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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Xeljanz® / Tofacitinib

PROTOCOL NO.: A3921030

PROTOCOL TITLE: A Phase 2 Randomized, Multicenter, Active Comparator-Controlled Trial to Evaluate the Safety and Efficacy of Coadministration of CP-690,550 and Mycophenolate Mofetil/Mycophenolate Sodium in De Novo Kidney Allograft Recipients

Study Centers: Seventy centers were included in this study of which 58 centers enrolled subjects from 15 countries: 28 centers in the United States; 5 centers in Australia; 4 centers in France; 3 centers in the Republic of Korea; 2 centers each in Italy, Portugal, Brazil, Belgium, Germany, Spain and Poland; and 1 center each in the Czech Republic, Canada, Netherland and Norway.

Study Initiation and Completion Dates: 15 August 2007 to 16 April 2010

Phase of Development: Phase 2

Study Objectives:

Primary Objectives:

- To compare the incidence of clinical biopsy-proven acute rejection (BPAR) (as interpreted by the central blinded pathologist) of combination regimens of tofacitinib and mycophenolate mofetil (MMF)/mycophenolate sodium (MPS) versus a cyclosporine (CsA)-based regimen in recipients of first renal allografts at Month 6 post-transplant;

- To compare glomerular filtration rate (GFR), as measured by iohexol serum clearance, of combination regimens of CP-690,550 and MMF/MPS versus a CsA-based regimen at Month 12 post-transplant.

Secondary Objectives:

- To evaluate the safety and tolerability of combination regimens of tofacitinib and MMF/MPS, including adverse events (AEs), clinically significant infections, malignancies, incidence and duration of delayed graft function (DGF), safety laboratory tests (including proteinuria), and estimated glomerular filtration rate (eGFR, as calculated from equations);

- To compare GFR, as measured by iohexol serum clearance, of combination regimens of tofacitinib and MMF/MPS versus a CsA-based regimen at Month 6 post-transplant;

- To compare the progression of chronic allograft lesions of combination regimens of tofacitinib and MMF/MPS versus a CsA-based regimen at Month 12 post-transplant;

- To evaluate the efficacy of combination regimens of tofacitinib and MMF/MPS, including clinical BPAR at Month 12 (as interpreted by the central pathologist), treated clinical acute rejection (episodes that were diagnosed based on local biopsy readout and received anti-rejection treatment), combined Banff rejection categories (of antibody-mediated rejection plus borderline changes plus acute rejection, as interpreted by the central pathologist), graft loss, subject death, and efficacy failure (defined as the first occurrence of clinical BPAR or graft loss including subject death);

- To evaluate the pharmacokinetics (PK) of tofacitinib and mycophenolic acid (MPA);

- To evaluate the effects of tofacitinib on lymphocyte subsets;

- To evaluate the effects of tofacitinib on health-outcomes assessments.

METHODS

Study Design: This was a Phase 2, randomized, multicenter, partially blinded, active comparator-controlled, and parallel-group trial. There were 3 treatment arms, consisting of 2 different tofacitinib regimens and a CsA-based control arm. Subjects in each treatment arm received basiliximab induction and long-term immunosuppression with MMF/MPS and corticosteroids. In each treatment arm, subjects were treated with study medications for 12 months. All subjects provided informed consent and underwent screening evaluations to determine their eligibility prior to their kidney transplant operations. After receiving their kidney allografts, they were randomized 1:1:1 to one of 2 tofacitinib regimens or CsA. Randomization was performed prior to 12 hours post-transplant.

Subjects were discharged after the routine postoperative course, and subsequent evaluations were performed as outpatients. Throughout the study procedures, day number referred to the number of days post-transplant (eg, Day 1 was the first 24-hour period post-transplant). Subjects were evaluated on Day 1; Day 2; Day 7 (only if the subject had not yet been discharged from the transplant center); and Day 14; and at Months 1, 2, 3, 4, 6, 9 and 12.

Throughout this study, subjects were monitored for clinical evidence of acute rejection, clinically significant infections, malignancies, and graft survival. In addition to plannedbiopsies scheduled at implantation and Month 12, allograft biopsy should have been considered when clinically indicated to assess the etiology of deteriorating renal function. The PK evaluations of tofacitinib and MPA, flow cytometry analysis of lymphocyte subsets, and health-outcomes assessments were also performed at various timepoints in the trial. The schedule of study activities is provided in Table 1. Screening had been performed within 30

days before dosing of study medications. There was a window of ±3 days for the Day 14 and Month 1 visits, ±5 days for Months 2, 3, and 4 visits, and ±14 days for Months 6, 9, 12, and Month 14 follow-up visits. Days refer to post-transplant days.

Table 1. Schedule of Activities

Schedule of Events	Screening	Day 1[a]	Day 2	Day 7[b]	Day 14	Month 1	Month 2	Month 3	Month 4	Month 6	Month 9	Month 12	Month 14 (or 2-Month Follow-up)
Full physical examination	X												
Limited physical examination		X[c]						X		X		X	X
Medical and medication history (update on Day 1)	X	X											
Drug and alcohol history	X												
Supine vital signs (blood pressure and heart rate)	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject weight	X					X		X		X	X	X	X
Single 12-lead electrocardiogram	X							X		X		X	
Safety laboratory tests (CBC with diff; Panel 1 blood chemistry)	X					X		X		X	X	X	X
Abbreviated safety laboratory tests (CBC with diff; Panel 2 blood chemistry-SCr, BUN, ALT, bilirubin, alkaline phosphatase)			X	X	X		X		X				
HbA1c	X							X		X		X	
Urinalysis with microscopy and random urine protein/creatinine ratio	X					X		X		X	X	X	X
FSH[d]	X												
Serum pregnancy test (WOCBP only)	X												
Urine pregnancy test (WOCBP only)		X			X	X		X		X	X	X	X
Review Historical Serology Results for HIV-1, HBV, HCV, CMV, and EBV	X												
HBV DNA PCR and HCV RNA PCR		X											
EBV DNA PCR		X				X		X		X	X	X	
CMV DNA PCR						X	X	X		X			
BKV DNA PCR						X	X	X		X	X	X	
GFR (iohexol serum clearance)										X		X	
Protocol allograft biopsy		X[e]										X	
Flow cytometry analysis for lymphocytes (even randomization number subjects only)						X		X		X		X	
Tofacitinibblood samples (tofacitinib-treated subjects only)[f]					X	X		X		X	X	X	

Table 1. Schedule of Activities

Schedule of Events	Screening	Day 1[a]	Day 2	Day 7[b]	Day 14	Month 1	Month 2	Month 3	Month 4	Month 6	Month 9	Month 12	Month 14 (or 2-Month Follow-up)
MPA PK blood samples for tofacitinib-treated subjects only[f]					X	X		X		X	X	X	
Trough blood samples for CsA levels (for CsA-treated subjects only, prior to AM dose)						X		X		X		X	
MPA PK blood samples for CsA-treated subjects only								X		X			
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment		X	X	X	X	X	X	X	X	X	X	X	X
Health outcome measures: SF-36v2, ESRD-SCL, SODA	X									X		X	
Randomization		X											
Dosing		X	→	→	→	→	→	→	→	→	→	→	
Drug dispensing/accountability				X	X	X	X	X	X	X	X	X	
Deidentified genetic sample (optional)[g]		X											

AM = morning; ALT = alanine transaminase; BKV = BK virus; BUN = blood urea nitrogen; CBC = complete blood count; CMV = cytomegalovirus; CsA = cyclosporine; diff = differential; DNA = deoxyribonucleic acid; EBV = Epstein Barr virus; ESRD-SCL = End-Stage renal disease symptom checklist transplantation module; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus-1; MPA = mycophenolic acid; PCR = polymerase chain reaction; PK = pharmacokinetic; RNA = ribonucleic acid; SCr = serum creatinine; SF-36v2 = Short Form 36 Version 2; SODA = Severity of Dyspepsia Assessment; WOCBP = women of childbearing potential.

a Day 1 was the first 24-hour period post-transplant.
b Day 7 procedures were performed only if the subject had not been discharged.
c Limited physical examination on Day 1 may have been performed within 24 hours of dosing.
d FSH at Screening was optional for postmenopausal women who were not on hormone replacement therapy.
e An allograft biopsy on Day 1 was performed at the time of implantation. This biopsy should have preferably been performed as a needle biopsy (though wedge biopsy was acceptable if needle biopsy could not be performed). At least 2 core specimens should have been obtained through 2 passes at biopsy.
f The tofacitinib and MPA PK sampling schedule, for subjects assigned to tofacitinib, depended on the randomization number of the individual subject.
g In this study, Korean sites did not perform pharmacogenomic sampling.

Number of Subjects (Planned and Analyzed): Approximately 300 subjects were planned to be enrolled from approximately 65 transplant centers. A total of 331 subjects were enrolled and assigned to study treatment. Nine subjects were assigned to study treatment, but were not treated; of the 322 subjects who received study treatment the following were enrolled: North America (139 subjects; 43.2%), South America (34 subjects; 10.6%), Europe (89 subjects; 27.6%), Korea (16 subjects; 5.0%), and Australia (44 subjects; 13.7%).

Diagnosis and Main Criteria for Inclusion:

Subjects were aged 18 to 70 years, inclusive, and must have had end-stage renal disease, been on regular renal replacement therapy (eg, dialysis), or have eGFR (estimated by the Cockcroft-Gault equation) ≤10 mL/min, and been scheduled to receive a primary kidney transplant from a deceased donor (irrespective of the number of human leukocyte antigen [HLA] antigen mismatches), or a HLA-mismatched living donor (either living-related or living-unrelated). Subjects must have had no known contraindications to the administration of Interleukin-2 receptor antagonist induction, MMF, corticosteroids, or CsA.

Study Treatment: The first oral doses of tofacitinib and CsA were administered as soon as oral medications were tolerated (within 12 hours post-transplant), and no later than 24 hours post-transplant in subjects who did not require dialysis support post-transplant. If subjects randomized to the control (CsA) arm required dialysis immediately post-transplant, the first dose of CsA may have been delayed up to 72 hours post-transplant. In any treatment arm, subjects who required dialysis (including intermittent dialysis support) for ≥14 consecutive days in the immediate post-transplant period were discontinued from the trial. For the purpose of this study, DGF was defined as the requirement of any dialysis within 7 days post-transplant.

All subjects received induction with a 20 mg intravenous (IV) dose of basiliximab within 2 hours prior to the transplant surgery. Subjects who were randomized to CsA and did not develop DGF, as well as subjects randomized to tofacitinib, received a second 20 mg dose of basiliximab 3-5 days after transplantation. In subjects who were randomized to CsA and developed DGF, basiliximab could have been discontinued at the Investigator's discretion, and thymoglobulin administered at 1.0-1.5 mg/kg/day for up to 6 doses per standard local practice.

Subjects received MMF 1 g BID (except in the control arm where Black subjects may have received up to 1.5 g BID) with the first dose of MMF administered within 12 hours post-transplant.

All subjects received a tapering steroid regimen. The corticosteroid regimen should have included an induction dose of IV methylprednisolone 125-500 mg (or equivalent) at the time of transplantation, followed by a taper to oral prednisone 5-10 mg/day (or equivalent) by Month 2, and to 5 mg/day of oral prednisone (or equivalent) by Month 3. This maintenance dosage continued through the 12-month duration of the trial.

All treatment arms were open-label to the sponsor. Treatment Arms 2 and 3 were blinded to the subjects and Investigators with respect to the tofacitinib dosage in Months 4-6. The treatment arms are further summarized in Table 2.

Table 2. Treatment Arms

Treatment Arm	CsA[a]	Tofacitinib Dosage[b]	MMF Dosage After Randomization[c]
1 (control arm)	Per target levels	None	1 g BID; up to 1.5 g BID in Black subjects
2	None	15 mg BID in Months 1-6, then 10 mg BID in Months 7-12	1 g BID
3	None	15 mg BID in Months 1-3, then 10 mg BID in Months 4-12	1 g BID

BID = twice daily; CsA = cyclosporine; DGF = delayed graft function; EC-MPS = enteric-coated mycophenolate sodium; MMF = mycophenolate mofetil.

a In Treatment Arm 1 (control arm), CsA was administered as CsA microemulsion BID in 2 equal doses approximately 12 hours apart. In subjects without DGF, the first dose was administered as soon as oral medications were tolerated (within 12 hours post-transplant) and no later than 24 hours post-transplant. In subjects with DGF, the first dose of CsA may have been delayed up to 72 hours post-transplant. CsA should have been started at 8-10 mg/kg/day and dosage should have been adjusted to achieve the following target 12-hour trough whole blood levels: 125-400 ng/mL in Months 1-3 and 100-300 ng/mL in Months 4-12.

b In Treatment Arms 2 and 3, tofacitinib was administered BID in 2 equal doses approximately 12 hours apart. The first dose should have been administered as soon as oral medications were tolerated (within 12 hours post-transplant) and no later than 24 hours post-transplant. Tofacitinib dosage in Months 4-6 in Treatment Arms 2 and 3 was blinded to the subjects and the Investigators.

c Subjects received MMF 1 g BID (except in the control arm where Black subjects may have received up to 1.5 g BID), with the first dose of MMF administered within 12 hours post-transplant. In individual cases where EC-MPS (Myfortic) was used instead of MMF (eg, due to reimbursement restrictions), myfortic 720 mg may have been substituted for MMF 1 g, and Myfortic 720 mg BID may have been substituted for MMF 1 g BID. The same formulation of MMF or Myfortic should have been used throughout the trial in any given subject. MMF should have been used instead of Myfortic in this trial when possible.

Outcomes Research Endpoints:

Primary Endpoints

- First clinical BPAR episode (as interpreted by the central blinded pathologist) within 6 months post-transplant. Clinical BPAR is defined as a BPAR associated with an increase in serum creatinine of ≥0.3 mg/dL and ≥20% from pre-rejection baseline;
- GFR, measured by iohexol serum clearance, at Month 12.

Secondary Endpoints

- GFR, as measured by iohexol serum clearance, at Month 6;
- Progression of chronic allograft lesions (as interpreted by the central pathologist) at Month 12;

- Other efficacy endpoints, such as clinical BPAR (as interpreted by the central pathologist) at Month 12, treated clinical acute rejection (episodes that were diagnosed based on local biopsy readout and receive anti-rejection treatment), combined Banff rejection categories (of antibody-mediated rejection plus borderline changes plus acute rejection, as interpreted by the central pathologist), graft loss, death and efficacy failure;

- Adverse events, clinically relevant infections, other estimates of GFR, pharmacokinetics, lymphocyte subsets, and health outcome assessments.

Safety Evaluations: At various intervals in this trial (Table 1), safety measurements including AE monitoring, physical examinations, clinical laboratory tests (including random urinary protein/creatinine ratio), hemoglobin A1c (HbA1c), electrocardiograms (ECGs), and monitoring of viral loads of EBV (whole blood), CMV (whole blood), and BKV (plasma) were performed.

Statistical Methods: All efficacy and safety analyses were based on the Full Analysis Set (FAS). The FAS included all subjects who were randomized to the study and received at least 1 dose of study medication. Two analysis sets were further defined for time to event variables: (1) FAS with Last Follow-up Risk Set: for those who died, time to death was used. For those lost to follow-up, date of the loss to follow-up was used. Otherwise, the maximum visit date or last date of data collection was used. (2) FAS with Last Dosing Risk Set: the last dosing date plus 7 days was used.

For each endpoint, the statistical comparisons summarized in Table 3 were made, as applicable:

Table 3. Statistical Comparisons

Comparison (Short Name)	Description of Tofacitinib Regimen	Control (Reference)
Treatment arm 2 vs control	Tofacitinib 15 mg BID in Months 1-6, then 10 mg BID in Months 7-12 + MMF 2 gm/day	CsA + MMF 2 gm/day
Treatment arm 3 vs control	Tofacitinib 15 mg BID in Months 1-3, then 10 mg BID in Months 4-12 + MMF 2 gm/day	CsA + MMF 2 gm/day

BID = twice daily; CsA = cyclosporine; MMF = mycophenolate mofetil; vs = versus.

The Hochberg multiple comparison method along with a gatekeeping strategy was applied to testing these 2 comparisons (Treatment Arm 2 versus [vs] Control and Treatment Arm 3 vs Control) for the 2 co-primary endpoints (binary first clinical BPAR diagnosed by the central pathologist at Month 6 and measured GFR at Month 12) only. No multiple comparison adjustments were made to any other endpoints/timepoints.

RESULTS

Subject Disposition and Demography: A total of 331 subjects were assigned to study treatment. Nine subjects were assigned to study treatment, but were not treated and a total of 322 subjects were treated. A total of 124 subjects discontinued from the study. More

subjects in the tofacitinib 15 mg BID in Months 1-6 arm (42.5%) and the tofacitinib 15 mg BID in Months 1-3 arm (44.9%) discontinued from the study than in the CsA arm (28.4%). A summary of subject disposition and subject discontinuation is provided in Table 4.

Table 4. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
Assigned to study treatment	110	110	111
Treated	109	106	107
Completed	77 (70.0)	60 (54.5)	59 (53.2)
Discontinued	32 (29.1)	46 (41.8)	48 (43.2)
Discontinuations from study[a]	31 (28.4)	45 (42.5)	48 (44.9)
Subject died[b]	2 (1.8)	0	1 (0.9)
Related to study drug	12 (11.0)	26 (24.5)	24 (22.4)
Adverse event	11 (10.1)	26 (24.5)	24 (22.4)
Lack of efficacy	1 (0.9)	0	0
Not related to study drug	17 (15.6)	19 (17.9)	23 (21.5)
Adverse event	8 (7.3)	12 (11.3)	16 (15.0)
Lost to follow-up	3 (2.8)	1 (0.9)	0
Other	1 (0.9)	3 (2.8)	3 (2.8)
Subject no longer willing to participate in study	5 (4.6)	3 (2.8)	4 (3.7)
Analyzed for safety			
Adverse event	109 (99.1)	106 (96.4)	107 (96.4)
Laboratory data	109 (99.1)	106 (96.4)	106 (95.5)

Includes post-Amendment-1 subjects only.
Two subjects were randomized to tofacitinib treatment arms, but actually took CsA. They are included in the tofacitinib arms for "assigned to study treatment", but are included in the CsA arm for "treated". For all summary tables, these 2 subjects were presented in the CsA arm, except for the clinical BPAR and measured GFR summary tables, where these subjects were excluded from the analyses.
Discontinued counts reflect subjects who discontinued from either end of treatment or end of study phase.
Percents were calculated based on the number of subjects assigned to study treatment.
BID = twice daily; CsA = cyclosporine.
a Discontinued status is determined from the subject summary page at end of study.
b Subjects who died after they discontinued are not counted.

A summary of subject demographic characteristics is presented in Table 5.

Most subjects in each treatment arm were male. The mean age of recipients was similar among treatment arms. The age of recipients ranged from 18 to 70 years of age. Most subjects in each treatment arm were White (66.8% of subjects who received study treatments), whereas 15.2% of subjects were Black. The recipient mean weight at Baseline was similar among treatment arms.

Table 5. Demographic Characteristics by Previous Study Treatment

Number of Subjects	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
Sex, n (%)			
Male	70 (64.2)	82 (77.4)	80 (74.8)
Female	39 (35.8)	24 (22.6)	27 (25.2)
Age (years), n (%)			
18-44	45 (41.3)	43 (40.6)	46 (43.0)
45-64	57 (52.3)	54 (50.9)	56 (52.3)
≥65	7 (6.4)	9 (8.5)	5 (4.7)
Mean	47.1	47.8	45.8
Standard deviation	12.9	12.1	12.6
Range	18-70	18-70	18-66
Race, n (%)			
White	78 (71.6)	66 (62.3)	71 (66.4)
Black	12 (11.0)	16 (15.1)	21 (19.6)
Asian	10 (9.2)	15 (14.2)	11 (10.3)
Other	9 (8.3)	9 (8.5)	4 (3.7)
Weight (kg)			
Mean	76.8	77.9	77.2
Standard deviation	15.7	20.9	19.1
Range	43.5-119.3	46.3-160.0	42.0-135.3

BID = twice daily; CsA = cyclosporine; n = number of subjects.

Efficacy Results:

Primary Efficacy Endpoints:

First Clinical Biopsy Proven Acute Rejection

A summary of the percent of subjects with first clinical BPAR at Month 6 estimated using Kaplan-Meier survival curves and treatment comparisons is provided in Table 6.

The clinical BPAR rates at Month 6 post-transplant were statistically non-inferior between the tofacitinib arm and the CsA arm.

Table 6. Percent of Subjects with First Clinical BPAR at Month 6 Estimated Using Kaplan-Meier Survival Curves and Treatment Comparisons (FAS with Last Dosing Risk Set)

Month 6 – Clinical BPAR	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
Number of events	9	11	7
Estimated rate % (SE)	8.96 (2.86)	11.42 (3.26)	7.14 (2.62)
Estimated rate difference % (CP-CsA)		2.46	-1.82
60% CI for difference		-1.19, 6.11	-5.08, 1.45
P-value[a]		0.5701	0.6400

BID = twice daily; BPAR = biopsy-proven acute rejection; CI = confidence interval; CP = Tofacitinib; CsA = cyclosporine; SE = standard error.
a P-value for comparing rate difference between tofacitinib and CsA using Wald test.

Measured Glomerular Filtration Rate by Iohexol Serum Clearance at Month 12

The differences between the CsA group and each tofacitinib arm were statistically significant, with higher measured GFRs in the tofacitinib arms. The lower 60% confidence limit of the difference in mean GFR was 7.6 mL/min (CP-690,550 15 mg BID for Months 1-6) and 7.8 mL/min (tofacitinib 15 mg BID for Months 1-3) at Month 12 post-transplant. A summary of least squares mean of measured GFR by iohexol serum clearance, and treatment comparisons at Month 12 for the Full Analysis Set, is provided in Table 7.

Table 7. Least Squares Means of Measured GFR (mL/min; Iohexol Serum Clearance) and Treatment Comparisons at Month 12 (Full Analysis Set)

Month 12	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
N	72	56	58
LSM (SE)	53.92 (2.38)	64.56 (2.69)	64.72 (2.64)
60% CI	51.92, 55.93	62.29, 66.83	62.49, 66.95
LSM difference (CP - CsA), %		10.64	10.80
60% CI for the difference		7.61, 13.67	7.80, 13.80
P-value		0.0034	0.0027

P-value was for comparison of tofacitinib with CsA. The model included treatment (discrete), time (discrete, 6 and 12 months), and treatment-by-time interaction as fixed effect and subject nested within treatment as random effect.
BID = twice daily; CI = confidence interval; CP = Tofacitinib; CsA = cyclosporine; GFR = glomerular filtration rate; LSM = least squares mean; N = number of subjects; SE = standard error.

Secondary Efficacy Endpoints

Measured Glomerular Filtration Rate by Iohexol Serum Clearance at Month 6

The differences between the CsA arm and each tofacitinib arm were statistically significant, with higher measured GFRs in the tofacitinib arms. A summary of least squares means of measured GFR, calculated by iohexol serum clearance, and treatment comparisons at Months 6 and 12 for the FAS, is provided in Table 8.

Table 8. Least Squares Means of Measured GFR (mL/min; Iohexol Serum Clearance) and Treatment Comparisons at Months 6 (FAS)

Month 6	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
N	80	64	67
LSM (SE)	57.15 (2.28)	67.39 (2.56)	73.56 (2.50)
60% CI	55.22, 59.07	65.23, 69.55	71.45, 75.67
LSM difference (CP - CsA)		10.24	16.41
60% CI for the difference		7.35, 13.13	13.55, 19.27
P-value		0.0032	0.0000

P-value was for comparison of tofacitinib with CsA. The model included treatment (discrete), time (discrete, 6 months), and treatment-by-time interaction as fixed effect and subject nested within treatment as random effect.
BID = twice daily; CP = Tofacitinib; CsA = cyclosporine; CI = confidence interval; GFR = glomerular filtration rate; LSM = least squares mean; N = number of subjects; SE = standard error.

Progression of Chronic Allograft Lesions at Month 12

The percent of subjects with any chronic allograft nephropathy (CAN) at Month 12 was 48.3% for CsA and 25.0% and 23.9% for tofacitinib 15 mg BID in Months 1-6 and Months 1-3, respectively. The distribution of the severity grades of CAN was significantly different between CsA and the tofacitinib arms, with more subjects in the CsA arm developing Grade II or III CAN. A summary of the number and percent of subjects with CAN by grades at Month 12 is provided in Table 9.

Table 9. Number and Percent of Subjects With CAN by Grades at Month 12 (FAS)

Month 12	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
N	58	52	46
Any CAN, n (%)	28 (48.28)	13 (25.00)	11 (23.91)
Grade I (mild)	15 (25.86)	10 (19.23)	6 (13.04)
Grade II (moderate)	7 (12.07)	2 (3.85)	4 (8.70)
Grade III (severe)	6 (10.34)	1 (1.92)	1 (2.17)
p-value[a]	58	0.0059	0.0111

Any CAN includes Grade I, Grade II, and Grade III of chronic allograft nephropathy.
BID = twice daily; CAN = chronic allograft nephropathy; CsA = cyclosporine; FAS = full analysis set; N/n = number of subjects.
a P-values pertain to the comparison for the ordinal variables Grade I, Grade II, and Grade III, based on Ridit Scores.

First Clinical Biopsy Proven Acute Rejection at Month 12

The first clinical BPAR rates at Month 12 post-transplant, estimated using Kaplan-Meier survival curves, were 9.0% for CsA and 11.4% and 7.1% for tofacitinib 15 mg BID for Months 1-6 and Months 1-3, respectively. The first clinical BPAR rates were comparable between each tofacitinib arm and the CsA arm at Month 12 (Table 10).

Table 10. Percent of Subjects with First Clinical BPAR estimated using Kaplan-Meier Survival Curves and Treatment Comparisons (FAS With Last Dosing Risk Set)

Month 12	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
N (n)	9 (74)	11 (55)	7 (54)
Estimated rate % (SE)	8.96 (2.86)	11.42 (3.26)	7.14 (2.62)
60% CI	6.55, 11.37	8.68, 14.16	4.94, 9.35
Estimated rate difference % (CP-CsA)		2.46	-1.82
60% CI for difference		-1.19, 6.11	-5.08, 1.45
P-value[a]		0.5701	0.6400
P-value[b]		0.5944	0.7305

Includes post-Amendment-1 subjects only.
BID = twice daily; BPAR = biopsy-proven acute rejection; CI = confidence interval; CP = tofacitinib; CsA = cyclosporine; FAS = full analysis set; N = cumulative number of events; n = number of subjects remaining at risk; SE = standard error.
a. P-value for comparing rate difference between tofacitinib and CsA using Wald test.
b. P-value for comparing survival curves between tofacitinib and CsA based on log-rank test.

Treated Clinical Acute Rejection

The treated clinical acute rejection rates at Month 12 post-transplant, estimated using Kaplan-Meier survival curves, were 24.8% for CsA and 26.9% and 18.7% for tofacitinib 15 mg BID for Months 1-6 and Months 1-3, respectively. A summary of the percent of subjects with treated clinical acute rejection at Month 6 and Month 12 estimated using Kaplan-Meier survival curves and treatment comparisons for the FAS with Last Dosing Risk Set is provided in Table 11.

Table 11. Percent of Subjects with Treated Clinical Acute Rejection Estimated Using Kaplan-Meier Survival Curves and Treatment Comparisons at Months 6 and 12 (FAS with Last-Dosing Risk Set)

	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
Month 6			
N	21	23	18
Estimated rate % (SE)	20.45 (4.00)	23.04 (4.24)	18.73 (4.01)
60% CI	17.09, 23.81	19.47, 26.61	15.36, 22.10
Estimated rate difference % (CP-CsA)		2.59	-1.72
60% CI for difference		-2.31, 7.50	6.48, 3.04
P-value[a]		0.6566	0.7612
Month 12			
N	25	26	18
Estimated rate % (SE)	24.75 (4.32)	26.89 (4.58)	18.73 (4.01)
60% CI	21.11, 28.39	23.04, 30.75	15.36, 22.10
Estimated rate difference % (CP-CsA)		2.14	-6.02
60% CI for difference		-3.15, 7.44	-10.98, -1.06
P-value[a]		0.7334	0.3070
P-value[b]		0.9069	0.3474

Endpoint was defined as AE (consisting of word of rejection) in conjunction with treatment given or withdrawn from study or other as AE action taken.
AE = Adverse event; BID = twice daily; CI = confidence interval; CP = tofacitinib; CsA = cyclosporine; FAS = full analysis set; N = cumulative number of events; SE = standard error.
a. P-value for comparing rate difference between tofacitinib and CsA using Wald test.
b. P-value for comparing survival curves between tofacitinib and CsA based on log-rank test.

Combined Banff rejection categories (antibody-mediated rejection plus Borderline changes plus acute rejection)

Summary of results for ordered categorical first BPAR (Banff Category 2 and 4) antibody-mediated rejection is presented in Table 12. The percent of subjects with antibody-treated acute rejection at Month 12 post-transplant, estimated using Kaplan-Meier survival curves, was 6.8% for CsA and 10.6% and 9.2% for tofacitinib 15 mg BID for Months 1-6 and Months 1-3, respectively. There were no statistically significant differences between CsA and either tofacitinib arm in percent of subjects with antibody-treated acute rejection.

Table 12. Ordered Categorical First BPAR (Banff Category 2 and 4) Antibody-mediated Rejection

Month 12	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
Ordered Categorical First BPAR (Banff Category 2) Antibody-mediated Rejection, n (%)			
Grade I	1 (0.9)	2 (1.9)	1 (0.9)
Grade II	4 (3.7)	0	0
Grade III	0	0	0
Ordered Categorical First BPAR (Banff Category 4) Cellular Acute Rejection, n (%)			
Grade IA	1 (0.9)	2 (1.9)	0
Grade IB	4 (3.7)	3 (2.8)	0
Grade IIA	8 (7.3)	7 (6.6)	11 (10.3)
Grade IIB	5 (4.6)	3 (2.8)	2 (1.9)
Grade III	0	1 (0.9)	0

BID=twice daily; BPAR=biopsy proven acute rejection; CsA=cyclosporine; n=number of subjects.

Graft Loss

The number (%) of subjects with graft loss (with death censored) at Month 12 estimated using Kaplan-Meier survival curves and treatment comparisons was 1 subject (0.9%) for CsA and 1 subject (0.9%) and 3 subjects (2.9%) for tofacitinib 15 mg BID in Months 1-6 and Months 1-3, respectively, for the FAS with the Last Dosing Risk Set. There were no statistically significant differences between tofacitinib and CsA treatment arms.

Table 13. Percent of Subjects with Graft Loss with Death Censored estimated using Kaplan-Meier Survival Curves and Treatment Comparisons (FAS With Last Dosing Risk Set)

Month 12	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
N (n)	1 (78)	1 (55)	3 (55)
Estimated rate % (SE)	0.92 (0.91)	0.94 (0.94)	2.94 (1.67)
60% CI	0.15, 1.69	0.15, 1.73	1.53, 4.34
Estimated rate difference % (CP-CsA)		0.03	2.02
60% CI for difference		-1.08, 1.13	0.41, 3.62
P-value[a]		0.9842	0.2899
P-value[b]		0.9816	0.2972

Includes post-Amendment-1 subjects only.
BID = twice daily; BPAR = biopsy-proven acute rejection; CI = confidence interval; CP = tofacitinib; CsA = cyclosporine; FAS = full analysis set; N = cumulative number of events; n = number of subjects remaining at risk; SE = standard error.
a. P-value for comparing rate difference between tofacitinib and CsA using Wald test.
b. P-value for comparing survival curves between tofacitinib and CsA based on log-rank test.

Subject Death

The number (%) of subjects who died by Month 12 estimated using Kaplan-Meier survival curves and treatment comparisons was 2 subjects (2.0%) for CsA and 2 subjects (2.1%) and no (0.0%) subjects for tofacitinib 15 mg BID in Months 1-6 and Months 1-3, respectively, for

the FAS with Last Dosing Risk Set. There were no statistically significant differences between tofacitinib and CsA treatment arms.

Efficacy Failure

There were no statistically significant differences between tofacitinib and CsA in the percent of subjects with efficacy failure at Months 6 or 12. A summary of the percent of subjects with efficacy failure (definition II; first occurrence of BPAR, graft loss, or subject death) estimated from Kaplan-Meier survival curves and treatment comparisons for the FAS with Last Dosing Risk Set is provided in Table 14.

Table 14. Percent of Subjects with Efficacy Failure at Months 6 and 12 Estimated Using Kaplan-Meier Survival Curves and Treatment Comparisons (FAS with Last-Dosing Risk Set)

	CsA	Tofacitinib 15 mg BID in Months 1-6	Tofacitinib 15 mg BID in Months 1-3
Month 6			
N	21	19	14
Estimated rate % (SE)	20.30 (3.97)	18.77 (3.90)	14.25 (3.56)
60% CI	16.96, 23.64	15.49, 22.05	11.25, 17.24
Estimated rate difference % (CP-CsA)		-1.54	-6.06
60% CI for difference		-6.22, 3.14	-10.54, -1.57
P-value[a]		0.7823	0.2556
Month 12			
N	22	20	16
Estimated rate % (SE)	21.34 (4.05)	20.06 (4.04)	17.23 (4.01)
60% CI	17.93, 24.75	16.65, 23.46	13.86, 20.61
Estimated rate difference % (CP-CsA)		-1.28	-4.11
60% CI for difference		-6.10, 3.53	-8.90, 0.69
P-value[a]		0.8226	0.4712
P-value[b]		0.9484	0.5710

Efficacy failure (definition II) is the first occurrence of BPAR, graft loss, or subject death.
BID = twice daily; BPAR = biopsy proven acute rejection; CI = confidence interval; CP =tofacitinib; CsA = cyclosporine; N = cumulative number of events; SE = standard error
a P-value for comparing rate difference between tofacitinib and CsA using Wald test.
b P-value for comparing survival curves between tofacitinib and CsA based on log-rank test.

Lymphocyte Subsets, and Health Outcome Assessments

There were statistically significantly lower LSM CD3+ and CD56+ cell counts at Month 6 and 12 for both CP-690,550 groups vs the CsA group. In contrast, there were statistically significantly higher LSM CD19+ cell counts at Month 12 for the CP-690,550 15 mg BID in Months 1-6 group vs the CsA group. There were no statistically significant differences in LSMs of the SF-36 v2 domains between either of the CP-690,550 groups and the CsA group at Month 6 or Month 12.

Safety Results:

Treatment-Emergent (All-Causality and Treatment-Related) Nonserious Adverse Events

Treatment-emergent nonserious AEs (all causalities and treatment-related) by system organ class (SOC) and preferred term that occurred in >5% of subjects in either treatment groups are summarized in Table 15.

Table 15. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:									
Evaluable for adverse events	109	-	-	106	-	-	107	-	-
With adverse events	102 (93.6)			102 (96.2)			105 (98.1)	-	-
Blood and lymphatic system disorders	36 (33.0)	45	9	63 (59.4)	107	48	54 (50.5)	73	29
Anaemia	26 (23.9)	30	6	46 (43.4)	63	31	38 (35.5)	48	20
Leukopenia	12 (11.0)	13	2	26 (24.5)	30	10	17 (15.9)	21	7
Neutropenia	2 (1.8)	2	1	12 (11.3)	14	7	4 (3.7)	4	2
Cardiac disorders	3 (2.8)	3	0	7 (6.6)	7	1	8 (7.5)	9	0
Tachycardia	3 (2.8)	3	0	7 (6.6)	7	1	8 (7.5)	9	0
Gastrointestinal disorders	60 (55.0)	148	12	66 (62.3)	170	25	68 (63.6)	143	14
Abdominal distension	10 (9.2)	11	1	6 (5.7)	6	0	8 (7.5)	8	0
Abdominal pain	15 (13.8)	16	1	15 (14.2)	18	1	4 (3.7)	4	1
Abdominal pain upper	6 (5.5)	6	1	6 (5.7)	7	2	2 (1.9)	2	1
Constipation	30 (27.5)	36	1	35 (33.0)	41	4	38 (35.5)	43	2
Diarrhoea	22 (20.2)	24	3	26 (24.5)	38	7	29 (27.1)	39	5
Dyspepsia	6 (5.5)	7	2	8 (7.5)	8	0	5 (4.7)	5	0
Nausea	23 (21.1)	26	2	29 (27.4)	35	10	25 (23.4)	30	5
Vomiting	18 (16.5)	22	1	15 (14.2)	17	1	12 (11.2)	12	0
General disorders and administration site conditions	48 (44.0)	75	9	48 (45.3)	82	17	43 (40.2)	71	9
Fatigue	11 (10.1)	12	0	9 (8.5)	12	5	15 (14.0)	16	4
Oedema	12 (11.0)	13	2	15 (14.2)	16	2	11 (10.3)	12	0
Oedema peripheral	30 (27.5)	38	5	25 (23.6)	30	2	19 (17.8)	21	2
Pyrexia	12 (11.0)	12	2	16 (15.1)	24	8	15 (14.0)	22	3
Immune system disorders	14 (12.8)	17	10	8 (7.5)	9	2	5 (4.7)	5	1
Transplant rejection	14 (12.8)	17	10	8 (7.5)	9	2	5 (4.7)	5	1
Infections and infestations	48 (44.0)	91	45	56 (52.8)	115	60	55 (51.4)	109	62
BK virus infection	6 (5.5)	7	5	14 (13.2)	15	14	15 (14.0)	17	15
Cytomegalovirus viraemia	12 (11.0)	14	10	21 (19.8)	24	17	18 (16.8)	24	20
Herpes zoster	3 (2.8)	3	2	5 (4.7)	5	3	6 (5.6)	8	3
Nasopharyngitis	4 (3.7)	5	3	7 (6.6)	7	5	7 (6.5)	7	3
Oral candidiasis	3 (2.8)	3	1	7 (6.6)	11	6	7 (6.5)	9	5
Upper respiratory tract infection	16 (14.7)	20	6	17 (16.0)	24	5	9 (8.4)	11	3

Table 15. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Urinary tract infection	25 (22.9)	39	18	19 (17.9)	29	10	22 (20.6)	33	13
Injury, poisoning and procedural complications	27 (24.8)	33	0	38 (35.8)	48	5	39 (36.4)	50	1
Complications of transplant surgery	3 (2.8)	3	0	2 (1.9)	3	0	6 (5.6)	7	0
Graft complication	10 (9.2)	10	0	7 (6.6)	7	0	14 (13.1)	14	0
Incision site pain	3 (2.8)	3	0	9 (8.5)	9	0	11 (10.3)	11	1
Procedural pain	14 (12.8)	15	0	21 (19.8)	21	0	15 (14.0)	16	0
Wound secretion	2 (1.8)	2	0	7 (6.6)	8	5	2 (1.9)	2	0
Investigations	25 (22.9)	28	8	22 (20.8)	30	9	25 (23.4)	31	6
Blood creatinine increased	12 (11.0)	14	6	11 (10.4)	14	5	15 (14.0)	19	6
Weight increased	14 (12.8)	14	2	15 (14.2)	16	4	12 (11.2)	12	0
Metabolism and nutrition disorders	56 (51.4)	102	30	69 (65.1)	124	33	60 (56.1)	101	21
Diabetes mellitus	6 (5.5)	6	1	5 (4.7)	6	2	4 (3.7)	4	0
Dyslipidaemia	5 (4.6)	5	4	7 (6.6)	7	3	6 (5.6)	7	3
Fluid overload	5 (4.6)	5	0	11 (10.4)	13	1	5 (4.7)	5	0
Hypercalcaemia	10 (9.2)	11	2	4 (3.8)	4	1	6 (5.6)	6	0
Hypercholesterolaemia	5 (4.6)	5	3	10 (9.4)	10	6	8 (7.5)	8	6
Hyperglycaemia	13 (11.9)	13	2	10 (9.4)	10	0	7 (6.5)	7	0
Hyperkalaemia	12 (11.0)	14	2	16 (15.1)	17	4	18 (16.8)	19	1
Hyperlipidaemia	13 (11.9)	13	8	10 (9.4)	10	6	10 (9.3)	10	5
Hypocalcaemia	4 (3.7)	4	0	12 (11.3)	15	4	4 (3.7)	6	0
Hypokalaemia	3 (2.8)	3	0	13 (12.3)	15	4	11 (10.3)	12	3
Hypomagnesaemia	8 (7.3)	10	5	2 (1.9)	3	0	6 (5.6)	6	1
Hypophosphataemia	13 (11.9)	13	3	14 (13.2)	14	2	10 (9.3)	11	2
Musculoskeletal and connective tissue disorders	12 (11.0)	20	3	25 (23.6)	33	6	21 (19.6)	32	7
Arthralgia	3 (2.8)	6	1	9 (8.5)	11	2	6 (5.6)	6	2
Back pain	4 (3.7)	5	0	7 (6.6)	7	1	11 (10.3)	12	1
Muscle spasms	5 (4.6)	5	1	5 (4.7)	6	0	8 (7.5)	9	3
Pain in extremity	4 (3.7)	4	1	9 (8.5)	9	3	5 (4.7)	5	1
Nervous system disorders	32 (29.4)	49	20	30 (28.3)	40	12	33 (30.8)	47	12
Dizziness	9 (8.3)	9	0	9 (8.5)	10	1	9 (8.4)	10	1
Headache	14 (12.8)	17	4	13 (12.3)	15	6	20 (18.7)	26	9
Hypoaesthesia	2 (1.8)	3	0	7 (6.6)	7	1	3 (2.8)	3	0

Table 15. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) in >5 % of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Tremor	19 (17.4)	20	16	8 (7.5)	8	4	8 (7.5)	8	2
Psychiatric disorders	15 (13.8)	16	4	10 (9.4)	12	3	13 (12.1)	16	4
Anxiety	3 (2.8)	3	0	5 (4.7)	5	2	6 (5.6)	6	2
Insomnia	13 (11.9)	13	4	6 (5.7)	7	1	10 (9.3)	10	2
Renal and urinary disorders	24 (22.0)	35	10	35 (33.0)	48	8	26 (24.3)	33	9
Dysuria	8 (7.3)	10	2	13 (12.3)	14	0	8 (7.5)	10	1
Haematuria	10 (9.2)	11	1	15 (14.2)	17	4	9 (8.4)	9	3
Hydronephrosis	3 (2.8)	3	1	6 (5.7)	7	0	4 (3.7)	4	0
Proteinuria	9 (8.3)	9	5	4 (3.8)	4	2	6 (5.6)	7	5
Renal tubular necrosis	2 (1.8)	2	1	6 (5.7)	6	2	3 (2.8)	3	0
Respiratory, thoracic and mediastinal disorders	18 (16.5)	20	2	24 (22.6)	30	5	16 (15.0)	18	3
Cough	7 (6.4)	7	1	16 (15.1)	16	3	7 (6.5)	8	1
Dyspnoea	7 (6.4)	7	0	11 (10.4)	13	2	8 (7.5)	9	2
Rhinorrhoea	6 (5.5)	6	1	1 (0.9)	1	0	1 (0.9)	1	0
Skin and subcutaneous tissue disorders	17 (15.6)	20	10	23 (21.7)	30	9	21 (19.6)	27	12
Acne	4 (3.7)	4	0	14 (13.2)	14	5	18 (16.8)	19	10
Hirsutism	9 (8.3)	9	9	1 (0.9)	1	0	0	0	0
Rash	7 (6.4)	7	1	12 (11.3)	15	4	6 (5.6)	8	2
Vascular disorders	33 (30.3)	39	12	36 (34.0)	49	15	34 (31.8)	39	5
Hypertension	30 (27.5)	33	12	24 (22.6)	27	11	23 (21.5)	24	4
Hypotension	6 (5.5)	6	0	18 (17.0)	22	4	13 (12.1)	15	1

Except for 'n1'and 'n2' subjects are only counted once per treatment for each row.
n The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1 The number of occurrences of treatment-emergent all causalities adverse events.
n2 The number of occurrences of treatment-emergent causally related to treatment adverse events, treatment-related.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events calculated using the corresponding gender count as denominator.
MedDRA (version 13.0) coding dictionary applied.
BID = twice daily; CsA = cyclosporine; MedDRA=Medical Dictionary for Regulatory Activities.

Treatment–Emergent (All-Causality and Treatment–Related) Serious Adverse Events (SAEs)

Treatment-emergent SAEs (all causalities and treatment-related) by SOC and preferred term in either treatment group are summarized in Table 16.

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by:	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:									
Evaluable for adverse events	109	-	-	106	-	-	107	-	-
With adverse events	65 (59.6)	-	-	76 (71.7)	-	-	74 (69.2)	-	-
Blood and lymphatic system disorders	2 (1.8)	3	0	11 (10.4)	15	8	14 (13.1)	15	11
Anaemia	2 (1.8)	3	0	5 (4.7)	5	3	8 (7.5)	8	6
Aplastic anaemia	0	0	0	0	0	0	1 (0.9)	1	1
Febrile neutropenia	0	0	0	0	0	0	1 (0.9)	1	1
Leukocytosis	0	0	0	0	0	0	1 (0.9)	1	0
Leukopenia	0	0	0	6 (5.7)	7	4	2 (1.9)	2	2
Neutropenia	0	0	0	2 (1.9)	2	1	2 (1.9)	2	1
Thrombocytopenia	0	0	0	1 (0.9)	1	0	0	0	0
Cardiac disorders	5 (4.6)	7	0	5 (4.7)	6	0	6 (5.6)	7	1
Angina pectoris	0	0	0	0	0	0	1 (0.9)	1	0
Angina unstable	1 (0.9)	1	0	0	0	0	0	0	0
Arrhythmia	0	0	0	1 (0.9)	1	0	0	0	0
Arrhythmia supraventricular	1 (0.9)	1	0	0	0	0	0	0	0
Atrial fibrillation	1 (0.9)	2	0	2 (1.9)	2	0	0	0	0
Atrial flutter	0	0	0	0	0	0	1 (0.9)	1	1
Bradycardia	1 (0.9)	1	0	0	0	0	0	0	0
Cardiac arrest	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Cardiac failure congestive	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Electromechanical dissociation	0	0	0	0	0	0	1 (0.9)	1	0
Left ventricular hypertrophy	0	0	0	0	0	0	1 (0.9)	1	0
Myocardial infarction	0	0	0	1 (0.9)	1	0	2 (1.9)	2	0
Tachycardia	0	0	0	0	0	0	1 (0.9)	1	0
Congenital, familial and genetic disorders	0	0	0	0	0	0	1 (0.9)	1	0
Congenital cystic kidney disease	0	0	0	0	0	0	1 (0.9)	1	0
Endocrine disorders	1 (0.9)	1	0	0	0	0	0	0	0
Adrenal mass	1 (0.9)	1	0	0	0	0	0	0	0
Eye disorders	0	0	0	1 (0.9)	1	0	0	0	0
Blindness cortical	0	0	0	1 (0.9)	1	0	0	0	0
Gastrointestinal disorders	10 (9.2)	15	0	15 (14.2)	20	4	9 (8.4)	10	2

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Abdominal distension	1 (0.9)	1	0	0	0	0	0	0	0
Abdominal pain	2 (1.8)	2	0	3 (2.8)	3	1	2 (1.9)	2	0
Abdominal pain upper	1 (0.9)	1	0	0	0	0	0	0	0
Ascites	0	0	0	0	0	0	1 (0.9)	1	0
Colitis	0	0	0	1 (0.9)	1	1	0	0	0
Colitis ischaemic	1 (0.9)	1	0	0	0	0	0	0	0
Constipation	0	0	0	2 (1.9)	2	0	0	0	0
Diarrhoea	0	0	0	4 (3.8)	4	1	1 (0.9)	1	1
Diarrhoea haemorrhagic	0	0	0	1 (0.9)	1	0	0	0	0
Diverticulum intestinal haemorrhagic	0	0	0	1 (0.9)	1	0	0	0	0
Gastritis	0	0	0	0	0	0	1 (0.9)	1	1
Haemorrhoidal haemorrhage	0	0	0	1 (0.9)	1	0	0	0	0
Ileus	0	0	0	1 (0.9)	1	0	0	0	0
Inguinal hernia	1 (0.9)	1	0	0	0	0	0	0	0
Intestinal perforation	1 (0.9)	1	0	0	0	0	0	0	0
Large intestine perforation	0	0	0	1 (0.9)	1	0	0	0	0
Nausea	2 (1.8)	2	0	0	0	0	2 (1.9)	2	0
Pancreatitis necrotising	1 (0.9)	1	0	0	0	0	0	0	0
Peritonitis	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Rectal haemorrhage	0	0	0	1 (0.9)	1	0	0	0	0
Reflux oesophagitis	0	0	0	1 (0.9)	1	0	0	0	0
Retroperitoneal haematoma	0	0	0	0	0	0	1 (0.9)	1	0
Small intestinal obstruction	1 (0.9)	1	0	0	0	0	1 (0.9)	1	0
Vomiting	3 (2.8)	3	0	2 (1.9)	2	1	1 (0.9)	1	0
General disorders and administration site conditions	3 (2.8)	4	1	8 (7.5)	11	7	4 (3.7)	5	3
Brain death	0	0	0	2 (1.9)	2	1	0	0	0
Chills	1 (0.9)	1	0	0	0	0	0	0	0
Condition aggravated	0	0	0	1 (0.9)	1	1	0	0	0
Drug interaction	0	0	0	1 (0.9)	1	1	1 (0.9)	1	1
Hernia	0	0	0	1 (0.9)	1	1	0	0	0
Multi-organ failure	1 (0.9)	1	0	0	0	0	0	0	0

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by:	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Oedema peripheral	0	0	0	1 (0.9)	1	0	0	0	0
Pyrexia	2 (1.8)	2	1	5 (4.7)	5	3	4 (3.7)	4	2
Hepatobiliary disorders	1 (0.9)	1	0	0	0	0	0	0	0
Hepatic function abnormal	1 (0.9)	1	0	0	0	0	0	0	0
Immune system disorders	17 (15.6)	21	14	19 (17.9)	21	17	15 (14.0)	15	13
Kidney transplant rejection	8 (7.3)	9	5	5 (4.7)	6	6	5 (4.7)	5	4
Serum sickness	0	0	0	1 (0.9)	1	0	0	0	0
Transplant rejection	9 (8.3)	12	9	14 (13.2)	14	11	10 (9.3)	10	9
Infections and infestations	24 (22.0)	43	18	39 (36.8)	78	51	35 (32.7)	58	27
Abdominal abscess	0	0	0	0	0	0	1 (0.9)	1	1
Acute sinusitis	0	0	0	0	0	0	1 (0.9)	1	0
Appendicitis	1 (0.9)	1	0	0	0	0	0	0	0
Arteriovenous fistula site infection	0	0	0	1 (0.9)	1	1	0	0	0
BK virus infection	0	0	0	1 (0.9)	1	1	4 (3.7)	4	3
Bacteraemia	3 (2.8)	3	2	0	0	0	1 (0.9)	1	0
Bacterial pyelonephritis	0	0	0	1 (0.9)	1	1	0	0	0
Bacterial sepsis	0	0	0	0	0	0	1 (0.9)	1	0
Bacteriuria	1 (0.9)	1	1	0	0	0	0	0	0
Bronchitis	0	0	0	0	0	0	1 (0.9)	1	0
Bronchopulmonary aspergillosis	0	0	0	1 (0.9)	1	1	1 (0.9)	1	1
Cellulitis	0	0	0	1 (0.9)	1	0	0	0	0
Cystitis	0	0	0	0	0	0	1 (0.9)	1	1
Cytomegalovirus colitis	0	0	0	1 (0.9)	1	1	1 (0.9)	1	1
Cytomegalovirus gastroenteritis	0	0	0	0	0	0	1 (0.9)	1	0
Cytomegalovirus infection	2 (1.8)	3	0	10 (9.4)	13	9	7 (6.5)	8	4
Cytomegalovirus oesophagitis	0	0	0	1 (0.9)	1	1	0	0	0
Cytomegalovirus viraemia	1 (0.9)	2	1	10 (9.4)	13	10	1 (0.9)	1	1
Diarrhoea infectious	0	0	0	1 (0.9)	1	1	0	0	0
Diverticulitis	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Enterococcal bacteraemia	0	0	0	0	0	0	1 (0.9)	1	0
Escherichia urinary tract infection	1 (0.9)	1	1	0	0	0	0	0	0
Gangrene	0	0	0	1 (0.9)	3	0	0	0	0

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Gastroenteritis	0	0	0	1 (0.9)	1	1	2 (1.9)	2	1
Gastroenteritis viral	0	0	0	0	0	0	1 (0.9)	1	1
Genital herpes	0	0	0	0	0	0	1 (0.9)	1	1
Haematoma infection	1 (0.9)	1	0	0	0	0	0	0	0
Herpes ophthalmic	1 (0.9)	1	0	0	0	0	0	0	0
Herpes virus infection	0	0	0	1 (0.9)	1	1	1 (0.9)	1	1
Herpes zoster	1 (0.9)	1	0	3 (2.8)	3	2	1 (0.9)	2	2
Incision site infection	0	0	0	1 (0.9)	1	0	0	0	0
Influenza	0	0	0	0	0	0	1 (0.9)	1	1
Keratitis herpetic	1 (0.9)	1	0	0	0	0	0	0	0
Klebsiella bacteraemia	0	0	0	1 (0.9)	1	1	0	0	0
Klebsiella sepsis	0	0	0	1 (0.9)	1	1	0	0	0
Localised infection	0	0	0	1 (0.9)	1	1	0	0	0
Lung infection	0	0	0	1 (0.9)	1	0	1 (0.9)	1	0
Oral herpes	0	0	0	1 (0.9)	1	0	0	0	0
Osteomyelitis	0	0	0	1 (0.9)	1	0	1 (0.9)	1	1
Perinephric abscess	1 (0.9)	1	1	0	0	0	0	0	0
Peritoneal infection	0	0	0	1 (0.9)	1	0	0	0	0
Pneumocystis jiroveci pneumonia	0	0	0	1 (0.9)	1	1	0	0	0
Pneumonia	4 (3.7)	4	1	2 (1.9)	2	1	1 (0.9)	1	0
Pneumonia respiratory syncytial viral	0	0	0	0	0	0	1 (0.9)	1	1
Polyomavirus-associated nephropathy	0	0	0	0	0	0	2 (1.9)	2	2
Postoperative wound infection	0	0	0	0	0	0	1 (0.9)	1	0
Prostatic abscess	0	0	0	0	0	0	1 (0.9)	1	1
Pseudomonas infection	0	0	0	0	0	0	1 (0.9)	1	0
Pyelonephritis	2 (1.8)	2	1	2 (1.9)	2	0	1 (0.9)	1	0
Pyelonephritis acute	1 (0.9)	1	0	0	0	0	1 (0.9)	1	0
Retinitis viral	0	0	0	1 (0.9)	1	1	1 (0.9)	1	1
Sepsis	1 (0.9)	1	0	3 (2.8)	3	2	2 (1.9)	2	1
Septic shock	1 (0.9)	1	0	2 (1.9)	2	2	1 (0.9)	1	0
Staphylococcal bacteraemia	0	0	0	0	0	0	1 (0.9)	1	1
Tuberculosis	1 (0.9)	1	1	0	0	0	0	0	0

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Tuberculosis gastrointestinal	0	0	0	0	0	0	1 (0.9)	1	0
Upper respiratory tract infection	1 (0.9)	1	1	1 (0.9)	1	0	0	0	0
Urinary tract infection	6 (5.5)	9	7	11 (10.4)	12	8	5 (4.7)	8	0
Urinary tract infection bacterial	1 (0.9)	1	0	0	0	0	0	0	0
Urinary tract infection enterococcal	1 (0.9)	1	0	0	0	0	0	0	0
Urinary tract infection fungal	0	0	0	1 (0.9)	1	1	0	0	0
Urosepsis	1 (0.9)	3	0	0	0	0	0	0	0
Viral infection	1 (0.9)	1	1	0	0	0	0	0	0
Wound infection	0	0	0	2 (1.9)	2	2	2 (1.9)	2	0
Injury, poisoning and procedural complications	14 (12.8)	16	2	15 (14.2)	18	4	10 (9.3)	17	2
Abdominal wound dehiscence	0	0	0	1 (0.9)	1	0	0	0	0
Anaemia postoperative	1 (0.9)	1	0	0	0	0	0	0	0
Ankle fracture	0	0	0	1 (0.9)	1	0	1 (0.9)	1	0
Arteriovenous fistula thrombosis	1 (0.9)	1	0	0	0	0	0	0	0
Chronic allograft nephropathy	1 (0.9)	1	1	0	0	0	0	0	0
Complications of transplanted kidney	0	0	0	1 (0.9)	1	0	0	0	0
Compression fracture	0	0	0	1 (0.9)	1	0	0	0	0
Femoral neck fracture	1 (0.9)	1	0	0	0	0	0	0	0
Graft complication	0	0	0	6 (5.7)	6	3	5 (4.7)	5	0
Graft dysfunction	3 (2.8)	3	1	2 (1.9)	2	0	0	0	0
Graft loss	1 (0.9)	1	0	0	0	0	0	0	0
Graft thrombosis	0	0	0	1 (0.9)	1	0	0	0	0
Overdose	0	0	0	0	0	0	1 (0.9)	3	0
Patella fracture	0	0	0	1 (0.9)	1	0	0	0	0
Perirenal haematoma	0	0	0	0	0	0	1 (0.9)	1	0
Post procedural discharge	1 (0.9)	1	0	0	0	0	0	0	0
Post procedural haematoma	0	0	0	0	0	0	1 (0.9)	1	0
Post procedural haematuria	1 (0.9)	1	0	0	0	0	0	0	0
Post procedural haemorrhage	2 (1.8)	2	0	0	0	0	0	0	0
Postoperative wound complication	0	0	0	1 (0.9)	1	0	0	0	0
Renal graft loss	0	0	0	1 (0.9)	1	0	0	0	0
Renal lymphocele	0	0	0	0	0	0	1 (0.9)	1	1

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by:	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Subdural haemorrhage	1 (0.9)	1	0	0	0	0	0	0	0
Urethral injury	1 (0.9)	1	0	0	0	0	0	0	0
Vascular pseudoaneurysm	0	0	0	1 (0.9)	1	0	0	0	0
Wound dehiscence	2 (1.8)	2	0	1 (0.9)	1	1	4 (3.7)	4	1
Wound secretion	0	0	0	0	0	0	1 (0.9)	1	0
Investigations	9 (8.3)	15	9	12 (11.3)	13	5	7 (6.5)	7	2
Blood creatine increased	0	0	0	1 (0.9)	1	0	0	0	0
Blood creatinine increased	9 (8.3)	12	7	7 (6.6)	7	3	6 (5.6)	6	2
Blood pressure increased	0	0	0	1 (0.9)	1	0	0	0	0
Blood urea increased	1 (0.9)	2	2	0	0	0	0	0	0
Electroencephalogram abnormal	0	0	0	1 (0.9)	1	1	0	0	0
Hepatic enzyme increased	0	0	0	1 (0.9)	1	1	0	0	0
Liver function test abnormal	0	0	0	1 (0.9)	1	0	0	0	0
Transaminases increased	0	0	0	0	0	0	1 (0.9)	1	0
Troponin I increased	0	0	0	1 (0.9)	1	0	0	0	0
White blood cell count increased	1 (0.9)	1	0	0	0	0	0	0	0
Metabolism and nutrition disorders	6 (5.5)	8	2	5 (4.7)	5	0	6 (5.6)	8	4
Dehydration	0	0	0	1 (0.9)	1	0	2 (1.9)	2	0
Diabetic ketoacidosis	2 (1.8)	2	0	0	0	0	0	0	0
Fluid overload	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Hypercreatininaemia	1 (0.9)	1	1	0	0	0	1 (0.9)	2	2
Hyperkalaemia	3 (2.8)	3	1	2 (1.9)	2	0	2 (1.9)	2	2
Hypocalcaemia	0	0	0	0	0	0	1 (0.9)	2	0
Hypoglycaemia	0	0	0	1 (0.9)	1	0	0	0	0
Type 2 diabetes mellitus	1 (0.9)	1	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	2 (1.8)	2	0	8 (7.5)	8	5	1 (0.9)	2	0
Arthralgia	1 (0.9)	1	0	0	0	0	0	0	0
Back pain	0	0	0	2 (1.9)	2	1	1 (0.9)	1	0
Muscular weakness	0	0	0	1 (0.9)	1	0	0	0	0
Myopathy	0	0	0	2 (1.9)	2	2	0	0	0
Myositis	0	0	0	0	0	0	1 (0.9)	1	0

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Osteonecrosis	0	0	0	1 (0.9)	1	0	0	0	0
Pain in extremity	0	0	0	1 (0.9)	1	1	0	0	0
Rhabdomyolysis	0	0	0	1 (0.9)	1	1	0	0	0
Spinal column stenosis	1 (0.9)	1	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	5 (4.7)	6	4	1 (0.9)	1	1
Epstein-Barr virus associated lymphoproliferative disorder	0		0	1 (0.9)	1	1	0	0	0
Hodgkin's disease	0		0	0	0	0	1 (0.9)	1	1
Non-Hodgkin's lymphoma	0		0	1 (0.9)	1	1	0	0	0
Prostate cancer	0		0	1 (0.9)	1	0	0	0	0
Prostate cancer metastatic	0		0	1 (0.9)	2	2	0	0	0
Renal cell carcinoma	0		0	1 (0.9)	1	0	0	0	0
Nervous system disorders	4 (3.7)	4	0	5 (4.7)	9	4	4 (3.7)	4	1
Areflexia	0	0	0	1 (0.9)	1	1	0	0	0
Brain oedema	0	0	0	1 (0.9)	2	2	0	0	0
Cerebral infarction	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Cerebrovascular accident	2 (1.8)	2	0	0	0	0	1 (0.9)	1	0
Dizziness	0	0	0	0	0	0	1 (0.9)	1	0
Embolic stroke	0	0	0	1 (0.9)	1	0	0	0	0
Encephalopathy	0	0	0	1 (0.9)	1	0	0	0	0
Headache	0	0	0	0	0	0	1 (0.9)	1	1
Intracranial pressure increased	0	0	0	1 (0.9)	1	1	0	0	0
Loss of consciousness	0	0	0	0	0	0	1 (0.9)	1	0
Sciatica	1 (0.9)	1	0	0	0	0	0	0	0
Transient ischaemic attack	0	0	0	2 (1.9)	2	0	0	0	0
Renal and urinary disorders	16 (14.7)	20	1	16 (15.1)	19	2	13 (12.1)	13	2
Bladder irritation	1 (0.9)	1	0	0	0	0	0	0	0
Bladder spasm	1 (0.9)	1	0	0	0	0	0	0	0
Haematuria	1 (0.9)	1	0	2 (1.9)	2	0	3 (2.8)	3	0
Haemorrhage urinary tract	0	0	0	0	0	0	1 (0.9)	1	0
Hydronephrosis	2 (1.8)	2	0	1 (0.9)	1	0	0	0	0

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Nephropathy toxic	1 (0.9)	1	1	0	0	0	1 (0.9)	1	1
Polyuria	0	0	0	1 (0.9)	1	1	0	0	0
Renal artery occlusion	0	0	0	0	0	0	1 (0.9)	1	0
Renal artery stenosis	2 (1.8)	3	0	0	0	0	0	0	0
Renal cyst	0	0	0	1 (0.9)	1	0	0	0	0
Renal failure	1 (0.9)	1	0	0	0	0	0	0	0
Renal failure acute	2 (1.8)	3	0	5 (4.7)	5	0	0	0	0
Renal impairment	1 (0.9)	1	0	1 (0.9)	1	1	0	0	0
Renal tubular necrosis	1 (0.9)	1	0	1 (0.9)	1	0	2 (1.9)	2	0
Renal vein thrombosis	0	0	0	0	0	0	1 (0.9)	1	1
Ureteric obstruction	1 (0.9)	1	0	0	0	0	1 (0.9)	1	0
Urethral stenosis	0	0	0	1 (0.9)	1	0	0	0	0
Urinary fistula	1 (0.9)	1	0	0	0	0	2 (1.9)	2	0
Urinary incontinence	1 (0.9)	1	0	2 (1.9)	2	0	0	0	0
Urinary retention	2 (1.8)	2	0	3 (2.8)	3	0	1 (0.9)	1	0
Urinary tract obstruction	0	0	0	1 (0.9)	1	0	0	0	0
Reproductive system and breast disorders	1 (0.9)	2	2	0	0	0	0	0	0
Epididymitis	1 (0.9)	2	2	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	5 (4.6)	5	0	5 (4.7)	6	0	4 (3.7)	4	1
Acute respiratory distress syndrome	0	0	0	1 (0.9)	1	0	0	0	0
Acute respiratory failure	0	0	0	1 (0.9)	1	0	0	0	0
Dyspnoea	0	0	0	0	0	0	1 (0.9)	1	0
Hypoxia	0	0	0	1 (0.9)	1	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0	1 (0.9)	1	1
Pleural effusion	1 (0.9)	1	0	0	0	0	0	0	0
Pneumonia aspiration	0	0	0	1 (0.9)	1	0	0	0	0
Pulmonary embolism	1 (0.9)	1	0	1 (0.9)	1	0	1 (0.9)	1	0
Pulmonary oedema	0	0	0	0	0	0	1 (0.9)	1	0
Respiratory failure	2 (1.8)	2	0	1 (0.9)	1	0	0	0	0
Sleep apnoea syndrome	1 (0.9)	1	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Decubitus ulcer	1 (0.9)	1	0	0	0	0	0	0	0

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	CsA			Tofacitinib 15 mg BID in Months 1-6			Tofacitinib 15 mg BID in Months 1-3		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Skin ulcer	0	0	0	1 (0.9)	1	0	0	0	0
Surgical and medical procedures	1 (0.9)	1	0	0	0	0	0	0	0
Bladder catheter removal	1 (0.9)	1	0	0	0	0	0	0	0
Vascular disorders	6 (5.5)	6	1	9 (8.5)	10	0	9 (8.4)	9	1
Arterial haemorrhage	0	0	0	0	0	0	1 (0.9)	1	0
Deep vein thrombosis	0	0	0	3 (2.8)	3	0	1 (0.9)	1	0
Haematoma	0	0	0	1 (0.9)	1	0	1 (0.9)	1	0
Haemorrhage	0	0	0	0	0	0	1 (0.9)	1	0
Hypertension	2 (1.8)	2	0	1 (0.9)	1	0	0	0	0
Hypotension	1 (0.9)	1	0	1 (0.9)	1	0	0	0	0
Ischaemia	0	0	0	1 (0.9)	1	0	0	0	0
Lymphocele	1 (0.9)	1	0	2 (1.9)	2	0	3 (2.8)	3	1
Malignant hypertension	1 (0.9)	1	1	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	0	0	0	1 (0.9)	1	0
Superior vena caval occlusion	0	0	0	0	0	0	1 (0.9)	1	0
Thrombosis	1 (0.9)	1	0	0	0	0	0	0	0
Vascular insufficiency	0	0	0	1 (0.9)	1	0	0	0	0

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
n The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1 The number of occurrences of treatment-emergent all causalities adverse events.
n2 The number of occurrences of treatment-emergent causally related to treatment adverse events, treatment-related.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events calculated using the corresponding gender count as denominator.
MedDRA (version 13.0) coding dictionary applied.
BID=twice daily; CsA=cyclosporine; MedDRA=Medical Dictionary for Regulatory Activities.

There were a total of 9 deaths reported to the study database (3 from each group). Three of these deaths occurred while the subject was receiving trial medications (2 CsA, 1 tofacitinib 15 mg BID in Months 1-6) (Table 17). A total of 22 (20.2%) CsA, 39 (36.8%) tofacitinib 15 mg BID in Months 1-6, and 41 (38.3%) tofacitinib 15 mg BID in Months 1-3 subjects permanently discontinued the study due to an AE. The most frequently reported reasons for permanent discontinuation were transplant rejection (26 subjects), and kidney transplant rejection (12 subjects). Fourteen (13.1%) tofacitinib 15 mg BID in Months 1-3 subjects had a dose reduction or temporary discontinuation of study medication due to an AE. The most frequently reported reasons for dose reductions or temporary discontinuations due to AEs were BK virus infection (9 subjects), blood creatinine increased (6 subjects), and anemia and urinary tract infection (4 subjects each).

Table 17. Summary of Deaths (All Causalities)

Serial No.	Sex/Age	Treatment Group	MedDRA (v13.0) Preferred Term Cause of Death	Day of Death	Day of Death After Last Dose of Trial Medication
1	Male/51	CsA	Cardiac arrest	14	NA
2	Male/69	CsA	Pneumonia	98	NA
3	Male/62	CsA	Multiorgan failure Pancreatitis necrotizing	67	26
4	Male/64	Tofacitinib 15 mg BID in Months 1-6	Brain death Cardiac arrest Sepsis Pneumonia Septic shock	98	3
5	Male/34	Tofacitinib 15 mg BID in Months 1-6	Scrotal hematocele Inflammation Brain death Rhabdomyolysis Renal failure chronic Peritonitis	10	NA
6	Male/68	Tofacitinib 15 mg BID in Months 1-6	Bronchopulmonary aspergillosis Cerebral infarction Pneumonia aspiration Cardiac arrest	172	82
7	Male/61	Tofacitinib 15 mg BID in Months 1-3	Cardiac arrest Electromechanical dissociation	100	52
8	Male/55	Tofacitinib 15 mg BID in Months 1-3	Bronchopulmonary aspergillosis	360	17
9	Male/54	CP-690,550 15 mg BID in Months 1-3	Hodgkin's disease	508	167

Day of death was calculated as death date minus first active therapy date + 1.
BID=twice daily; CsA=cyclosporine; NA=not applicable, death occurred during treatment with study medication; MedDRA=Medical Dictionary for Regulatory Activities; v=version.

CONCLUSIONS:

- The primary objectives of the study were met with demonstration of the following in each of the tofacitinib groups compared with the CsA control group:
    - Non-inferiority in the incidence of 6-month clinical BPAR (and 6- and 12-month BPAR) rate, and
    - Statistically significantly higher measured GFR at Month 12.
- In addition, compared with the CsA control group, there was a lower incidence of CAN and progression of chronic allograft lesions, and a trend toward lower incidence of new-onset diabetes after transplant in each of the tofacitinib groups.
- There were more discontinuations in the tofacitinib groups.
- There was more serious infections, opportunistic viral infections, and post-transplant lymphoproliferative disease in the tofacitinib groups.
- There were higher incidence rates of anemia and leukopenia in the tofacitinib groups.