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

PROTOCOL NO.: A3921053

PROTOCOL TITLE:

An Observational Study to Collect Follow-Up Clinical Data From Kidney Transplant Recipients Who Received Tofacitinib (CP-690,550) in Completed Phase 2 Studies

Study Centers:

A total of 39 centers took part in the study, including 19 centers in the United States; 5 centers in Australia; 3 centers in France; 2 centers each in Brazil, Germany, and Spain; 1 center each in Belgium, Canada, Czech Republic, Italy, the Netherlands, and Norway.

Study Initiation Date and Final Completion Date:

30 August 2011 and 04 July 2012

Phase of Development:

Phase 2

Study Objective:

To evaluate the clinical outcomes of eligible subjects through 12 months after discontinuation of tofacitinib.

METHODS

Study Design:

This was an observational study. No study treatments were administered. Subjects randomized to tofacitinib in completed Study A3921009 (A 6-Month, Phase 2, Multicenter, Randomized, Open-Label, Comparative Study of 2 Dose Levels of CP-690,550 Administered Concomitantly With Interleukin-2 Receptor Antagonist Induction Therapy, Mycophenolate Mofetil and Corticosteroids Versus a Tacrolimus-Based Immunosuppressive Regimen for the Prevention of Allograft Rejection in De Novo Renal Allograft Recipients) or Study A3921030 (A Phase 2 Randomized, Multicenter, Active Comparator Controlled Trial to Evaluate the Safety and Efficacy of Co-Administration of CP-690,550 and Mycophenolate Mofetil/Mycophenolate Sodium in De Novo Kidney Allograft Recipients), but discontinued tofacitinib prior to the end of the planned treatment duration, or subjects who did not enroll in long-term extension studies after completing tofacitinib treatment, were eligible to participate in this follow-up study. For subjects who consented, data on the occurrence of specific adverse events (AEs; post-transplant lymphoproliferative disease [PTLD], central

nervous system [CNS] infection, graft failure, and death), were collected through 12 months after the last tofacitinib dose. If the specified AEs occurred within 12 months after the last tofacitinib dose, relevant source documents (eg, the hospital's or the Physician's subject chart) were obtained.

Number of Subjects (Planned and Analyzed):

The planned study population was to include all subjects who had discontinued tofacitinib prior to the planned treatment duration of Study A3921009 (6 months post-transplant) or Study A3921030 (12 months post-transplant), or who did not enroll in extended previous studies. A total of 100 subjects were evaluated, and 83 subjects completed the study and were analyzed.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male and female subjects ranging in age from 18 to 70 years who had discontinued tofacitinib prior to the planned treatment duration of Study A3921009 (6 months post-transplant) or Study A3921030 (12 months post-transplant), or who did not enroll in extension studies were eligible to particpate.

Main Exclusion Criteria: Data not available.

Study Treatment:

No study drug was given in this follow-up evaluation.

Efficacy Endpoints:

No efficacy evaluations were performed.

Safety Evaluations:

The outcome measures collected for this study were limited to PTLD, CNS infection, graft failure, or death occurring within 12 months after the last tofacitinib dose. If any of these events were reported for an eligible subject, additional relevant data were collected. If any of the AEs described below met a criterion for a serious adverse event (SAE) and was deemed to have a causal relationship to tofacitinib, the event was to have been reported as an SAE.

Statistical Methods:

The safety analysis set included all eligible subjects who provided their consent for this study.

Only descriptive statistics were reported including the proportion of the occurrence of PTLD, CNS infection, graft failure, and vital status (ie, alive or dead) within 12 months after the last tofacitinib dose.

A summary table for the safety endpoints was generated. The Clopper-Pearson 2-sided 95% confidence intervals were reported also for descriptive purposes.

RESULTS

Subjects Disposition and Demography:

A total of 100 subjects were eligible to participate in this follow-up evaluation. Of these 100 subjects, 10 could not be contacted. Of these 10 who could not be contacted, the study sites were able to confirm that 5 of the subjects were alive; the status of the remaining 5 could not be confirmed (unknown). Of the 90 subjects who were contacted, 7 did not provide consent. Therefore, a total of 83 subjects were evaluated for follow-up.

A summary of evaluated subjects is presented in Table 1.

Table 1. Summary of Subjects Evaluated

	Total	Tofacitinib					
		Study A3921030				Study A3921009	
		Pre-Amend 1 10 mg BID	Pre-Amend 1 15 mg BID	15 mg BID Months 1-6	15 mg BID Months 1-3	15 mg BID	30 mg BID
Number of eligible subjects at sites that participated	100	2	1	47	40	6	4
Number of subjects consented	83	1	1	40	33	5	3
Number of subjects who refused	7	1	0	2	4	0	0
Number of subjects unable to contact	10	0	0	5	3	1	1
Alive (as reported by site)	5	0	0	2	1	1	1
Unknown	5	0	0	3	2	0	0

BID = twice daily; Pre-amend = pre-amendment.

Efficacy Results:

No efficacy evaluations were performed.

Safety Results:

Of the 83 subjects who were contacted and provided consent, no subjects had PTLD, and no subjects had any type of CNS infection (Table 2). Among the 17 subjects who either refused participation or could not be contacted, no PTLD, CNS infection, graft loss, or death had been reported by the study sites to the safety database of any of the tofacitinib transplant studies.

A total of 5 subjects had reported graft failure, including 1 subject whose graft failure had already been reported in Study A3921030. Of the remaining 4 subjects who reported graft

failure in the current study, all were from Study A3921030: Two (2) subjects treated with tofacitinib 15 mg BID in Months 1 to 6, and 2 subjects treated with tofacitinib 15 mg BID in Months 1 to 3. Of the 5 reported cases of graft failure, 4 were considered unrelated to tofacitinib.

A summary of subjects with graft failure is presented in Table 2.

Table 2. Summary of Subjects With Graft Failure

	Total (N=83)	Number (Clopper-Pearson 2-sided 95% Confidence Interval)					
		Study A3921030				Study A3921009	
		Pre-Amend 1 10 mg BID (N=1)	Pre-Amend 1 15 mg BID (N=1)	15 mg BID Months 1-6 (N=40)	15 mg BID Months 1-3 (N=33)	15 mg BID (N=5)	30 mg BID (N=3)
Graft failure	5 (0.02,0.14)	0 (0.00,0.98)	0 (0.00,0.98)	2 (0.01,0.17)	3 (0.02,0.24)	0 (0.00,0.52)	0 (0.00,0.71)

No deaths, CNS infections or PTLD were reported.
BID = twice daily; CNS = central nervous system; Pre-amend = pre-amendment; PTLD = post-transplant lymphoproliferative disease.

Serious Adverse Events: Data not available.

Adverse Events: Data not available

Discontinuations due to Adverse Events: Data not available.

Deaths: No deaths were reported during the study.

CONCLUSIONS:

Among 83 subjects who prematurely discontinued tofacitinib in prior Phase 2 studies and consented to participate in the current study, no cases of PTLD or CNS infections have been reported. Among the 17 subjects who did not participate in this follow up, no cases of PTLD, CNS infection, graft failure, or death have been reported in the safety databases. In addition, none of the 4 new reported cases of graft failure were considered by the Investigator to be related to tofacitinib. Therefore, the results of this follow-up study indicate that there were no additional safety concerns related to PTLD or CNS infection after tofacitinib discontinuation.