CP group (95% CI: 0.057 to 2.886) with crude incidence rate =0 for the CP ≥10 mg group and crude incidence rate of 0.607/100 subject years (95% CI: 0.086 to 4.312) for the All Other CP group.

Table 5. Exposure Estimates and Incidence Rates for Important Infections by Previous Study Treatment, During Study

	CP ≥10 mg	All Other CP	All CP	Placebo	Adalimumab
Age (mean, ± SD, range)	57.21, ±10.80, 27-79	54.73, ±11.57, 24-82	55.60, ±11.33, 24-82	51.82, ±13.45, 25-75	52.33, ±16.04, 37-69
Gender (% female)	83.33	80.9	81.75	77.27	100
Total subjects exposure (n)	48	89	137	22	3
Total subject-yr of drug exposure	81.31	166.61	247.92	41.57	2.94
Important infections					
Events (n)	-	1	1	-	-
Unique subjects with events (n)	-	1	1	-	-
Incidence (proportion)	-	0.0112	0.0073	-	-
Total subject-yr of exposure for event	81.31	164.63	245.94	41.57	2.94
Incidence rate per 100 subject-yr (95% CI)-crude	0.000 (0.000, .)	0.607 (0.086, 4.312)	0.407 (0.057, 2.886)	0.000 (0.000, .)	0.000 (0.000, .)

Includes all AEs reported on the infection log that were adjudicated as important.
The last dose previously taken refers to what subject was last administered prior to enrolling in this study, ie, during the qualifying study.
AE = adverse event; CI = confidence interval; CP = CP-690,550 (tofacitinib); n = number of subjects meeting the prespecified criteria; SD = standard deviation.

For the All CP group, the exposure for herpes zoster was 245.48 subject years (78.86 subject years for the CP ≥10 mg group and 166.61 subject years for the All Other CP group). Treatment-emergent herpes zoster was reported in 2 subjects in the CP ≥10 mg group. One subject was diagnosed on Day 129 from first dose of study medication and resolved on Day 154; another subject was diagnosed on Day 434 from first dose of study medication.

The crude incidence rate for herpes zoster was 0.815/100 subject years for the All CP group (95% CI: 0.204 to 3.258) with crude incidence rate =0 for the All Other CP group, and crude incidence rate of 2.536/100 subject years (95% CI: 0.634 to 10.140) for the CP ≥10 mg group.

Immunosuppressive and Immunomodulatory Therapies:

- Methotrexate use was reported in 75% of the subjects in the CP ≥10 mg group and 77.5% of the subjects in the All Other CP group.
- Traditional DMARDs other than methotrexate were used by 22.9% of subjects in the CP ≥10 mg group and 32.6% of subjects in the All Other CP group.
- Any one of the other biologic DMARDs were used by 8.3% of subjects in the CP ≥10 mg group and 5.6% of subjects in the All Other CP group.
- Any one of the TNF inhibitors including adalimumab were taken by 10.4% of subjects in the CP ≥10 mg group and 18.0% of subjects in the All Other CP group.
- Any one of the glucocorticoids were taken by approximately 65% of subjects in both the CP ≥10 mg group and the All Other CP group.

AEs: No subject reported LPD or lymphoma at any time during the study. A single important infection AE (tuberculosis) which was a serious adverse event (SAE) was reported in the All Other CP group. Table 6 and Table 7 present the data for treatment-emergent non-serious AEs and SAEs by previous study treatment.

Table 6. Treatment Emergent Non Serious Adverse Events by Previous Study Treatment for Events Having a Frequency Rate ≥2

	CP ≥10 mg n (%)	All Other CP n (%)	Placebo n (%)	Adalimumab n (%)
Number (%) of subjects:				
Evaluable for adverse events	48	89	22	3
With adverse events	3 (6.3)	2 (2.2)	1 (4.5)	0
Number (%) of subjects with adverse events by:				
System organ class				
MedDRA preferred term				
Infections and infestations	3 (6.3)	2 (2.2)	1 (4.5)	0
Herpes zoster	2 (4.2)	0	0	0
Pneumonia	1 (2.1)	0	0	0
Tooth abscess	0	0	1 (4.5)	0
Urinary tract infection	1 (2.1)	2 (2.2)	1 (4.5)	0

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.1) coding dictionary was applied.
The last dose previously taken refers to what subject was last administered prior to enrolling in this study, ie, during the qualifying study.
CP = CP-690,550 (tofacitinib); MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Table 7. Treatment Emergent Serious Adverse Events by Previous Study Treatment

	CP ≥10 mg n (%)	All Other CP n (%)	Placebo n (%)	Adalimumab n (%)
Number (%) of subjects:				
Evaluable for adverse events	48	89	22	3
With adverse events	0	1 (1.1)	0	0
Number (%) of subjects with adverse events by:				
System organ class				
MedDRA preferred term				
Infections and infestations	0	1 (1.1)	0	0
Tuberculosis	0	1 (1.1)	0	0

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.1) coding dictionary was applied.
The last dose previously taken refers to what subject was last administered prior to enrolling in this study, ie, during the qualifying study.
CP = CP-690,550 (tofacitinib); MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Discontinuations due to AEs: No subject discontinued from the study due to AEs.

Deaths: The deaths were determined to be not related to the study medication given in the qualifying study and did not require reporting to the safety database.

Efficacy was not evaluated in the study.

CONCLUSIONS:

- No subject reported LPD or lymphoma at any time during the study.
- The safety findings in this long-term observational follow-up study were in agreement with the known safety profile of CP-690,550, with no new safety concerns identified. The events of interest were as expected for this indication and subject population.
- Methotrexate was the most common DMARD, used by approximately 75% of the subjects. Concomitant glucocorticoid use was reported by 65% of the subjects. Other concomitant traditional DMARDs, other biologic DMARDs and TNF inhibitors including adalimumab were also used by the subjects.
- Compared with baseline, the HAQ-DI scores at 6, 12, 18, and 24 months did not worsen over time.