AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Tofacitinib citrate

Proprietary Product Name: Xeljanz

Sponsor: Pfizer Australia Pty Ltd

Date of CER
First round: 10 September 2012
Second round: 30 December 2012

About the Therapeutic Goods Administration (TGA)

· The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.

· The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

· To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

· This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.

· The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.

· For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 3 of 72

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 4 of 72

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	20% improvement in disease activity
ACR50	50% improvement in disease activity
ACR70	70% improvement in disease activity
ACR90	90% improvement in disease activity
ACRn	absolute value of the ACR score
AE	Amount of drug eliminated in urine
AE24	Cumulative amount of drug recovered unchanged in the urine up to 24 hours postdose
AE24%	Percentage of the cumulative amount of drug recovered unchanged in the urine up to 24 hours postdose
AE	adverse event
AHD	amount of CP-690,550 in dialysate collected within the collection period
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time profile
AUC0-inf	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC0-last	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC0-tau	Area under the concentration-time curve from zero to interval (tau)
bd	twice daily
BID	twice daily
BMI	body mass index
BOCF	Baseline observation carried forward

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 5 of 72

Abbreviation	Meaning
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
Clast	last quantifiable concentration
CL/F	apparent clearance
CLHD	dialyzer clearance: CLHD=AHD/(fu • Cmid • t)
CLR	renal clearance
Cmax	maximum plasma concentration
Cmid	the corresponding mid-time CP-690,550 plasma concentration
CP-690,550	tofacitinib
CRCL	creatinine clearance
CRP	C-reactive protein
CV	coefficient of variation
CXR	chest X-ray
CYP	cytochrome P450
D	duration of absorption (in association with a zero order absorption model)
DAE	adverse event leading to discontinuation
DAS	disease activity score
DAS28-3(CRP)	disease activity score using C-reactive protein
DAS28-4(ESR)	disease activity score erythrocyte sedimentation rate
DBP	diastolic blood pressure
DMARD	disease modifying anti-rheumatic drugs
DNA	deoxyribose nucleic acid
E	dialyser efficiency
EBV	Epstein Barr Virus

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 6 of 72

Abbreviation	Meaning
ECG	electrocardiogram
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
EQ-5D	EuroQol EQ-5D health state profile
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	fluorescence activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FID	formulation identification
FSH	follicle-stimulating hormone
fu	fraction unbound
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCRU	Rheumatoid Arthritis Healthcare Resource Utilization Questionnaire
HDLc	high density lipoprotein cholesterol
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPF	high-powered field
HPLC-MS/MS	high-performance liquid chromatography tandem mass spectrometry
HR	hour(s)

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 7 of 72

Abbreviation	Meaning
ICH	international conference on harmonization
IL	interleukin
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
kel	terminal phase rate constant
LDLc	low density lipoprotein cholesterol
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mPASI	modified psoriasis area and severity index
mTSS	modified Total Sharp Score
MTX	methotrexate
OPC	oral powder for constitution
PD	Pharmacodynamic
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PR	pulse rate (vital signs)
Qb	blood flow entering the dialyzer
OC	oral contraceptive
QFT-G	QuantiFERON® – TB Gold In-Tube Test
QT	QT interval of the ECG
QTc	Corrected QT interval
QTcB	QTc (Bazett's correction)
QTcF	QTc (Fridericia's correction)
QTcP	QTc (Population correction)

Abbreviation	Meaning
RA	Rheumatoid Arthritis
RBC	red blood cell
RE	relative error
RF	Rheumatoid Factor
SAE	serious adverse event
SCID	severe combined immunodeficiency disorder
SD	single dose or standard deviation, as applicable
SE	standard error
SBP	systolic blood pressure
TB	tuberculosis
TEAE	treatment emergent adverse event
t1/2	terminal half-life
Tmax	time for Cmax
T/R	test compared to reference
UGT	uridine glucuronosyl transferase
ULN	upper limit of normal
URTI	upper respiratory tract infection
V/F	apparent volume of distribution
Vss	volume of distribution in steady state
WBC	white blood cell
WCC	White cell count
WLQ	Work Limitations Questionnaire

1. Introduction

This is a Category1 submission to register a New Chemical Entity: tofacitinib citrate (JAQINUS / XELJANZ) 5 mg and 10 mg tablets.

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 9 of 72

Tofacitinib is an immunomodulatory agent. Tofacitinib (CP-690,550) is stated to be a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signalling through the common gamma chain-containing receptors for several cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signalling by additional pro-inflammatory cytokines, such as IL-6 and IFN-γ. At higher exposures, inhibition of erythropoietin signalling could occur via inhibition of JAK2 signalling.

The proposed indication is:

> *JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate.*

2. Clinical rationale

The Sponsor has developed tofacitinib as an immunomodulatory agent for the treatment of RA. RA is a debilitating condition that has high morbidity and increases mortality in comparison with the healthy population. There is currently no cure for RA and treatments are aimed at decreasing symptoms, improving physical wellbeing and preventing disease progression. There are currently three main classes of agents for treating RA: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs). All of these drugs have significant adverse effects and incomplete efficacy. Hence, there is considerable scope for improving the treatment of RA.

2.1. Guidance

The Sponsor consulted with the TGA prior to submission.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The Clinical Dossier represents a complete clinical development program.

The submission contained the following clinical information:

Module 5

- 23 clinical pharmacology studies, including 20 that provided pharmacokinetic data and three additional studies that provided pharmacodynamic data.

- Two population pharmacokinetic analyses.

- Five pivotal efficacy/safety studies.

- Five dose-finding studies.

- Two long-term follow-on studies.

· An Integrated Summary of Efficacy, an Integrated Summary of Safety, and ten analyses of combined data.

Module 1

· Application letter, application form, draft Australian PI and CMI.

Module 2

· Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission did not include paediatric data.

The EMA has agreed a waiver for the indication requested in the present application on the grounds that the condition does not occur in the paediatric age group. The EMA has agreed to a paediatric investigation plan for the treatment of juvenile idiopathic arthritis (extended oligoarthritis, RF+ polyarthritis, RF- polyarthritis, enthesitis related arthritis, psoriatic arthritis, systemic JIA) for children from 2 years to less than 18 years of age, for the film-coated tablet and oral solution. The plan includes the development of an age-appropriate oral liquid formulation.

3.3. Good clinical practice

The studies presented in the submission are stated to have been conducted according to GCP. The study reports are consistent with adherence to GCP.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Effect of food on the bioavailability of CP-690,550	Study A3921005
	Effect of food on the bioavailability of CP-690,550	Study A3921076
	† Absolute bioequivalence of single doses of CP-690,550 formulations intended for marketing and those used in the studies	Study A3921075
	General PK- Single dose PK of CP-690,550	Study A3921077
	Single dose PK of CP-690,550	Study A3921002
	Single dose PK of CP-690,550	Study A3921010

PK topic	Subtopic	Study ID
	Multi-dose PK of CP-690,550	Study A3921036
	Multi-dose PK of CP-690,550	Study A3921065
PK in special populations	PK in Subjects with Psoriasis, Multi-dose § PK in Subjects with Rheumatoid arthritis	Study A3921003
		Study A3921013
	PK in Subjects with Renal impairment	Study A3921004
	PK in Subjects with Renal impairment	Study A3921006
	PK in Subjects with Hepatic impairment	StudyA3921015
PK interactions	Effect of Fluconazole on CP-690,550	Study A3921014
	Effect of Tacrolimus, cyclosporine on CP-690,550	Study A3921020
	Effect of Ketoconazole on CP-690,550	Study A3921054
	Effect of Rifampin on CP-690,550	Study A3921056
	Effect of CP-690,550 on Midazolam	Study A3921059
	Effect of CP-690,550 on Ethinyloestradiol/ levonorgestril	Study A3921071
	Effect of CP-690,550 on Metformin	Study A3921143
Population PK analyses	§ PK in the Target population	Study PMAR-00178
	PK in Healthy volunteers	Study PMAR-00210

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.1.1. Bioavailability studies

Study A3921005 was a Phase I, open label, randomised, crossover bioavailability study of CP-690,550 tablets and powder under fasted conditions and the effect of food in 12 healthy male volunteers, aged 18 to 45 years. The study treatments were:

· 50 mg tablets (two x 20 mg, two x 5 mg) under fasted conditions

· 50 mg tablets (two x 20 mg, two x 5 mg) under fed conditions

· 50 mg oral powder for constitution under fasted conditions

The treatments were administered as three single doses of 50 mg CP-690,550 separated by at least a 7-day washout. In the comparison of tofacitinib tablets versus powder, the mean (95% CI) ratio T/R for AUC0-inf was 96.32 (91.52 to 101.36) % and for Cmax was 76.41 (68.67 to

85.03) %. This indicates similar total exposure but more rapid absorption with the powder. In the comparison of tofacitinib tablets fed versus fasted, the mean (95% CI) ratio T/R for AUC0-inf was 114.96 (109.23 to 120.98) % and for Cmax was 74.25 (66.72 to 82.63). This indicates a 15% increase in total exposure, and slower absorption, in the fed state.

Study A3921076 was an open label, Phase I, randomised, two-period, two-sequence, single dose, crossover bioavailability study to evaluate the effect of food on PK CP-690,550 tablets in healthy volunteers. The study was conducted in Singapore during September 2010. The study included 16 male subjects, aged 23 to 52 years, BMI range 19.0 to 30.3 kg/m², and all were Asian. All subjects completed the study. The study treatments were:

·   Tofacitinib 10mg immediate release tablet administered following a standard high-fat FDA breakfast

·   Tofacitinib 10mg immediate release tablet administered in the fasted state

There was a washout period of at least 72 hours between doses. The mean ratio (90% CI) fed/fasted for AUC0-inf was 106.03 (102.62 to 109.56) %, for AUC0-last was 105.87 (102.44 to 109.41) % and for Cmax was 68.18 (58.39 to 79.61) %. Administration in the fed state resulted in an increase in AUC0-inf of 6% and a decrease in Cmax of 32%.

4.1.2.   Bioequivalence studies

Study A3921075 was an open-label, Phase I, randomised, three-way cross-over, single-dose, bioequivalence study to compare various formulations of CP-690,550 in healthy volunteers. The study was conducted at a single centre in Singapore during September 2010. The study treatments were:

·   One x 10 mg commercial image tablet formulation **[information redacted]**

·   Two x 5 mg Phase III tablets **[information redacted]**

·   Two x 5 mg Phase 2B tablets **[information redacted]**

The treatments were administered as a single dose, with a washout period of at least 72 hours, and after a 10 hour fast. There were 26 male subjects aged 21 to 52 years, all Asian, and 24 completed the study. Bioequivalence was demonstrated between all three treatments. The ratio (90% CI) for AUC0-inf for commercial tablets / Phase III was 99.54 (96.69 to 102.47) % for Commercial Tablets / Phase IIB was 98.97 (96.13 to 101.88) % and for Phase III / Phase IIB was 99.43 (96.62 to 102.31) %. The ratio (90% CI) for Cmax for commercial tablets / Phase III was 105.20 (95.57 to 115.80) % for Commercial Tablets / Phase IIB was 93.88 (85.31 to 103.32) % and for Phase III / Phase IIB was 89.24 (81.20 to 98.08) %.

4.1.3.   Basic pharmacokinetics in healthy volunteers

Study A3921077 was an open label, single centre, Phase I, randomised, two-way crossover, single-dose, study to estimate the absolute oral bioavailability of CP-690,550 in healthy volunteers. The study was conducted at a single centre in Singapore from July to August 2010. PK parameters were estimated using non-compartmental analysis. The study included 12 male volunteers aged 23 to 54 years, all Asian, and all subjects completed. The study treatments were:

·   10 mg CP-690,550 tablet administered orally

·   10 mg CP-690,550 administered intravenously over 30 minutes

There was a washout period of 72 hours between doses. One subject did not receive the entire intravenous dose and the calculations were adjusted accordingly. Absolute bioavailability was 74%. From the intravenous dose, the geometric mean (CV%) clearance was 412.3 (19) mL/min, Vss was 87.08 (16) L, and t½ was 3.523 (9) hours. The median (range) Tmax for the oral dose was 0.584 (0.333 to 0.667) hours.

Study A3921002 was a double-blind, Phase I, single oral dose, placebo-controlled, cohort (parallel group) dose escalation study to evaluate the safety, toleration, PK and PD of CP-690,550 in healthy volunteers. The study was conducted at two centres in the US from April 2002 to August 2002. The study treatments were CP-690,550 in single oral doses of 0.1 mg, 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, 60 mg and 100 mg. There were nine treatment groups. The study included 95 healthy adult volunteers aged 19 to 45 years. There were 92 males and three females. There were 58 White, 19 Black, twelve Hispanic, and three other subjects. Blood samples were collected pre-dose and 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. Timed urine samples were collected during the intervals 0-6, 6-12, 12-24 hours, 24-48 hours and 48-72 hours. The PK parameters were estimated using non-compartmental analysis. Some PD outcome measures were performed, including: WCC with differential (absolute cell count and % cell count of basophils, eosinophils, lymphocytes, monocytes and neutrophils), platelet count (PLC), reticulocyte count and lymphocyte subsets by FACS analysis for CD3+, CD4+, CD8+, CD16+, and CD19+. Analysis was performed for mRNA for nine gene targets: B cell lymphoma (Bcl)-2, Bcl-2 associated X protein (Bax), granzyme B, interferon-gamma, interleukin IL-7 and IL-15, perforin, interferon-gamma inducible protein 10 kD (IP-10), and Fas Ligand (Fas-L). The PK parameters for CP-690,550 were dose proportional in the range 3 mg to 100 mg (following oral administration).

Study A3921010 was a non-randomized, open-label, single-dose study of [14C]CP-690,550 to investigate the metabolic profile and the routes of excretion. The study was conducted at one centre in the US from March 2004 to April 2004. The study included six healthy male volunteers aged 29 to 53 years. The subjects were administered a single oral dose of 50 mg [14C]CP-690,550, as powder, following an 8 hour fast. Blood and urine samples were collected over 168 hours. Mean (SD) recovery in urine was 80.1 (3.6) %, in faeces 13.8 (1.9) % and total 93.9 (3.6) %. Approximately 30% of the administered radioactivity was excreted as unchanged drug in the urine.

The major primary metabolic pathways of CP-690,550 included

· oxidation of the pyrrolopyrimidine ring (M8 and M9),

· oxidation of the piperidine ring (M18)

· piperidine ring side chain oxidation (M2 and M4)

· glucuronidation (M20)

· N-demethylation to form M1

A total of ten metabolites were identified in urine by LCMS. The major urinary metabolites were hydroxylated metabolite (M9, 19.6%), 2-carboxy-ethanone (M4, 8.2%), **N-desmethyl and** 2-hydroxy-ethanone (M2, 3.6%) and **M2** glucuronide (M29), two dihydroxylated metabolites (M11 and M14) and the CP-690,550 glucuronide (M20). In addition to unchanged drug, a total of seven metabolites were identified in faeces by LCMS. The major faecal metabolites were two hydroxylated metabolites (M9, M18), 2-carboxy-ethanone (M4), 2-hydroxy-ethanone (M2) and two dihydroxylated metabolites (M11 and M14) **and a hydroxylated and pyridine ketone metabolite (M22)**[1].

Study A3921036 was a randomised, subject- and Investigator-blind, Sponsor-open, placebo-controlled, single- and multiple-dose escalation study in healthy adult male and female Japanese and Western subjects. Plasma and urine samples were collected for the PK analysis. Fasting serum lipids were also assessed. CYP2C19 genotyping was performed. The study was conducted at a single centre in the US from May to July 2007. There were two dosing cohorts:

· Cohort A: 1 mg, 5 mg or 30 mg (6 x 5mg tablets) as a single dose

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[1] Text in bold in this paragraph show amendments from the original CER text

- Cohort B: 15 mg (3 x 5 mg) as a single dose on Day 1, and multiple dosing (q12h) on days 4 to 7

A total of 25 subjects were entered into the study. Two withdrew: one due to not meeting entry criteria, one due to AE. In Cohort A there were eight Japanese and Westerner subjects. Cohort B were all Japanese. There were 21 males and four females. The age range was 24 to 52 years.

For the single dose data, AUC and Cmax were dose proportional and were not affected by race. For the multiple dose data, t½ did not alter over the multiple dosing interval. Steady state was reached within 24 hours. The geometric mean (CV%) accumulation ratio was 1.15 (10%). Approximately 20% of the dose was excreted as unchanged drug in the urine over the first 24 hours after dosing. Mean renal clearance was approximately 150 mL/min and was not affected by dose or race. In the multiple dose cohort the arithmetic mean (CV%) Ae12 was 3.91 mg (46%) on Day 1 and 3.49 mg (49%) on Day 8. The geometric mean (CV%) CLR was 158 mL/min (32%) on Day 1 and 120 mL/min (33%) on Day 8. There were two subjects with poor metaboliser CYP2C19 genotype but there was no affect on PK parameters.

Study A3921065 was an open label, single and multiple dose study to investigate the PK, safety and tolerability of CP-690,550 in healthy Han Chinese subjects. The study was conducted at a single centre in China during October 2010. The subjects were administered 10 mg CP-690,550 as immediate release tablets as a single dose on Day 1, and 10 mg twice daily from Day 2 through to Day 6[2]. All doses were administered in the fasted state. The study included twelve healthy Han Chinese volunteers, six male, six female, aged 22 to 35 years, and the BMI range was 19.2 to 24. The PK parameters were similar following single and multiple doses. Arithmetic mean (CV%) t½ was 3.319 hours (12%) following single dose and 2.479 hours (11%) following multiple dose. The geometric mean (CV%) accumulation ratio was 1.036 (10%).

4.1.4. Basic pharmacokinetics in subjects with medical conditions

Study A3921003 was a placebo-controlled, parallel group, dose escalation study in which the Investigator and subjects were blinded to treatment, but the Sponsor was unblinded, to assess PK, PD, safety and tolerability in medically stable subjects with psoriasis. The PD outcomes included lymphocyte subsets, FBC and gene expression assessed by mRNA. The study was conducted at a single centre in the US from November 2002 to April 2004. The study treatment was CP-690,550, dosed in six cohorts with: 5 mg OPC twice daily, 10 mg OPC twice daily, 20 mg OPC twice daily, 30 mg OPC twice daily, 60 mg tablet once daily, and 50 mg tablet twice daily. There were placebo controls for each cohort. The study included 59 healthy subjects with active psoriasis; 37 (63%) male, 22 (37%) female; age range 23 to 63 years; BMI range 19.8 to 35.7 kg/m². There appeared to be some accumulation with multiple dosing with the mean accumulation ratios ranging from 0.974 to 1.62. AUC and Cmax were mostly dose proportional. The mean unbound renal clearances of CP-690,550 were slightly greater than GFR for all cohorts (after being corrected for in vitro human plasma protein binding) indicating some active renal secretion of CP-690,550. The mean percent of administered dose excreted unchanged in the urine ranged from 18.3% to 27.2%.

Study A3921013 was an open-label, non-randomized, fixed sequence, drug-drug interaction study in subjects who had a diagnosis of RA for at least 6 months and were receiving a stable weekly oral MTX dose (15-25 mg/week) for a minimum of 28 days to evaluate the PK interaction between MTX and CP-690,550. The study was conducted at two centres in the US from April 2005 to June 2006. The study treatments were: CP-690,550 30 mg q12h from Day 3 to the morning of Day 7; and MTX (individualised dose) on Days 1 and 7. Twelve subjects with RA were enrolled: four males, eight females, and the age range was 36 to 73 years. All twelve

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[2] AusPAR clarification: all eligible subjects received CP-690,550 10 mg once daily (QD) on Day 1 and Day 6, and 10-mg twice daily (BID) on Days 2 through 5

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 15 of 72

completed and were included in the analysis. There was no apparent change in the PK parameters of CP-690,550 in combination with MTX. However, there was a 10% decrease in MTX AUC0-24 and 13% decrease in Cmax in combination with CP-690,550. This is unlikely to be clinically significant.

Study A3921004 was an open-label, non-randomised, single-dose study of CP-690,550 to assess the PK, non-renal clearance, dialyzability, and protein binding of CP-690,550 in subjects with ESRD. The study was conducted at two centres in the US from February 2003 to June 2003. The study treatment was CP-690,550 10 mg OPC, as a single dose by oral administration. There were two treatment periods. In Period 1 CP-690,550 was administered as a single dose 1 to 2 hours after dialysis, and in Period 2 as a single dose 4 hours prior to dialysis. Mean (SD) clearance was 501 (243) mL/min and t½ was 3.46 (1.18) hours. The fraction unbound to plasma proteins in subjects with ESRD was approximately 0.4. CP-690,550 was dialysable.

Study A3921006 was an open-label, non-randomized, parallel-group, single dose study to evaluate the pharmacokinetics of CP-690,550 administered orally as a single dose in subjects with impaired renal function, compared to healthy subjects. The study was conducted at three centres in the US from October 2003 to March 2004. The study treatment was a single 10 mg oral dose of CP-690,550 (two 5 mg tablets) administered fasted. The study included 24 subjects, including six subjects with normal renal function, six with mild renal impairment, six with moderate renal impairment and six with severe renal impairment. These groups were defined as:

·   Normal renal function: estimated creatinine clearance (Cockroft-Gault) >80 mL/min

·   Mild renal impairment: >50 and ≤80 mL/min

·   Moderate renal impairment: ≥30 and ≤50 mL/min

·   Severe renal impairment: <30 mL/min

There were 13 males, eleven females, and the age range was 40 to 64 years. In mild renal impairment AUC0-inf was increased by 37% but Cmax was not significantly increased). In moderate renal impairment AUC0-inf was increased by 43% but Cmax was not significantly increased. In severe renal impairment AUC0-inf was increased by 123% and Cmax was increased by 18%.

StudyA3921015 was an open-label, single dose, single treatment, non-randomised, partially sequential study of CP-690,550 10 mg in male and female subjects with mild or moderate hepatic impairment. The control (healthy) subjects were matched for age, weight and gender. The study was conducted at one center in the US from November 2009 to January 2010. The study enrolled 18 subjects: six with mild hepatic impairment; six with moderate hepatic impairment, and six normal controls. Mild hepatic impairment was defined as a Child-Pugh Score of 5 or 6, and moderate hepatic impairment was defined as a Child-Pugh Score of 7 to 9. There were 15 males, three females, and the age range was 36 to 64 years. All the subjects completed the study. The study treatment was a single, oral dose of 10 mg CP-690,550 after a standardised breakfast. There was no clinically significant difference in AUC0-inf or Cmax between normal subjects and those with mild hepatic impairment. However, there was a 65% increase in AUC0-inf and a 49% increase in Cmax in subjects with moderate hepatic impairment. CYP2C19 genotype did not appear to affect the PK parameters.

4.1.5.   Extrinsic factor studies

Study A3921014 was an open-label, single fixed-sequence, crossover study of the effects of multiple-dose fluconazole upon the PK of single-dose CP-690,550. The study was conducted at one centre in the US from November 2005 to December 2005. The study enrolled twelve healthy male volunteers, with an age range of 23 to 49 years. The study treatments were:

·   Period 1: 30 mg CP-690,550 as a single dose on Day 1

- Period 2: fluconazole 400 mg on Day 1 and 200 mg daily on Days 2 to 7; CP-690,550 30 mg as a single dose on Day 5

CP-690,550 was administered as a 20 mg tablet plus two 5 mg tablets. In combination with fluconazole, CP690,550 AUC0-inf increased by 79% and Cmax by 27%. Plasma t½ increased from 2.97 hours to 4.00 hours. CL/F decreased from 31.7 L/hour to 17.2 L/hour. The proportion of the dose recovered unchanged in urine increased from 26.0% to 30.9%, but CLR decreased from 7.57 L/hour to 5.24 L/hour. These data indicate that fluconazole exhibited clinically significant inhibition of both metabolic clearance and renal clearance (presumably by inhibiting the active transport of CP-690,550).

Study A3921020 was a Phase 1, open-label, single, fixed-sequence, two cohort study to estimate the effect of multiple dose tacrolimus and cyclosporine on the PK of a single oral dose of CP-690,550 in healthy male volunteers. The study was conducted at a single centre in Singapore from June 2009 to August 2009. The two treatment cohorts were:

- Cohort A:
  - Period 1: 10 mg CP-690,550 oral, washout of 24 hours
  - Period 2: tacrolimus 5 mg twice daily until the morning of Day 8; 10 mg CP-690,550 on the morning of Day 8
- Cohort B:
  - Period 1: 10 mg CP-690,550 oral, washout of 24 hours
  - Period 2: cyclosporine 200 mg twice daily until the morning of Day 6; 10 mg CP-690,550 on the morning of Day 6

There were twelve subjects in each cohort (24 in total), all were male, 23 were Asian, and the age range was 22 to 49 years. Two subjects in Cohort A withdrew: abdominal distension and dyspepsia/chills. Concomitant tacrolimus increased the AUC0-inf by 21% and decreased Cmax by 9%. Concomitant cyclosporine increased AUC0-inf by 73% and decreased Cmax by 17%.

Study A3921054 was an open label, single fixed sequence study designed to evaluate the effect of multiple dose ketoconazole on the PK of a single 10 mg oral dose of CP-690,550. The study was conducted at one centre in Belgium during September 2010. The study treatments were:

- Period 1: 10 mg CP-690,550, oral administration, fasted state
- Period 2: ketoconazole 400 mg once daily for 3 days, on Day 3 10 mg CP-690,550

The study included twelve male volunteers, all were White, and the age range was 22 to 53 years. All subjects completed the study. Ketoconazole increased AUC0-inf by 103% and increased Cmax by 16%.

Study A3921056 was a Phase 1, open-label, 2-period, single fixed-sequence study designed to evaluate the effect of repeat-dose oral rifampin on single-dose CP-690,550 PK in healthy subjects. The study was conducted at one centre in the US from August 2010 to October 2010. The study treatments were:

- Period 1: single 30 mg dose of CP-690,550, administered orally in the fasted state
- Period 2: rifampin 600 mg orally, daily for 7 days, and on Day 8 a single 30 mg dose of CP-690,550, administered orally in the fasted state

The study included twelve healthy male volunteers. Six were Black, three were White, one was Asian, and two were of other race. The age range was 23 to 50 years. All the subjects completed the study. Rifampin decreased AUC0-inf by 84% and Cmax by 74%. This effect was also seen in subjects that were either rapid or poor CYP2C19 metabolisers.

Study A3921059 was a Phase 1, randomized, two-way crossover, multiple-dose, open-label study of multiple-dose CP-690,550 on the PK of a single, oral dose of midazolam in healthy volunteers. The study was conducted at a single centre in the US from June 2009 to July 2009. The study treatments were:

· Midazolam 2 mg, oral syrup

· CP-690,550 30 mg orally, twice daily for 7 days, and on Day 7 a single dose of midazolam 2 mg oral syrup

There was a washout period of 7 days between CP-690,550 and the single dose of midazolam. Subjects were randomized to treatment sequence. The study included 25 healthy male volunteers aged 22 to 55 years. One subject discontinued because of a protocol violation. CP-690,550 did not exhibit a clinically significant effect on the PK of midazolam.

Study A3921071 was a Phase 1, randomized, two-way crossover, multiple-dose, open-label, two sequence, study of the effect of multiple-dose CP-690,550 on single-dose oral contraceptive PK in healthy female volunteers. The study was conducted at a single centre in Belgium from June 2010 to July 2010. The study treatments were:

· Single dose of one tablet of Microgynon 30 (ethinyloestradiol 30 μg and levonorgestril 150 μg)

· CP-690,550 50 mg twice daily for 9 days, and also on the morning of Day 10, and on Day 10 a Single dose of one tablet of Microgynon 30 (ethinyloestradiol 30 μg and levonorgestril 150 μg)

There was a 10 day washout period between CP-690,550/Microgynon and the single dose of Microgynon. Subjects were randomized to treatment sequence. The study included 20 healthy female volunteers; 18 were White, and the age range was 19 to 50 years. There was no clinically significant effect of CP-690,550 on the AUC0-inf of either ethinyloestradiol or levonorgestril, but the Cmax of ethinyloestradiol was decreased by 10% and the Cmax of levonorgestril was increased by 12%. These effects are unlikely to be clinically significant.

Study A3921143 was an open-label, fixed-sequence study designed to evaluate the potential effect of CP-690,550 on the PK of metformin (a probe drug for organic cationic transport) in healthy volunteers. The study was conducted at one centre in Belgium from July 2011 to August 2011. The study treatments were:

· Metformin 500 mg on Days 1 and 4

· CP-690,550 30 mg orally twice daily from Day **2** to Day 4

The study included 24 healthy male volunteers aged 20 to 55 years. Metformin Cmax was decreased by 7.5% but there was no change in AUC0-last or CLR. The change in Cmax is unlikely to be clinically significant.

4.2.   Population pharmacokinetic analyses

4.2.1.   Study PMAR-00178

4.2.1.1.   Objective of the analysis

The objectives of Study PMAR-00178 were:

· To characterize CP-690,550 PK in patients with RA

· To identify any covariates that are important determinants of CP-690,550 exposure

4.2.1.2. Data

The data were extracted from five Phase II studies of CP-690,550 in subjects with RA. These included three monotherapy studies (Study A3921019, Study A3921035 and Study A3921040) and three studies in combination with MTX (Study A3921025 and Study A3921039). The dose levels in monotherapy were 1 mg, 3 mg, 5 mg, 10 mg, 15 mg and 30 mg twice daily. The dose levels in combination with MTX were: 1 mg, 3 mg, 5 mg, 10 mg, 15 mg and 20 mg twice daily. There were 6039 observations from 1070 subjects. There were 887 females, 183 males, with an age range of 18 to 81 years and a weight range of 31.4 to 147 kg. There were 543 Caucasian, 360 Japanese, 107 Hispanic, 26 other Asian, 19 African American and 15 subjects of other race. The range for CRCL (as estimated by the Cockroft-Gault equation) was 39.9 to 140 mL/min.

4.2.1.3. Methods

The data were analysed using NONMEM Version 7.1.2. The structural model was one compartment with zero order absorption and first order elimination. The PK parameters were CL/F, V/F and D. There was a covariance term to describe the interaction between CL/F and V/F (i.e a block-diagonal error model). The inter-individual variability was modelled as exponential and the residual variability was proportional. The covariate analysis was performed to assess the magnitude of any covariate effects rather than to develop a descriptive model.

4.2.1.4. Results:

The typical estimates of CL/F and V/F from the base model were 20.6 L/h and 90.2 L respectively. CL/F increased with increasing CLCR. Age, weight, gender and race did not have significant covariate effects.

4.2.2. Study PMAR-00210

4.2.2.1. Objective of the analysis

The objective of Study PMAR-00210 was: to evaluate and quantify the relationship between a selection of covariates and CP-690,550 exposure using non-compartmental parameters (AUC and Cmax) obtained from healthy human volunteers who participated in CP-690,550 Phase 1 clinical trials.

4.2.2.2. Data

The data were obtained from 16 Phase I studies. There were 532 evaluable AUC and Cmax values from 356 subjects. There were 278 males, 58 females, the age range was 18 to 65 years, WT range was 49 to 117.9 kg and CRCL range was 64.64 to 207.9 mL/min.

4.2.2.3. Methods

The analysis used a two-stage approach whereby the parameters AUC and Cmax were calculated separately for each individual on a per-study basis. These data were then analysed using linear and nonlinear mixed effects models to assess the effects of potential covariates using R version 2.10.1. The covariates included weight, age, CRCL, gender, race (Caucasian, Black, Other, Asian, Japanese, and Chinese), formulation, and fed status. The covariate modelling approach was intended to estimate covariate effects rather than to develop the best explanatory model.

4.2.2.4. Results:

AUC increased in the fed state and Cmax decreased. AUC and Cmax were higher in females and with Asian race. Cmax increased with lower weight. However, there may be some correlation between these covariates that may have been eliminated if a stepwise approach had been used in the model building.

4.3.   Summary of pharmacokinetics

Food increased the total exposure to CP-690,550 by 15% in Study A3921005 and by 6% in Study A3921076 but slowed oral absorption and decreased Cmax by around 30% in both studies.

The formulations used in development and those intended for marketing were demonstrated to be bioequivalent in Study A3921075.

The absolute bioavailability of CP-690,550 was 74%, and following intravenous dosing, the geometric mean (CV%) clearance was 412.3 (19%) mL/min, Vss was 87.08 (16%) L, and t½ was 3.523 (9%) hours (Study A3921077). Following oral administration, the PK parameters for CP-690,550 were dose proportional in the range 3 mg to 100 mg (Study A3921002).

Approximately 30% of a CP-690,550 dose was excreted unchanged in the urine. The remaining elimination was as urinary metabolites (50% of dose) and faecal parent drug and metabolites (14%) (Study A3921010). Mean urinary clearance of unchanged drug was approximately 150 mL/min and was not affected by dose or race (Study A3921036). With multiple dosing the geometric mean (CV%) accumulation ratio was 1.15 (10%) (Study A3921036) and in a Han Chinese population was 1.036 (10%) (Study A3921065).

In subjects with medically stable psoriasis, there appeared to be some accumulation with multiple dosing with the mean accumulation ratios ranging from 0.974 to 1.62. AUC and Cmax were mostly dose proportional. The mean unbound renal clearances of CP-690,550 were slightly greater than GFR indicating some active renal secretion of CP-690,550. The mean percent of administered dose excreted unchanged in the urine ranged from 18.3% to 27.2%.

In subjects with RA there was no apparent change in the PK parameters of CP-690,550 in combination with MTX (Study A3921013). However, there was a 10% decrease in MTX AUC24 and 13% decrease in Cmax in combination with CP-690,550. This is unlikely to be clinically significant.

In mild renal impairment AUC0-inf was increased by 37% but Cmax was not significantly increased (Study A3921006). In moderate renal impairment AUC0-inf was increased by 43% but Cmax was not significantly increased. In severe renal impairment AUC0-inf was increased by 123% and Cmax was increased by 18%. Clearance of CP-690,550 was impaired in subjects with ESRD, but CP-690,550 was found to be dialysable (Study A3921004). The fu was 0.4.

There was no clinically significant difference in AUC0-inf or Cmax between normal subjects and those with mild hepatic impairment (StudyA3921015). However, there was a 65% increase in AUC0-inf and a 49% increase in Cmax in subjects with moderate hepatic impairment.

In healthy subjects AUC increased in the fed state and Cmax decreased (Study PMAR-00210). AUC and Cmax were higher in females and with Asian race. Cmax increased with lower weight. However, age did not have a significant effect on the PK parameters. However, there may be some correlation between these covariates that may have been eliminated if a stepwise approach had been used in the model building.

In subjects with RA, CL/F increased with increasing CLCR (Study PMAR-00178). Age, weight, gender and race did not have significant effects on CL/F.

The following drug interactions were investigated:

·   In combination with fluconazole, CP690,550 AUC0-inf increased by 79% and Cmax by 27% (Study A3921014). Plasma t½ increased from 2.97 hours to 4.00 hours. CL/F decreased from 31.7 L/hour to 17.2 L/hour. The proportion of the dose recovered unchanged in urine increased from 26.0% to 30.9%, but CLR decreased from 7.57 L/hour to 5.24 L/hour (Study A3921014). These data indicate that fluconazole exhibited clinically significant inhibition of both metabolic clearance and renal clearance (possibly by inhibiting the active transport of CP-690,550).

· Concomitant tacrolimus increased the AUC0-inf by 21% and decreased Cmax by 9% (Study A3921020).

· Concomitant cyclosporine increased AUC0-inf by 73% and decreased Cmax by 17% (Study A3921020).

· Ketoconazole increased AUC0-inf by 103% and increased Cmax by 16% (Study A3921054).

· Rifampin decreased AUC0-inf by 84% and Cmax by 74% (Study A3921056).

· CP-690,550 did not exhibit a clinically significant effect on the PK of midazolam (Study A3921059).

· There was no clinically significant effect of CP-690,550 on the AUC0-inf of either ethinyloestradiol or levonorgestril, but the Cmax of ethinyloestradiol was decreased by 10% and the Cmax of levonorgestril was increased by 12% (Study A3921071).

· There was no clinically significant effect of CP-690,550 on the PK of metformin (Study A3921143).

4.4.   Evaluator's overall conclusions on pharmacokinetics

The PK of CP-690,550 have been satisfactorily described in the development program except for the following unresolved issues:

· There were few elderly subjects in the PK analyses. Hence clearance in subjects in the older age groups has not been satisfactorily examined.

· Inhibition of glucuronidation has been reported with imatinib, another tyrosine kinase inhibitor, sufficient to lead to potentially serious interactions with drugs such as paracetamol. As yet it is not known whether this could be a class interaction. Hence, effects upon glucuronidation should be examined.

· The mechanism for active renal secretion of CP-690,550 has not been determined. Hence there are potential interactions that have not been excluded.

5.   Pharmacodynamics

5.1.   Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Table 2: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect of CP-690,550 on interleukin expression	Study A3921002
	Effect of CP-690,550 on haemopoietic cells	Study A3921003
Secondary Pharmacology	Effect of CP-690,550 on QTc (Thorough QT study)	Study A3921028
	Effect of CP-690,550 on renal function	Study A3921033
	Effect of CP-690,550 on plasma lipids	Study A3921036
	Effect of CP-690,550 on plasma lipids	Study A3921109

* Indicates the primary aim of the study.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

In Study A3921002 there were decreased gene expression data for the dose range 10 mg to 100 mg for Bcl-2 and IP-10 at 4 and 8 hours post-dose relative to placebo. There were no other apparent effects on PD parameters.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

In Study A3921003, the PD outcome measures were:

- Lymphocyte Subset Analysis: absolute (Abs) and relative cell counts were done in each sample for the lymphocyte subsets CD3+, CD4+, CD8+, CD16+/56+, and CD19+ using FACS.

- FBC.

- Gene Expression Analysis (mRNA Isolation) in peripheral blood: 15 gene targets including Bcl-2, BAX, CD25, CXCL10, FOXP3, Granzyme B, IL-2, IFN-γ, IL-15, IL-7, PCNA, perforin, SOCS3, TNFSF5, and FasL.

- Gene Expression mRNA in psoriatic plaque biopsies: 15 gene targets analyzed including Bcl-2, BAX, CD25, CXCL10, Granzyme B, IL-2, IL-8, iNOS, IFN-γ, IL-15, IL-7, K-16, PCNA, perforin, and FasL. Gene expression levels were determined relative to the non-lesional baseline value and the lesional baseline values normalized to the housekeeping gene 18S rRNA, respectively.

- mPASI.

- Physicians global assessment of severity.

- Immune Cell Function Assay: the degree of immunosuppression induced by the administration of CP-690,550 was to be evaluated using a bioluminescent assay in which the concentration of ATP released by CD4+ cells was measured.

- Immunohistochemistry in psoriatic plaque biopsies: Immunohistochemistry analysis of dermal and epidermal cells was done using the markers CD11c+, CD25+, CD3+, CD8+ and CD83+. Expression of K16 by suprabasal keratinocytes was assessed qualitatively.

- PKPD analysis: Percent changes from baseline for the individual Day 14 mPASI scores were analyzed using a naïve-pooled analysis with Day 14, 24-hour systemic exposure (AUC0-tau*2 for the BID cohorts and AUC0-tau for the QD cohort) as the independent variable. A sigmoid Emax model was used to explain the relationship between the two variables.

CP-690,550 appeared to increase counts of CD3+, CD4+, CD8+, CD16+/56+, and CD19+ lymphocyte subsets on individual days during the dosing period, decreased counts around Day 18 and/or 21 (following final dosing on Day 14), and there were counts comparable to that of placebo on Days 28 and 42. The 5 mg dose had little effect on FACS counts, and the 50 mg twice daily dose had the greatest effect. Total lymphocyte counts paralleled these changes. For the 50 mg dose, neutrophil counts decreased by no more than 40% during the dosing period, increased by no more than approximately 40% around Day 15 and were comparable to placebo on Days 28 and 42. Reticulocytes decreased by no more than 40% in the 30 mg twice daily and 50 mg twice daily groups during the dosing period and through Day 21, and increased by no more than 80% on Days 28 and 42. Platelet count decreased by no more than 30% on Days 21 and 28 in the 30 mg and 50 mg twice daily groups. There was a decrease in haemoglobin of no more than 6% in the 20 mg and higher dose groups. The gene expression data were only available for Cohorts 5 and 6 and were not considered to be reliable by the Sponsor due to "technical questions about its reliability". Improvement was demonstrated for mPASI and global scores. Skin biopsies were available for eight subjects. Six had been treated with CP-690,550, and two with placebo. Histochemistry indicated improvement in one (50%) subject in the placebo group and three (50%) in the treatment groups. The PKPD model estimated the EC50 value to be 2696 ng h/mL (for AUC0-tau).

5.2.2.2. Secondary pharmacodynamic effects

5.2.2.2.1. Effects on QTc

Study A3921028 was a Phase 1, single-dose, randomized, three-treatment, three-period cross-over, sponsor-open, placebo-and positive-controlled trial to evaluate the effect of a single 100 mg dose of CP-690,550 on the QTc interval. ECGs were measured over a 24 hour period post-dose. The study was conducted at two centres (one each in Singapore and Belgium) from November 2007 to February 2008. The study treatments were:

- CP-690,550 100 mg, oral

- Placebo

- Moxifloxacin 400 mg (positive control)

There was a washout period between treatments of 7 Days. The study included 60 healthy volunteers: 32 (53.3%) male, 28 (46.6%) female, age range 21 to 51 years. There were no increases in mean QTcF postdose indicating concern. The greatest mean (95% CI) postdose increase in QTcF was 16 hours postdose: 2.15 (0.29 to 4.00) ms. One subject in the CP-690,550 group had an absolute QTcF interval between 450 and <480 ms, compared with three in the placebo group and seven in the moxifloxacin.

5.2.2.2.2. Effects on renal function

Study A3921033 was a randomized, sponsor-open, placebo-controlled trial conducted in healthy subjects to evaluate the effects of CP-690,550 on renal function and plasma lipids. The

study was conducted at a single centre in the US from October 2006 to January 2007. The study treatments were either CP-690,550 15 mg or placebo q12h for 14 days. The study included 34 healthy male volunteers; 23 treated with CP-690,550 and eleven with placebo. The age range was 19 to 55 years. Iohexol clearance, CRCL and PAH renal clearance were unchanged relative to baseline and to placebo in the CP-690,550 group.

5.2.2.2.3. Effects on plasma lipids

In Study A3921036 there was an increase in total cholesterol levels in the active treatment groups, but no consistent changes in the other plasma lipids.

In Study A3921033 there were some changes to plasma lipids with 14 days of CP-690,550, but none of the changes were clinically significant. There was a 13% increase in triglycerides and a 7.36% rise in lipoprotein (a) in the CP-690,550 group but similar increases occurred in the placebo group. In the CP-690,550 group there was little change in total cholesterol, HDL-C, LDL-C, Apoprotein A-I, Apoprotein-B, HDL/LDL ratio and Apoprotein B/Apoprotien A-I ratio. Hence, there did not appear to be any clinically significant changes in plasma lipids.

Study A3921109 was a Phase 2 study of the effects of open label CP-690,550 and double blind atorvastatin on serum lipids in subjects with RA. The study was conducted at 14 centres (five in Korea and nine in the US) from February 2010 to November 2010. The study treatments were CP-690,550 10 mg twice daily for 12 weeks and after 6 weeks of treatment, subjects were randomised to either atorvastatin 10 mg or placebo for 6 weeks. The study included 111 subjects with active RA that were treated, and 92 completed. There were 99 females, 12 males, and the age range was 20 to 77 years. The effects of atorvastatin in comparison with placebo were:

LDL decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -41.14 (-47.47 to -34.82) mg/dL p-value <0.0001.

- Total cholesterol decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -24.91 (-29.07 to -20.74) mg/dL p<0.0001

- Apolipoprotein B decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -33.37 (-38.48 to -28.27) mg/dL p<0.0001

- Triglycerides decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -16.19 (-28.87 to -3.51) mg/dL p=0.0127

- Total VLDL and chylomicron particles decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -49.25 (-75.27 to -23.24) nmol/L p=0.0003

- Small VLDL particles decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -75.14 (-106.78 to -43.50) nmol/L p<0.0001

- Total LDL particles decreased in the atorvastatin group compared with placebo: treatment difference (95% CI) -36.02 (-43.45 to -28.58) p<0.0001

There was no significant difference in Apolipoprotein A-1, large VLDL and chylomicron particles, medium VLDL particles or HDL. ACR 20 response rate at Week 12 was 38 (82.6%) in the atorvastatin group and 30 (65.2%) in the placebo. The Sponsor concluded that the addition of atorvastatin to CP-690,550 treatment reduced total cholesterol, LDL and triglycerides, decreased in the ratio of LDL to HDL, and maintained increases in HDL and HDL particle size.

5.3.   Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic data demonstrated effects on lymphocyte subsets but it is not clear how these changes relate to effect. There were decreases in neutrophil, reticulocyte and platelet

counts of between 30% and 40% [for CP-690,550 doses of 30 mg twice daily and 50 mg twice daily].

CP-690,550 does not have significant QTc prolongation effects.

CP-690,550 15 mg twice daily for two weeks did not alter renal function in healthy volunteers.

In the Phase 1 studies there did not appear to be significant changes in plasma lipids but these studies were of short duration (up to 2 weeks). However, in longer duration studies there were significant elevations in HDL, LDL and total cholesterol. In combination with C-690,550 atorvastatin reduced total cholesterol, LDL and triglycerides, decreased in the ratio of LDL to HDL, and maintained increases in HDL and HDL particle size.

6. Dosage selection for the pivotal studies

6.1. Dose finding and proof of concept studies

6.1.1. Study A3921019

Study A3921019 was a Phase 2A, randomised, double blind, placebo controlled, parallel group study in subjects with RA to compare the efficacy of three dose levels of oral CP-690,550 monotherapy. The study was conducted as a proof of concept and dose finding study. The study was conducted at 53 centres in the US, Mexico, Brazil, and Europe from January 2005 to June 2006. The study included subjects at least 18 years of age with a diagnosis of RA (using ACR criteria) and continuing active disease; with a history of inadequate response or intolerance to either 15 mg or greater of MTX or any of the following: etanercept, infliximab, or adalimumab; and had discontinued all DMARD and immunosuppressive/ immunomodulatory therapy for at least 4 weeks prior to the first dose of study drug. The study treatments were:

· CP-690,550 5 mg twice daily

· CP-690,550 15 mg twice daily

· CP-690,550 30 mg twice daily

· Placebo twice daily

The CP-690,550 doses were made up from 20 mg (FID G02722AA) and 5 mg (FID G02721AA) tablets. Treatment was for 6 weeks with a 6 week follow-up period. The primary efficacy outcome measure was ACR20. Secondary efficacy outcome measures were: ACR50, ACR70, AUC for ACR-n, the components of the ACR responses, DAS, DAS28-3(CRP), HAQ and the SF-36 health survey. Safety outcome measures were: AEs, laboratory tests, vital signs, ECG, and EBV DNA.

A total of 439 subjects were screened and 264 were randomised to treatment. There were 61 subjects randomised to 5 mg, 69 to 15 mg, 69 to 30 mg and 65 to placebo. Of these subjects, 58 (95.1%) in the 5 mg, 60 (87.0%) in the 15 mg, 52 (75.4%) in the 30 mg and 48 (73.8%) in the placebo completed the study. There were 226 (85.6%) females, 38 (14.4%) males, and the age range was 18 to 78 years. The treatment groups were similar in demographic characteristics. ACR20 was 70.49% in the 5 mg group, 81.16% in the 15 mg group, 76.81% in the 30 mg group and 29.23% in the placebo. ACR50 was 32.79% in the 5 mg group, 53.62% in the 15 mg group, 50.72% in the 30 mg group and 6.15% in the placebo. ACR70 was 13.11% in the 5 mg group, 21.74% in the 15 mg group, 27.54% in the 30 mg group and none[3] in the placebo. There was a plateau in ACR-n AUC at 15 mg. There was significant improvement in HAQ-DI at all time points in all the active treatment groups. There were improvements in all modalities of the SF-36 in the active treatment groups.

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[3] Erratum: actual ACR70 in the placebo group was 3.08%

6.1.2. Study A3921025

Study A3921025 was a Phase 2b, randomized, double-blind, placebo-controlled, parallel group dose-finding study of CP-690,550 as add-on therapy to MTX in subjects with active RA. The study was conducted at 72 centres, including 25 in the US, from January 2007 to August 2008. The study included subjects ≥18 years age with active RA (≥6 joints tender or painful on motion and ≥6 joints swollen); ESR >ULN or CRP >7 mg/L; and who had been taking oral or parenteral MTX continuously for ≥4 months, and on a stable dosage of 7.5 to 25 mg weekly for ≥6 weeks prior to first dose of study drug. The study treatments were:

·   1 mg CP-690,550 twice daily

·   3 mg CP-690,550 twice daily

·   5 mg CP-690,550 twice daily

·   10 mg CP-690,550 twice daily

·   20 mg CP-690,550 once daily

·   15 mg CP-690,550 twice daily

·   Placebo twice daily

The study duration was 24 weeks in total: 12 weeks double blind followed by another 12 weeks following reassignment to 5 mg twice daily for all subjects who did not achieve ACR20 response[4] for a further 12 weeks. Responders continued on their initial assigned dose for the additional 12 weeks. Doses of CP-690,550 were made up from 1 mg tablets (FID D0602458) and 5 mg tablets (FID D0602459). Subjects were randomised in a 1:1:1:1:1:1:1 ratio. The efficacy outcome variables were: ACR20 (primary efficacy outcome measure), ACR50, ACR70, DAS, DAS28-3(CRP), HAQ-DI, SF-36 health survey, EuroQol EQ-5D, MOS-Sleep Scale, and the FACIT-Fatigue scale. Safety outcome measures were: AEs, laboratory tests, vital signs, and ECG.

A total of 685 subjects were screened, 509 were randomised, and 507 received treatment and were included in the analysis. There were 71 subjects randomised to 1 mg, 68 to 3 mg, 71 to 5 mg, 75 to 10 mg, 75 to 15 mg, 80 to 20 mg and 69 to placebo. The highest completer rate was in the 10 mg group at 88%. There were 406 (80.1%) females, 101 (19.9%) males, and the age range was 18 to 81 years. The treatment groups were similar in demographic characteristics. For ACR20 peak response was 58% at the 10 mg dose level. However for ACR50 and ACR70 peak response was at the 15 mg dose level. For patient's global Assessment of response, there was a plateau from the 5 mg dose. Physician's Global Assessment of response peaked at the 15 mg dose. For HAQ-DI peak response was at the 5 mg dose level. The reduction in CRP concentration plateaued at the 5 mg dose level. At Week 12, the greatest reduction in DAS was -2.06 at the 15 mg dose level. At Week 12, the 20 mg once daily dose level had the best response for SF-36. Improvement in EQ-5D peaked at the 10 mg dose level. There was no significant change in mean FACIT scores.

A posthoc analysis was performed in Study PMAR-00177 that constructed dose response curves that were used to help determine the dose taken through to Phase 3.

6.1.3. Study A3921035

Study A3921035 was a Phase 2B, randomised, double blind, placebo controlled, active comparator (adalimumab), parallel group study to characterize the dose-response of CP-690,550 over the range of 1 to 15 mg twice daily compared with adalimumab or placebo in subjects with RA. The study was conducted at 59 centres, including 19 in the US, from

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[4] AusPAR clarification: re-assignment occurred for subjects who failed to achieve a minimum improvement of at least 20% reduction in both swollen and painful/tender joint counts over baseline at the Week 12 visit

September 2007 to January 2009. The study included subjects ≥18 years age, with a diagnosis of RA, based upon the ACR Criteria, with at least 4 of the 7 criteria, for at least 6 months prior to randomization; and who met the ACR 1991 Revised Criteria for Global Functional Status in RA, Class I, II or III; had active disease; and had an adequate study of therapy with at least one DMARD. The study treatments were:

· 1 mg CP-690,550 twice daily

· 3 mg CP-690,550 twice daily

· 5 mg CP-690,550 twice daily

· 10 mg CP-690,550 twice daily

· 15 mg CP-690,550 twice daily

· Adalimumab 40 mg subcutaneously, second weekly for 10 weeks followed by 5 mg CP-690,550 twice daily for a further 12 weeks

· Placebo

Treatment duration was for 24 weeks. After 12 weeks non-responders were reassigned to 5 mg twice daily. The efficacy outcome measures were: ACR20 (primary efficacy outcome measure), ACR50, ACR70, ACR90, DAS, DAS28-3(CRP), DAS28-4(ESR), HAQ-DI, SF-36 health survey, EuroQol EQ-5D, MOS-Sleep Scale, and the FACIT-Fatigue scale. The safety outcome measures were: AEs, laboratory tests, vital signs and ECGs.

A total of 555 subjects were screened, 386 were randomised and 384 received treatment: 54 with 1 mg, 51 with 3 mg, 49 with 5 mg, 61 with 10 mg, 57 with 15 mg, 53 with adalimumab and 59 with placebo. The highest proportions of non-completers were in the adalimumab and placebo groups. There were 333 (86.7%) females, 51 (13.3%) males, and the age range was 45 to 64 years. The treatment groups were similar in demographic characteristics.

ACR20 response at Week 12 peaked in the 10 mg group at 75.41 %, with a slight increase to 75.44% in the 15 mg group. ACR50, ACR70 and ACR90 responses all appeared to peak at the 10 mg dose; and at the 10 mg dose, CP-690,550 appeared to have greater efficacy than adalimumab. The patient's and physician's global assessments both peaked at the 15 mg dose level, but these were only slightly above the 10 mg dose level. Similarly, the decrease in CRP was greatest in the 15 mg group, but only a little better than 10 mg. The results were similar for HAQ-DI, SF-36 health survey, EuroQol EQ-5D, MOS-Sleep Scale, and the FACIT-Fatigue scale.

6.1.4.   Study A3921039

Study A3921039 was a Phase 2, multi-center, randomized, placebo controlled, parallel group, double blind study to evaluate the dose response of CP-690,550 in the range 1 to 10 mg in Japanese subjects with RA. The study was conducted at 19 centres in Japan from January 2008 to September 2008. The study included subjects with RA between the ages of 20 and 70 years, with the diagnosis of RA based on the 1987 revised criteria of the ACR and active disease at both screening and baseline visits, defined as ≥6 joints tender or painful on motion and ≥6 joints swollen; with an ESR >ULN or CRP >0.7 mg/dL; and who had received MTX for at least 4 months consecutively, and must have received doses of at least 6 mg/week for at least 6 weeks prior to baseline. The study treatments were:

· 1 mg CP-690,550 twice daily

· 3 mg CP-690,550 twice daily

· 5 mg CP-690,550 twice daily

· 10 mg CP-690,550 twice daily

· Placebo twice daily

All subjects were treated with MTX and folic acid concurrently. The efficacy outcome measures were: ACR20 (primary efficacy outcome measure), ACR50, ACR70, DAS, DAS28-3(CRP), DAS28-4(ESR), HAQ-DI, SF-36 health survey, EuroQol EQ-5D, MOS-Sleep Scale and the FACIT-Fatigue scale. Safety outcome measures were: AEs, laboratory tests, vital signs, and ECGs.

A total of 165 subjects were screened, 140 were randomised, 136 were treated and 106 completed the study. The discontinuation rate was highest in the 10 mg and placebo groups. In the 10 mg group there were four DAEs. There were 117 females, 19 males, and the age range was 24 to 70 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline efficacy measures. For the primary efficacy outcome measure, ACR20, all active treatment groups were superior to placebo and peak effect was at the 5 mg dose level. Also for ACR50, Patient and Physician's Global Assessments, fall in CRP, and ACRn, peak effect was at the 5 mg dose level. For ACR70, ACR90, HAQ-DI and DAS, peak effect was at the 10 mg dose level. Across the physical and pain domains of the SF-36 and also the FACIT there were improvements in the 5 mg and 10 mg dose groups. There was a decrease in somnolence but no change in sleep duration.

6.1.5.   Study A3921040

Study A3921040 was a Phase 2, multi-center, randomised, double-blind, placebo-controlled, parallel group dose finding study of CP-690,550 monotherapy in Japanese subjects with RA. The study was conducted at 47 centres in Japan from March 2009 to July 2010. The study included subjects aged between 20 and 70 years; with a diagnosis of RA based on the 1987 revised criteria of the ACR and active disease at both screening and baseline visits, defined as ≥6 joints tender or painful on motion and ≥6 joints swollen; with an ESR >ULN or CRP >0.7 mg/dL; meeting ACR 1991 Revised Criteria for Global Functional Classification in RA, Class I, II or III; and had failed an adequate trial of therapy (at least 8 weeks of treatment) with at least one DMARD due to lack of efficacy or toxicity, or changed drugs by necessity for safety reasons. The study treatments were:

· 1 mg CP-690,550 twice daily

· 3 mg CP-690,550 twice daily

· 5 mg CP-690,550 twice daily

· 10 mg CP-690,550 twice daily

· 15 mg CP-690,550 twice daily

· Placebo twice daily

Subjects were randomized in a 1:1:1:1:1:1 ratio. Treatment duration was 12 weeks. CP-690,550 doses were made up from 1 mg and 5 mg tablets. The efficacy outcome measures were: ACR20 (primary efficacy outcome measure), ACR50, ACR70, ACR90, ACR individual components, AUC for ACRn, DAS, DAS28-3(CRP), DAS28-4(ESR), HAQ-DI, SF-36 health survey, and EuroQol EQ-5D. The safety outcome measures were: AEs, laboratory tests, vital signs, and ECGs.

A total of 383 subjects were screened, 318 were randomized, and 317 received treatment: 53 with 1 mg, 53 with 3 mg, 52 with 5 mg, 53 with 10 mg, 54 with 15 mg and 52 with placebo. A total of 299 subjects completed. There were 264 (88.3%) females, 53 (16.7%) males, and the age range was 20 to 70 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline efficacy measures. For the primary efficacy outcome measure, ACR20, efficacy was greatest with the 15 mg dose level at 90.74%. Efficacy was also greatest at the 15 mg dose level for ACR50. However, for ACR70, ACR90, painful joint count, Patient's and Physician's Global Assessments, DAS-4(ESR) and FACIT score the greatest effects were at the 10 mg dose level. There were significant improvements in

all domains of the SF-36 for the 3 mg, 5 mg, 10 mg and 15 mg dose levels in comparison with placebo (p<0.05).

A comparison was made between the Japanese subjects in Study A3921040 and Caucasian subjects in Study A3921035 in Study PMAR-00186. The response rate at equivalent doses was predicted to be higher in the Japanese population, but the differences did not appear to be clinically or statistically significant.

6.1.6. Studies using combined data

A number of studies were performed using the Phase 2 data to make predictions pertinent to the Phase 3 study program:

- Study PMAR-00180 used data from Study A3921019 to develop a model for the effect of CP-690,550 on absolute neutrophil count. Model evaluation was performed using longitudinal mean data from other Phase 2 studies (Study A3921025, Study A3921035, Study A3921039, and Study A3921040) and also from two long-term open-label extension studies (Study A3921024 and Study A3921041). The final model estimated a median steady state decrease from baseline in absolute neutrophil count of 1.1 and 1.6 (10^9/L) for 5mg BID and 10 mg BID, respectively, after 6 months of treatment.

- Study PMAR-00181 modelled the effect CP-690,550 on LDL. The study used a nonlinear mixed effects model and data from Study A3921019, Study A3921035, Study A3921040, Study A3921025 and Study A3921039 to develop the model. Data from Study A3921024 and Study A3921041 were used to evaluate the model. The model predicted a mean (95% CI) increased from baseline in LDL after 12 weeks treatment of 13.4% (9.3% to 17.8%) with 5 mg twice daily and 18.1% (12.9% to 24.9%) with 10 mg twice daily.

- Study PMAR-00182 modelled the effect of CP-690,550 on serum ALT levels. The study predicted <1% subjects having elevations in ALT >3 x ULN.

- Study PMAR-00183 modelled the effect of CP-690,550 on serum creatinine as a reversible process with onset over 6 weeks and offset over 6 weeks.

- Study PMAR-00184 modelled Phase 1 and Phase 2 CP-690,550 plasma concentrations and blood pressure recordings and predicted no clinically significant effects of CP-690,550 upon blood pressure.

- Study PMAR-0187 modelled Phase 2 data from Study A3921019, Study A3921035, and Study A3921025 to determine the effect of CP-690,550 on lymphocyte subpopulations (CD3+ [Pan T-lymphocytes], CD3+CD4+ [Helper T-lymphocytes with MHC-II], CD3+CD8+ [Cytotoxic T-lymphocytes with MHC-I], CD16/56+ [Natural Killer Cells] and CD19+ [B-lymphocytes]). Changes in CD3+, CD4+, or CD8+ counts were variable and did not show a consistent pattern of dose response across studies. NK cells (CD16/56+) showed a dose-dependent decrease, while B cells (CD19+) showed a dose-dependent increase across the studies. The final model estimated an ED50 of 5 mg twice daily for changes in NK cells, with 10 mg twice daily corresponding to ED65. It was estimated that NK cells will achieve nadir (steady state) in approximately 8-10 weeks after initiation of therapy with recovery upon cessation of treatment to within 10% of baseline within approximately 4 weeks. In monotherapy studies, 5 and 10 mg twice daily doses were estimated to have 36% and 47% reductions in NK cells respectively.

- Study PMAR-00223 was a summary report of the above studies of combined data.

These studies appear to have been performed as a preliminary to Phase 3 development and have been superseded by the actual values observed in the Phase 3 studies.

6.2. Evaluator's conclusions on the dose finding studies

The Sponsor evaluated the dose response relationships for CP-690,550 satisfactorily prior to dose selection for the Phase 3 studies.

In monotherapy the dose range 5 mg to 30 mg twice daily was investigated in Study A3921019 and efficacy appeared to peak at the 15 mg dose. For ACR20 the response rate at Week 6 was 81.16% in the 15 mg group. In Study A3921035, that studied the dose range 1 mg to 15 mg twice daily, ACR20 response at Week 12 peaked in the 10 mg group at 75.41 %, with a slight increase to 75.44% in the 15 mg group. In Study A3921040, in Japanese subjects, the dose range 1 mg to 15 mg twice daily was evaluated in monotherapy and for the primary efficacy outcome measure, ACR20, efficacy was greatest with the 15 mg dose level at 90.74%. However, for ACR70, ACR90, painful joint count, Patient's and Physician's Global Assessments, DAS-4(ESR) and FACIT score the greatest effects were at the 10 mg dose level.

In combination with MTX, the dose range 1 mg to 30[5] mg twice daily was studied in Study A3921025 and the peak response for ACR20 was 58% at the 10 mg dose level at Week 12. In Study A3921039, CP-690,550 in the dose range 1 mg to 10 mg twice daily was evaluated in Japanese subjects and for ACR20, all active treatment groups were superior to placebo but peak effect was at the 5 mg dose level.

In addition, the Sponsor performed a number of combined studies using Phase 1 and Phase 2 data to predict the dose response relationships for efficacy and for adverse effects. These studies also supported the choice of the 5 mg and 10 mg twice daily regimens for adopting into the Phase 3 trials.

7. Clinical efficacy

7.1. Efficacy data

7.1.1. Pivotal efficacy studies in combination with MTX

7.1.1.1. Study A3921032

7.1.1.1.1. Study design, objectives, locations and dates

Study A3921032 was a multicentre, Phase 3, randomised, 6-month, double-blind, 3-month placebo controlled, parallel-group efficacy and safety study of CP-690,550 as add-on therapy to MTX in subjects with RA. The study was conducted at 82 centres including 33 in the US from October 2009 to March 2011.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

· At least 18 years of age

· RA with evidence of disease activity by joint counts and laboratory markers of inflammation:

– ACR classification criteria for the diagnosis of RA by satisfying at least four of the seven criteria (below)

– Active disease at both screening and baseline, as defined by having both: six tender/painful joints on motion (out of 68 joints assessed); and six swollen joints (out of 66 joints assessed)

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[5] Erratum: the dose range studied was 1 mg to 15 mg twice daily

- – Active disease, as defined by one of the following criteria at screening: ESR >28 mm/hour; or CRP >7 mg/L
- – Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA (below)

American College of Rheumatology (ACR) 1987 Revised Classification Criteria

Patients must have a diagnosis of rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) 1987 Revised Criteria. These criteria require that patients fulfill at least four (4) of the seven (7) criteria; criteria 1 through 4 must have been present for at least 6 weeks.

1. Morning Stiffness:

Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.

2. Arthritis of three or more joint areas:

At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

3. Arthritis of hand joints:

At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.

4. Symmetric arthritis:

Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).

5. Rheumatoid nodules:

Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.

6. Serum rheumatoid factor:

Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.

7. Radiographic changes:

Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Criteria for Classification of Functional Status in Rheumatoid Arthritis

Class I: Completely able to perform usual activities of daily living (self-care, vocational, and avocational).

Class II: Able to perform usual self-care and vocational activities, but limited in avocational activities.

Class III: Able to perform usual self-care activities, but limited in vocational and avocational activities.

Class IV: Limited in ability to perform usual self-care, vocational, and avocational activities.

Usual self-care activities including dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex- specific.

· Ongoing treatment with an adequate and stable dose of MTX, including all local standard-of-care practices for the administration of MTX (including dosage, laboratory testing, follow-up care [including contraception requirements], contraindications, and folate supplementation) would apply care throughout the study. Minimum guidelines for MTX and folate supplementation therapy during study were as follows:

– The patient must have taken oral or parenteral MTX continuously for at least 4 months before the first dose of study medication and be on a stable dose of 7.5 mg to 25 mg weekly for at least 6 weeks before the first dose of study medication. Stable weekly doses less than 15 mg were allowed only in the presence of intolerance to or toxicity from higher doses or where higher doses would violate the local label

– Patients should have been on an adequate and stable dose of folate supplementation (not less than 5 mg weekly) for at least 4 weeks before the first dose of study medication

· In the opinion of the investigator, at least one approved TNF-inhibiting biologic agent administered in accordance with its labelling recommendations was inadequately effective and/or not tolerated

· Sexually active women of childbearing potential and men whose partners were women of childbearing potential were required to use adequate contraceptive methods during participation in this study

· No evidence of active or latent or inadequately treated infection with TB

· For traditional DMARDs, the following minimum washout criteria applied:

– Minocycline, Penicillamine, and Sulfasalazine: 4 weeks

– Leflunomide: 8 weeks

– Auranofin, injectable gold: 8 weeks

– Antimalarials (hydroxychloroquine, chloroquine): antimalarials were allowed in this study

– Biologic Response Modifiers: Anakinra, Enbrel: 4 weeks; Adalimumab: 6 weeks; Infliximab: 8 weeks: Golimumab: 10 weeks; Abatacept, tocilizumab, certolizumab pegol: 12 weeks; Rituximab or other selective B-lymphocyte-depleting agents:1 year

– Oral corticosteroids: patients who were already on oral corticosteroids must have been on a stable dose of ≤10 mg/day of prednisone or equivalent for 4 weeks

– Intra-articular, intramuscular, or intravenous corticosteroids: none were allowed to be administered within 4 weeks before the first dose of study drug.

– Cyclosporine, Tacrolimus, Azathioprine: 4 weeks

– Prosorba Device/Column: 4 weeks

– Patients receiving non-prohibited concomitant medications for any reason must have been on a stable regimen, which was defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever was longer) before the first study dose

The exclusion criteria included:

· Any prior treatment with non-B-lymphocyte-selective lymphocyte depleting agents/therapies, such as alemtuzumab (Campath) or alkylating agents (eg, cyclophosphamide or chlorambucil) or total lymphoid irradiation

- Blood dyscrasias, including haemoglobin <9 g/dL or hematocrit <30%; WCC <3.0 × 10^9/L; absolute neutrophil count <1.2 × 10^9/L; platelet count <100 × 10^9/L

- Estimated GFR <40 mL/min based on Cockcroft-Gault calculation

- AST or ALT >1.5 × ULN

- Current or recent history of uncontrolled, clinically significant renal, hepatic, haematological, gastrointestinal, endocrine, metabolic, pulmonary, cardiac, or neurological disease

- History of any other autoimmune rheumatic disease other than Sjogren's syndrome

- History of an infected joint prosthesis at any time, with the prosthesis still in situ

- History of any lymphoproliferative disorder, such as Epstein Barr virus (EBV)-related lymphoproliferative disorder, history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease

- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months before the first dose of study drug

- History of any infection requiring antimicrobial therapy within 2 weeks before the first dose of study drug

- History of recurrent (more than 1 episode) herpes zoster, disseminated (a single episode) herpes zoster, or disseminated (a single episode) herpes simplex

- Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks before the first dose of study drug, expected to be vaccinated or exposed to these vaccines during treatment, or during the 6 weeks following discontinuation of study drug

- History of alcohol or substance abuse, unless in full remission for greater than 6 months before the first dose of study drug

- Screening 12-lead electrocardiogram (ECG) that demonstrated clinically relevant abnormalities that may affect patient safety or interpretation of study results

- Malignancy or a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ

- Significant trauma or major surgery within 1 month before the Screening Visit

- Infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses

7.1.1.1.3.   Study treatments

The study treatments were:

- 5 mg CP-690,550 twice daily

- 10 mg CP-690,550 twice daily

- Placebo, switched to 5 mg CP-690,550 twice daily after 3 months

- Placebo, switched to 10 mg CP-690,550 twice daily after 3 months

- CP-690,550 doses were made up from 5 mg tablets, **[information redacted]**.

7.1.1.1.4.   Efficacy variables and outcomes

The primary efficacy outcome measures were:

- ACR20 at Month 3

· HAQ-DI at Month 3

· Proportion of subjects with DAS28-4(ESR) <2.6 at Month 3

The secondary efficacy outcome measures were:

· ACR20 (other than Month 3)

· ACR50

· ACR70

· DAS28-3(CRP)

· DAS28-4(ESR)

· HAQ-DI

· SF-36 health survey

· EuroQol EQ-5D

· MOSS-SS

· FACIT-fatigue scale

· HCRU

· WLQ

The safety outcome measures were: AEs, laboratory tests, vital signs, and ECGs.

7.1.1.1.5. *Randomisation and blinding methods*

Subjects were randomised in a 2:2:1:1 ratio using an automated web/telephone system and a predetermined schedule.

7.1.1.1.6. *Analysis populations*

The efficacy (FAS) and safety analyses included all treated subjects.

7.1.1.1.7. *Sample size*

The sample size calculations were performed for each of the three primary efficacy outcome measures separately, using a step-down procedure:

· Over 90% power for the ACR20 analysis, the first endpoint in the step-down procedure, assuming a difference in response rates of at least 20% (with the placebo response at 30%) at Month 3

· Over 90% power for the analysis of the HAQ-DI, the second endpoint in the step-down procedure, for differences of 0.3 or greater at Month 3, assuming a standard deviation of 0.75

· Over 90% power for DAS28-4(ESR) <2.6, the third endpoint in the step-down procedure, assuming a difference in response rates of at least 15% (with the placebo response at 10%) at Month 3

The final sample size calculation was for a total of 396 subjects.

7.1.1.1.8. *Statistical methods*

Hypothesis tests were performed using the normal approximation in binomial proportions for categorical outcome measures and a mixed effects repeated measures model for continuous outcome variables. The mixed effects models included visit, geographic region and baseline values as covariates. The only subgroup analysis was for prior treatment with TNFα inhibitors. Imputation of missing variables was performed using LOCF.

Multiplicity was addressed by: in order to preserve type I error, each objective was assessed sequentially, using a step-down approach, where statistical significance could be claimed for the endpoint only if the previous endpoint in the sequence met the requirements for significance. Additionally, as there were two doses within each endpoint, the gate-keeping or step-down approach was to be applied, ie, the highest dose (CP-690,550 10 mg twice daily) at a given endpoint could achieve significance only if the 5 mg twice daily dose at the prior endpoint was significant.

7.1.1.1.9. Participant flow

There were 133 subjects randomised to 5 mg, 134 to 10 mg, 66 to placebo/5 mg and 66 to placebo/10 mg. Of these 107 (80.5%) in the 5 mg group completed, 103 (76.9%) in the 10 mg group, 53 (80.3%) in the placebo/5 mg and 48 (72.7%) in the placebo/10 mg. Subject disposition is summarized in Table 3.

Table 3: Patient Disposition (Study A3921032)

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 589				
Assigned to Study Treatment	133	134	66	66
Treated	133	134	66	66
Completed	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)
Discontinued	26 (19.5)	31 (23.1)	13 (19.7)	18 (27.3)
Patient Died	0	0	0	1 (1.5)
Related to Study Drug	10 (7.5)	12 (9.0)	6 (9.1)	8 (12.1)
Adverse event	8 (6.0)	7 (5.2)	3 (4.5)	0
Lack of efficacy	2 (1.5)	5 (3.7)	3 (4.5)	8 (12.1)
Not Related to Study Drug	16 (12.0)	19 (14.2)	7 (10.6)	9 (13.6)
Adverse event	4 (3.0)	5 (3.7)	1 (1.5)	4 (6.1)
Other	1 (0.8)	1 (0.7)	1 (1.5)	0
Protocol violation	2 (1.5)	8 (6.0)	3 (4.5)	4 (6.1)
Patient no longer willing to participate in study	9 (6.8)	5 (3.7)	2 (3.0)	1 (1.5)

7.1.1.1.10. Major protocol violations/deviations

There were 53 subjects with incorrect dosing of study drug and 22 that took prohibited concomitant medication.

7.1.1.1.11. Baseline data

There were 335 females, 64 males and the age range was 20 to 84 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics and outcome measures. All subjects had received prior MTX, 123 (30.8 %) patients had taken traditional DMARDs other than MTX and 46 (11.5%) patients had taken biologic DMARDs other than TNF inhibitors before screening; with similar proportions in each of the treatment groups.

7.1.1.1.12. Results for the primary efficacy outcomes

At Month 3:

- ACR20 was achieved by significantly more subjects in the active treatment groups: 41.67% subjects in the 5 mg group (p=0.0024), 48.12% in the 10 mg (p<0.0001) and 24.43% in the placebo

- HAQ-DI decreased from baseline to a greater extent in the active treatment groups: -0.43 in the 5 mg group (p<0.0001), -0.46 in the 10 mg (p<0.0001) and -0.18 in the placebo

- The proportion of subjects with DAS28-4(ESR) <2.6 was greater in the active treatment groups 6.72% in the 5 mg (p=0.0496), 8.80% in the 10 mg (p=0.0105) and 1.67% in the placebo

7.1.1.1.13. Results for other efficacy outcomes

- ACR20 response rates were greater in the active treatment groups compared to placebo up to 3 months, and this response was maintained to 6 months

- ACR50 response rates were greater in the active treatment groups compared to placebo up to 3 months, and this response was maintained to 6 months

- ACR70 response rates were greater in the active treatment groups compared to placebo up to 3 months, and this response was maintained to 6 months

- The decrease in HAQ-DI was maintained through 6 months of treatment

- In the active treatment groups there was a decrease in DAS28-4(ESR) relative to placebo at Month 3 that was maintained through to Month 6

- In the active treatment groups there was a decrease in DAS28-3(CRP) relative to placebo at Month 3 that was maintained through to Month 6

- In the active treatment groups there was a improvement in EQ-5D relative to placebo at Month 3 that was maintained through to Month 6

- Relative to placebo, at Month 3, there were significant improvements in all of the domains of the SF-36 health survey

- Summary statistics for HCRU were provided but it is not clear whether there was any significant improvement for the treatment groups.

- For the WLQ, in the active treatment groups relative to placebo there were significant improvements in time management scale, mental/interpersonal demands scale and output demands scale but not for physical demands scale.

There were similar improvement in the individual components of the ACR, such as Patent's and Physician's Global Assessments, swollen and tender joint counts and pain scores. There was a decrease in sleep disturbance MOSS-SS subscale in the active treatment groups. There was an improvement relative to placebo at Month 3 in the FACIT fatigue scale.

There was no significant difference in efficacy between the two dosing levels[6].

Efficacy was not influenced by prior treatment with TNFα inhibitors.

7.1.1.2. Study A3921044

7.1.1.2.1. Study design, objectives, locations and dates

Study A3921044 was a multicentre, Phase 3, randomised, 2-year, double-blind, placebo-controlled, parallel group study of CP-690,550 as add-on therapy to MTX in subjects with RA. The results from the first year were presented in the report as an interim analysis. The study was conducted at 111 centres: including 33 in the US from March 2009 to April 2011.

7.1.1.2.2. Inclusion and exclusion criteria

The inclusion criteria were similar to Study A3921032, but in addition included:

- Active, moderate to severe RA with joint erosions or positive immunoglobulin M (IgM) Rheumatoid Factor (RF+) or antibodies to cyclic citrullinated peptide (anti-CCP)

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[6] There was no statistical comparison between tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

· Evidence of at least three distinct joint erosions on posteroanterior (PA) hand and wrist or anteroposterior (AP) foot radiographs (locally read) or if radiographic evidence of joint erosion was not available, the patient must have had an RF+, as determined by an acceptable laboratory method, or antibodies to anti-CCP+, as determined by an acceptable laboratory method

The exclusion criteria were similar to those for Study A3921032 with the addition of:

· Prior treatment with non B cell-specific lymphocyte depleting agents/therapies, (eg, alemtuzumab, alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation). Patients who had received rituximab or other selective B lymphocyte depleting agents were eligible if they had not received such therapy for at least 1 year prior to study Baseline and had normal CD 19/20+ counts by fluorescence activated cell sorting (FACS) analysis

7.1.1.2.3. Study treatments

The study treatments were:

· 5 mg CP-690,550 twice daily

· 10 mg CP-690,550 twice daily

· Placebo / 5 mg CP-690,550 twice daily

· Placebo / 10 mg CP-690,550 twice daily

CP-690,550 doses were made up from 5 mg tablets, **[information redacted]**. Study duration was for **2 years (data up to 12 months were provided)** (3 to 6 months of placebo then reallocation if not an ACR20 responder[7]). For placebo allocated subjects, if after 3 months subjects did not have ACR20 response they were advanced to active treatment, otherwise they advanced after 6 months.

7.1.1.2.4. Efficacy variables and outcomes

There were four primary efficacy endpoints:

· ACR20 at Month 6

· Structure preservation as measured by the mTSS change from Baseline at Month 6

· Physical function as measured by the HAQ-DI change from Baseline at Month 3

· Incidence of DAS28-4(ESR) <2.6 at Month 6

The secondary efficacy outcome measures were the same as for Study A3921032 with the addition of mTSS.

The safety outcome measures were AEs, physical examination and laboratory tests.

7.1.1.2.5. Randomisation and blinding methods

Subjects were randomised in the ratio 4:4:1:1 using an automated web/telephone system and a predetermined schedule.

7.1.1.2.6. Analysis populations

The FAS and safety analysis set included all patients who were randomized to the study and received at least one dose of either CP-690,550 or placebo.

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[7] Clarification: if there was not at least a 20% improvement in both the tender/painful and swollen joint counts as reported in the study database, the patient was considered a nonresponder and reallocation occurred.

7.1.1.2.7. Sample size

The sample size was determined based on the endpoint: the preservation of joint structure as measured by mTSS at Month 6. The analysis was based on a power of 90% and an α of 0.05 and assumed a mean (SD) change from baseline for mTSS of 1.4 (3.4) for the placebo group and 0.6 (1.8) for the 10 mg CP-690,550.

7.1.1.2.8. Statistical methods

Imputation was applied to missing values due to a patient dropping from the study for any reason (eg, lack of efficacy or AE) by setting the ACR value (ACR20, ACR50, and ACR70) to non-responsive from that visit onward (that is, Baseline observation carried forward, BOCF).

Hypothesis tests were performed using:

·   For ACR20 and incidence of DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial variables

·   For the change from Baseline in the HAQ-DI at Month 3, a mixed-effect model with repeated measures. The Baseline value was a covariate; fixed effects included treatment, visit, and treatment by visit interaction, with patients as a random effect and structured covariance matrix

·   For change from Baseline in mTSS, an analysis of variance (ANOVA) model

7.1.1.2.9. Participant flow

A total of 1291 subjects were screened, 800 were randomised to treatment and 797 received treatment. There were 321 treated subjects in the 5 mg group, 316 in the 10 mg, 81 in the placebo/5 mg and 79 in the placebo/10 mg. Of the treated subjects, 250 (77.9%) in the 5 mg group, 265 (83.1%) in the 10 mg, 64 (79.0%) in the placebo/5 mg and 64 (81.0%) in the placebo/10 mg completed the first 12 months of the study. The FAS included 316 (98.4%) subjects in the 5 mg group, 309 (96.9%) in the 10 mg, 79 (97.5%) in the placebo/5 mg and 77 (97.5%) in the placebo/10 mg.

7.1.1.2.10. Major protocol violations/deviations

The most frequent protocol violations were taking prohibited concomitant drugs (39 subjects) and not having the required washout period for prior treatments (20).

7.1.1.2.11. Baseline data

There were 679 (85.2%) females, 118 (14.8%) males and the age range was 18 to 82 years. The treatment groups were similar in the patterns of prior DMARD use, but the placebo group had less prior treatment with TNFα inhibitors. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics and outcome measures.

7.1.1.2.12. Results for the primary efficacy outcome

The results for the primary efficacy analysis were:

·   For ACR response at Month 6, there were 51.46% responders in the 5 mg group, 61.81% in the 10 mg and 25.32% in the placebo (p<0.0001)

·   For mTSS the change (progression) from baseline to Month 6 was significantly less in the 10 mg group than placebo: LS mean change 0.12[8] compared with 0.47 (p=0.0376); but there was no significant difference for the 5 mg dose: **LS mean** 0.12

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[8] Erratum: correct LS mean value is 0.06 for the 10 mg group

- For HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 groups: LS mean change -0.40 for 5 mg, -0.54 for 10 mg and -0.15 for placebo (p<0.0001)

- The proportion of subjects achieving DAS28-4(ESR) was greater in the CP-690,550 groups: 7.17% for 5 mg (p<0.0034), 15.95% for 10 mg (p<0.0001) compared with 1.55% for placebo

7.1.1.2.13.   Results for other efficacy outcomes

- ACR20 response rates were greater in the active treatment groups compared to placebo up to 6 months, and this response was maintained to 12 months

- ACR50 response rates were greater in the active treatment groups compared to placebo up to 6 months, and this response was maintained to 12 months

- ACR70 response rates were greater in the active treatment groups compared to placebo up to 6 months, and this response was maintained to 12 months

- The proportion of subjects with no progression in mTSS to 12 months was greater in the CP-690,550 groups: 86.01% for 5 mg, 86.44% for 10 mg compared with 74.10% for placebo (p<0.01). Subgroup analysis indicated progression in mTSS was not affected by anti-CCP status, disease duration, baseline DAS28-4(ESR) or baseline radiographic progression.

- The decrease in HAQ-DI was maintained through 12 months of treatment

- In the active treatment groups there was a decrease in DAS28-4(ESR) relative to placebo at Month 3 that was maintained through to Month 12

- In the active treatment groups there was a decrease in DAS28-3(CRP) relative to placebo at Month 3 that was maintained through to Month 12

- Relative to placebo, at Month 3 and Month 6, there were significant improvements in all of the domains of the SF-36 health survey for both CP-690,550 dose levels

- Relative to placebo, FACIT fatigue scales improved in both treatment groups and the improvement was maintained through to Month 12

- In the active treatment groups there was a improvement in EQ-5D relative to placebo at Month 3 that was maintained through to Month 12

- Summary statistics for HCRU were provided but it is not clear whether there was any significant improvement for the treatment groups.

- For the WLQ, in the active treatment groups relative to placebo there no significant differences at Month 6.

At Month 6 there was no difference between CP-690,550 and placebo in MOSS-SS subscores.

There was no significant difference between the two dose levels in efficacy outcome measures[9].

7.1.1.3.   Study A3921064

7.1.1.3.1.   Study design, objectives, locations and dates

Study A3821064 was a multicentre, Phase 3 randomised, 1-year, double blind, placebo controlled, parallel group study to compare CP-690,550 with placebo and adalimumab in the treatment of RA in subjects on a stable dose of MTX. The study was conducted at 115 centres, including 25 in the US, from May 2009 to March 2011.

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[9] There was no statistical comparison between tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

7.1.1.3.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were similar to those for Study A3921032, except with the removal of the requirement to have failed prior treatment with a TNF-α inhibitor and the addition of the exclusions:

· Subjects who have failed any TNF-α inhibitor for either lack of efficacy or a TNF-α inhibitor mechanism related AE

· Subjects who have previously received adalimumab therapy for any reason

· Subjects who are contraindicated for treatment with adalimumab in accordance with the approved local label. Patients meeting the New York Heart Association Class III and Class IV congestive heart failure (Class III: patients with marked limitation of activity; they are comfortable only at rest; Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest)

7.1.1.3.3. Study treatments

The study treatments were:

· 5 mg CP-690,550, orally twice daily

· 10 mg CP-690,550, orally twice daily

· Placebo / 5 mg CP-690,550, orally twice daily

· Placebo / 10 mg CP-690,550, orally twice daily

· Adalimumab 40 mg by subcutaneous injection every 2 weeks

If after 3 months subjects in the two placebo groups did not have ACR20 response they were advanced to active treatment[10], otherwise they advanced after 6 months. CP-690,550 doses were made up from 5 mg tablets, **[information redacted]**.

7.1.1.3.4. Efficacy variables and outcomes

The primary efficacy outcome measures were:

· ACR20 at Month 6

· HAQ-DI at Month 3

· Proportion of subjects with DAS28-4(ESR) <2.6 at Month 6

The secondary efficacy outcome measures were the same as for Study A3921032, as were the safety outcome variables.

7.1.1.3.5. Randomisation and blinding methods

Subjects were randomised in the ratio 4:4:1:1:4 using an automated web/telephone system and a predetermined schedule. There were placebos for both adalumimab and CP-690,550.

7.1.1.3.6. Analysis populations

The FAS and safety analysis set included all patients who were randomised to the study and received at least one dose of either CP-690,550, adalimumab or placebo.

7.1.1.3.7. Sample size

The sample size calculation was performed using an α of 0.05 and:

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[10] Clarification: advancement occurred if there was not a 20% improvement in both the tender/painful and swollen joint counts.

- For the ACR20 analysis, the sample size was planned to yield over 90% power, assuming a difference in response rates of at least 20% (with the placebo response at 30%)

- For the analysis of the HAQ-DI, the sample size resulted in over 90% power for differences of 0.3 or greater, assuming a standard deviation of 0.75

- For the analysis of DAS28-4(ESR)<2.6, the sample size resulted in approximately 94% (93.8%) power for differences in response rates of at least 15% with placebo response at 10%

7.1.1.3.8.   Statistical methods

Hypothesis tests were performed in the same manner as for Study A3921032. Imputation for missing variables was performed using LOCF.

7.1.1.3.9.   Participant flow

There were 1042 subjects screened, 717 were assigned to treatment and all received study treatment. There were 204 subjects in the 5 mg group, 201 in the 10 mg, 56 on the placebo/5 mg, 52 in the placebo/10 mg and 204 in the adalimumab. A total of 150 (70%) subjects in the 5 mg group completed, as did 158 (78.6%) in the 10 mg, 47 (83.9%) in the placebo/5 mg, 39 (75%) in the placebo/10 mg and 162 (79.4%) in the adalimumab. Subject disposition is summarised in Table 4.

Table 4: Subject Disposition by Treatment Sequence (Study A3821064)

Number (%) of Patients	CP-690,550 5 mg	CP-690,550 10 mg	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID	Adalimumab 40 mg SC q 2 weeks
Screened: 1042					
Assigned to study treatment	204	201	56	52	204
Treated	204	201	56	52	204
Completed	150 (73.5)	158 (78.6)	47 (83.9)	39 (75.0)	162 (79.4)
Discontinued	54 (26.5)	43 (21.4)	9 (16.1)	13 (25.0)	42 (20.6)
Patient died	0	0	0	0	1 (0.5)
Related to study drug	25 (12.3)	22 (10.9)	5 (8.9)	5 (9.6)	22 (10.8)
Adverse event	19 (9.3)	15 (7.5)	2 (3.6)	2 (3.8)	16 (7.8)
Lack of efficacy	6 (2.9)	7 (3.5)	3 (5.4)	3 (5.8)	6 (2.9)
Not related to study drug	29 (14.2)	21 (10.4)	4 (7.1)	8 (15.4)	19 (9.3)
Adverse event	5 (2.5)	9 (4.5)	0	3 (5.8)	6 (2.9)
Lost to follow-up	2 (1.0)	1 (0.5)	0	0	0
Other	18 (8.8)	9 (4.5)	4 (7.1)	4 (7.7)	12 (5.9)
Patient no longer willing to participate in study	4 (2.0)	2 (1.0)	0	1 (1.9)	1 (0.5)

7.1.1.3.10.   Major protocol violations/deviations

The most common protocol deviations were: lack of CXR (74), one or more questionnaires not completed (55), incorrect joint joints entered (52), molecular profiling samples taken without consent (46), CRP/ESR unblinded (46), incorrect dosing (22), one or more tests not performed (21), prohibited concomitant medications (19) and lack of adherence to dosing schedule (19).

7.1.1.3.11.   Baseline data

There were 586 (81.7%) females, 131 (18.3%) males and the age range was 18 to 83 years. Previous TNF-α inhibitor treatment had been received by twelve (5.9%) subjects in the 5 mg group, 14 (7.0%) in the 10 mg, four (7.1%) in the placebo/5 mg, five (9.6%) in the placebo/10 mg and 16 (7.8%) in the adalimumab. Prior DMARD treatment was similar for the five treatment groups. The demographic characteristics were similar for the five treatment groups. Baseline and disease characteristics were similar for the five treatment groups.

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 41 of 72

7.1.1.3.12. Results for the primary efficacy outcome

The results for the primary efficacy analysis were:

- For ACR20 response at Month 6, there were 51.53% responders in the 5 mg group (p<0.0001 compared to placebo), 52.55% in the 10 mg (p<0.0001 compared to placebo), 47.24% in the adalimumab (p=0.0007 compared to placebo), and 28.30% in the placebo

- For HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 and adalimumab groups compared to placebo: LS mean change -0.55 for 5 mg, -0.61 for 10 mg, -0.49 for adalimumab and -0.24 for placebo (p<0.0001)

- The proportion of subjects achieving DAS28-4(ESR) <2.6 at Month 6 was greater in the CP-690,550 and adalimumab groups relative to placebo: 6.21% for 5 mg (p=0.0151), 11.41% for 10 mg (p<0.0001), 6.74% for adalimumab (p=0.0091) and 1.09% for placebo

Results for other efficacy outcomes

- ACR20 response rates were greater in the CP-690,550 and adalimumab groups compared to placebo at 3 months, and this response was maintained to 12 months

- ACR50 response rates were greater in the CP-690,550 and adalimumab groups compared to placebo at 3 months, and this response increased to 12 months

- ACR70 response rates were greater in the CP-690,550 and adalimumab groups compared to placebo at 3 months, and this response increased to 12 months

- The decrease in HAQ-DI was maintained through 12 months of treatment

- In the active treatment groups there was a decrease in DAS28-4(ESR) relative to placebo at Month 3 that was maintained through to Month 12

- In the active treatment groups there was a decrease in DAS28-3(CRP) relative to placebo at Month 3 that was maintained through to Month 6

- Relative to placebo, at Month 6, there were significant improvements in all of the domains of the SF-36 health survey for both CP-690,550 dose levels, but the improvements for adalimumab were less apparent

- Relative to placebo, at Month 6, for the CP-690,550 5mg and 10 mg dose levels there was significant improvement in the MOSS subscales for overall sleep problems, sleep problems and sleep disturbance. At Month 6, adalimumab resulted in some improvement in sleep disturbance

- Relative to placebo, FACIT fatigue scales improved in the CP-690,550 and adalimumab groups at Month 3 and the improvement was maintained through to Month 6

- In the active treatment groups there was a improvement in EQ-5D relative to placebo at Month 3 that was maintained through to Month 6

- Summary statistics for HCRU were provided but it is not clear whether there was any significant improvement for the treatment groups.

- For the WLQ, in the 5 mg and adalimumab groups relative to placebo there were no significant differences at Months 3 or 6, but for the 10 mg dose there was a improvement in time management and in output demands at Month 3

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 42 of 72

There was no significant difference in response between the CP-690,550 5 mg and 10 mg dose levels[11], or between CP-690,550 and adalimumab in efficacy outcome measures.

7.1.2. Pivotal studies as monotherapy

7.1.2.1. Study A3921045

7.1.2.1.1. Study design, objectives, locations and dates

Study A3921045 was a multicentre, Phase 3, randomised, 6-month, double blind, placebo controlled, parallel group trial of CP-690,550 as monotherapy in subjects with RA and an inadequate response to a DMARD. The study was conducted at 94 centres, including 30 in the US, from February 2009 to June 2010.

7.1.2.1.2. Inclusion and exclusion criteria

Similar inclusion criteria to Study A3921032 except for:

· Subject must have an inadequate response to at least one DMARD (traditional or biologic) due to lack of efficacy or toxicity.

· No requirement for prior or concomitant treatment with MTX

· All DMARDs, traditional and biological, including MTX were to be discontinued with an adequate washout period prior to study treatment.

The exclusion criteria were similar to those for Study A3921032.

7.1.2.1.3. Study treatments

· 5 mg CP-690,550 twice daily

· 10 mg CP-690,550 twice daily

· Placebo for 3 months then 5 mg CP-690,550 twice daily

· Placebo for 3 months then 10 mg CP-690,550 twice daily

CP-690,550 doses were made up from 5 mg tablets **[information redacted]**.

7.1.2.1.4. Efficacy variables and outcomes

The study outcome measures were the same as for Study A3921032.

7.1.2.1.5. Randomisation and blinding methods

Subjects were randomised in a 4:4:1:1 ratio.

7.1.2.1.6. Analysis populations

The FAS included all patients who were randomised to the study and received at least one dose of the randomised study drug: CP-690,550 or placebo.

7.1.2.1.7. Sample size

The sample size calculation was the same as for Study A3921032 and in addition allowance was made for a 25% drop-out rate.

7.1.2.1.8. Statistical methods

Missing values were imputed using LOCF.

· Hypothesis tests were performed using:

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[11] There was no statistical comparison between tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

- For ACR20 and incidence of DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial variables

- For the change from Baseline in the HAQ-DI at Month 3, a mixed-effect model with repeated measures as treatment effect model. The Baseline value was a covariate; fixed effects included treatment, visit, treatment by visit interaction, and geographic region, with patients as a random effect and structured covariance matrix

7.1.2.1.9.   Participant flow

A total of 954 subjects were screened, 611 were randomised to treatment and 610 received at least one dose of study medication: 243 in the 5 mg group, 245 in the 10 mg, 61 in the placebo/5 mg and 61 in the placebo/10 mg. Of these subjects 555 (91.0%) completed, including 232 (95.1%) in the 5 mg group, 218 (89.0%) in the 10 mg, 54 (88.5%) in the placebo/5 mg and 51 (83.6%) in the placebo/10 mg. The FAS comprised 241 (98.8%) subjects in the 5 mg group, 243 (99.2%) in the 10 mg, 61 (100.0%) in the placebo/5 mg and 61 (100.0%) in the placebo/10 mg.

7.1.2.1.10.   Major protocol violations/deviations

The most common protocol violations were that 14 subjects did not have CXR prior to screening and nine subjects received prohibited concomitant medication.

7.1.2.1.11.   Baseline data

There were 82 (13.4%) males, 528 (86.6%) females and the age range was 21 to 81 years. The treatment groups were similar in demographic characteristics. The study groups were similar in baseline disease characteristics and efficacy outcome variables. Prior to screening, 518 (84.9%) subjects had taken MTX, 405 (66.4%) had taken traditional DMARDs other than MTX and 41 (6.7%) had taken other biologic DMARDs. Concomitant antimalarials were taken by 45 (18.4%) subjects in the 5 mg group, 41 (16.7%) in the 10 mg, eight (13.1%) in the placebo/5 mg and seven (11.5%) in the placebo/10 mg. During the study one subject in the CP-690,550 group was commenced on MTX and one in the placebo/10 mg group was commenced on leflunomide.

7.1.2.1.12.   Results for the primary efficacy outcome

The results for the primary efficacy analysis were:

- For ACR20 response at Month 3, there were 59.75% responders in the 5 mg group, 65.70% in the 10 mg and 26.67% in the placebo (p<0.0001)

- For HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 groups: LS mean change -0.50 for 5 mg, -0.57 for 10 mg and -0.19 for placebo (p<0.0001)

- There was no significant difference between CP-690,550 and placebo in the proportion of subjects achieving DAS28-4(ESR) <2.6 at Month 3: 5.60% for 5 mg, 8.73% for 10 mg, and 4.39% for placebo

Results for other efficacy outcomes

- ACR20 response rates were greater in the active treatment groups compared to placebo at 3 months, and this response was maintained to 6 months

- ACR50 response rates were greater in the active treatment groups compared to placebo at 3 months, and this response was maintained to 6 months

- ACR70 response rates were greater in the active treatment groups compared to placebo at 3 months, and this response was maintained to 6 months

- The decrease in HAQ-DI was maintained through 6 months of treatment

- In the active treatment groups there was a decrease in DAS28-4(ESR) relative to placebo at Month 3 that was maintained through to Month 6

- In the active treatment groups there was a decrease in DAS28-3(CRP) relative to placebo at Month 3 that was maintained through to Month 6

- Relative to placebo, at Month 3, there were significant improvements in all of the domains of the SF-36 health survey for both CP-690,550 dose levels

- Relative to placebo, at Month 3, for the 10 mg dose there was significant improvement in the MOSS subscales for overall sleep problems, sleep problems, somnolence and sleep adequacy

- Relative to placebo, FACIT fatigue scales improved in both treatment groups at Month 3 and the improvement was maintained through to Month 6

- In the active treatment groups there was a improvement in EQ-5D relative to placebo at Month 3 that was maintained through to Month 6

- Summary statistics for HCRU were provided but it is not clear whether there was any significant improvement for the treatment groups.

- For the WLQ, in the active treatment groups relative to placebo there no significant differences at Month 3

There was no significant difference in response between the 5 mg and 10 mg dose levels in efficacy outcome measures[12].

7.1.3. Pivotal studies as concurrent treatment with DMARDS

7.1.3.1. Study A3921046

7.1.3.1.1. Study design, objectives, locations and dates

Study A3921046 was a multicentre, Phase 3, randomised, 1-year, double blind, placebo controlled, parallel group study of two dose levels of CP-690,550 in subjects with RA and concurrent treatment with DMARDs. The study was conducted at 114 centres from May 2009 to January 2011.

7.1.3.1.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were similar to those for Study A3921032 with the addition of:

- Active disease at both screening and baseline, as defined by having both: four tender/painful joints on motion (out of 68 joints assessed); and four swollen joints (out of 66 joints assessed)

- The subject must have remained on at least one background traditional DMARD and be dosed in accordance with the local regulatory label and willing to remain on that traditional DMARD throughout the course of the study. Combination therapy was allowed as consistent with local standards. The Traditional DMARDs included MTX, sulfasalazine, leflunomide, hydroxychloroquine sulfate, injectable gold, and penicillamine. Others could be included after discussion with the Sponsor.

7.1.3.1.3. Study treatments

The study treatments were:

- 5 mg CP-690,550 twice daily

- 10 mg CP-690,550 twice daily

- Placebo / 5 mg CP-690,550 twice daily

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[12] There was no statistical comparison between tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 45 of 72

· Placebo / 10 mg CP-690,550 twice daily

CP-690,550 doses were made up from 5 mg tablets, **[information redacted]**. Study duration was for 12 months (3 to 6 months of placebo with reallocation). For placebo allocated subjects, if after 3 months subjects did not have ACR20 response they were advanced to active treatment[13], otherwise they advanced after 6 months.

7.1.3.1.4. Efficacy variables and outcomes

The study outcome measures were the same as for Study A3921032 except that the primary efficacy outcomes were measured at Month 6[14].

7.1.3.1.5. Randomisation and blinding methods

Subjects were randomised in the ratio 4:4:1:1.

7.1.3.1.6. Analysis populations

The FAS included all subjects that were randomised and received at least one dose of CP-690,550 or placebo.

7.1.3.1.7. Sample size

The sample size was not actually stated in the study report or in the protocol. However it was stated to have been determined for each of the primary endpoints using the following criteria:

· For each of the endpoints α was 0.05.

· For ACR20 the sample size yielded over 90% power assuming a difference in response rates of at least 20% with the placebo response at 30%

· For HAQ-DI the sample size resulted in over 90% power (97%) for differences of 0.3 or greater, assuming a SD of 0.75

· For DAS28-4(ESR) <2.6, there was over 90% power (99%) for differences in response rates of at least 15% with placebo response of 10%

In order to address multiplicity, a step-down approach was used, as for Study A3921032.

7.1.3.1.8. Statistical methods

Hypothesis tests were performed in the same manner as for Study A3921032.

7.1.3.1.9. Participant flow

There were 1281 subjects screened, 795 randomised and 792 received study treatment: 315 in the 5 mg group, 318 in the 10 mg group, 79 in the placebo/5 mg and 80 in the placebo/10 mg. Of these subjects, 261 (82.1%) in the 5 mg group, 252 (79.2%) in the 10 mg, 71 (89.9%) in the placebo/5 mg and 67 (83.8%) in the placebo/10 mg completed the protocol.

7.1.3.1.10. Major protocol violations/deviations

The most common protocol deviations were: CXR not obtained (61), one or more medications not given at a stable dose (38) and ECG not performed at one or more visits (24).

7.1.3.1.11. Baseline data

There were 645 (81.4%) females, 147 (18.6%) males, and the age range was 18 to 86 years. MTX was the most common DMARD prior to screening. TNFα inhibitors were taken prior to screening by 23 (7.3%) subjects in the 5 mg group, 19 (6.0%) in the 10 mg group, five (6.3%) in the placebo/5 mg and five (6.3%) in the placebo/10 mg. The most common DMARD taken in combination was MTX followed by leflunomide, and the distribution was similar for the four

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[13] Advancement occurred if there was not a 20% improvement in both the tender/painful and swollen joint counts.
[14] AusPAR clarification: HAQ-DI primary endpoint was assessed at Month 3.

treatment groups. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics and efficacy outcome variables.

7.1.3.1.12.   Results for the primary efficacy outcome

The results for the primary efficacy analysis were:

- For ACR20 response at Month 6, there were 52.73% responders in the 5 mg group, 58.25% in the 10 mg and 31.21% in the placebo (p<0.0001)

- For HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 groups: LS mean change -0.46 for 5 mg, -0.56 for 10 mg and -0.21 for placebo (p<0.0001)

- The proportion of subjects achieving DAS28-4(ESR) <2.6 at Month 6 was greater in the CP-690,550 groups relative to placebo: 9.13% for 5 mg (p=0.0038), 13.33% for 10 mg (p<0.0001), and 2.70% for placebo

7.1.3.1.13.   Results for other efficacy outcomes

- ACR20 response rates were greater in the active treatment groups compared to placebo at 3 months, and this response was maintained to 12 months. ACR20 response was not influenced by the type of background DMARD

- ACR50 response rates were greater in the active treatment groups compared to placebo at 3 months, and this response was maintained to 12 months

- ACR70 response rates were greater in the active treatment groups compared to placebo at 3 months, and this response was maintained to 12 months

- The decrease in HAQ-DI was maintained through 12 months of treatment

- In the active treatment groups there was a decrease in DAS28-4(ESR) relative to placebo at Month 3 that was maintained through to Month 12

- In the active treatment groups there was a decrease in DAS28-3(CRP) relative to placebo at Month 3 that was maintained through to Month 12

- Relative to placebo, at Month 3, there were significant improvements in all of the domains of the SF-36 health survey for both CP-690,550 dose levels). Statistical significance was not demonstrated for some of the scores at Month 6, but this could be attributed to a smaller placebo group.

- Relative to placebo, at Month 3, for the 10 mg dose there was significant improvement in the MOSS subscales for overall sleep problems, sleep problems, somnolence and sleep adequacy. Significant differences were not demonstrated at Month 6, but this could be attributed to a decrease in the size of the placebo group.

- Relative to placebo, FACIT fatigue scales improved in both treatment groups at Month 3 and the improvement was maintained through to Month 12

- In the active treatment groups there was an improvement in EQ-5D relative to placebo at Month 3 that was maintained through to Month 6

- Summary statistics for HCRU were provided but it is not clear whether there was any significant improvement for the treatment groups.

- For the WLQ, in the active treatment groups relative to placebo there no significant differences at Month 3

There was no significant difference in response between the 5 mg and 10 mg dose levels in efficacy outcome measures[15].

7.1.4. Other efficacy studies

7.1.4.1. Long term follow-on studies

Study A3921024 / A3921041 was a long-term tolerability, safety and efficacy conducted in subjects who had completed Studies A3921019, A3921025, A3921032, A3921035, A3921044, A3921045, A3921046, A3921064, A3921069, A3921073, A3921109, A3921039, and A3921040. The efficacy outcome measures were ACR20, ACR50, ACR70, HAQ-DI score and DAS28-4(ESR). A total of 3227 subjects were included: 1321 treated with CP-690,550 5 mg twice daily and 1906 treated with 10 mg twice daily. Of these, 2019 were also on background DMARDs and 1208 were on CP-690,550 monotherapy. There were 2680 (83.1%) females, 546 (16.9%) males and the age range was 18 to 86 years. The demographic characteristics of the study population are summarised in Table 5.

Table 5: Demographic Characteristics (All Patients) (Study A3921024 / A3921041)

No. (%) of Patients	CP-690,550		
	5 mg BID	10 mg BID	All Doses
Number of patients	1321	1905	3226
Age (years)			
<18	0	0	0
18-44	315 (23.8)	373 (19.6)	688 (21.3)
45-64	792 (60.0)	1205 (63.3)	1997 (61.9)
≥65	214 (16.2)	327 (17.2)	541 (16.8)
Mean	52.7	53.7	53.3
SD	11.9	11.4	11.6
Range	18-81	18-86	18-86
Gender			
Male	221 (16.7)	325 (17.1)	546 (16.9)
Female	1100 (83.3)	1580 (82.9)	2680 (83.1)
Race			
White	642 (48.6)	1386 (72.8)	2028 (62.9)
Black	22 (1.7)	70 (3.7)	92 (2.9)
Asian	532 (40.3)	329 (17.3)	861 (26.7)
Hispanic	14 (1.1)	0	14 (0.4)
Other	108 (8.2)	115 (6.0)	223 (6.9)
Unspecified	3 (0.2)	5 (0.3)	8 (0.2)
Weight (kg)			
Mean	66.2	73.4	70.5
SD	17.2	19.9	19.2
Range	31.4-146.9	30.5-188.0	30.5-188.0
N	1319 (99.8)	1905 (100.0)	3224 (99.9)
Body Mass Index (kg/m^2)^a			
Mean	25.6	27.5	26.7
SD	5.7	6.7	6.4
Range	15.5-46.9	13.9-70.8	13.9-70.8
N	1318 (99.8)	1905 (100.0)	3223 (99.9)
Height (cm)			
Mean	160.5	163.0	162.0
SD	8.7	9.0	9.0
Range	130.0-198.0	125.3-197.0	125.3-198.0
N	1318 (99.8)	1905 (100.0)	3223 (99.9)

BID=twice daily; SD=standard deviation; No.=number; N=number of patients
Includes Studies A3921024 and A3921041. Patient 1024-13741003 is not included in this table as this patient has missing demographic information.

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[15] There was no statistical comparison between tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

At the date of cutoff there were 1022 (77%) subjects ongoing in the 5 mg group and 1768 (92.8%) in the 10 mg. There were 970 subjects treated for more than 12 months, 659 for more than 24 months and 62 for more than 36 months. Efficacy (as measured by ACR20, ACR50 and ACR70) appeared to be maintained for up to 3 years). Reduction in HAQ-DI score was maintained for up to 36 months. Reduction in DAS28-4(ESR) score was maintained for up to 36 months.

A series of table and figures with combined efficacy data were provided in the folder titled: ISE (Integrated Summary of Efficacy). There was no explanatory text with the tables. Hence the methodology behind the analysis was not explained. Most of the tables were repeated from the individual efficacy studies, but there was an exploratory analysis of the effect of patient characteristics on efficacy that found no substantial effects.

7.2. Evaluator's conclusions on clinical efficacy

Efficacy for both dose levels (5 mg twice daily and 10 mg twice daily) was demonstrated in combination with MTX. For ACR20:

- In Study A3921032, ACR20 was achieved by significantly more subjects in the active treatment groups: 41.67% subjects in the 5 mg group (p=0.0024), 48.12% in the 10 mg (p<0.0001) and 24.43% in the placebo

- In Study A3921044, for ACR response at Month 6, there were 51.46% responders in the 5 mg group, 61.81% in the 10 mg and 25.32% in the placebo (p<0.0001)

- In Study A3821064, for ACR20 response at Month 6, there were 51.53% responders in the 5 mg group (p<0.0001 compared to placebo), 52.55% in the 10 mg (p<0.0001 compared to placebo), 47.24% in the adalimumab (p=0.0007 compared to placebo), and 28.30% in the placebo

For mTSS:

- In Study A3921044, for mTSS the change (progression) from baseline to Month 6 was significantly less in the 10 mg group than placebo: LS mean change 0.12[16] compared with 0.47 (p=0.0376); but there was no significant difference for the 5 mg dose: **LS mean:** 0.12

For HAQ-DI

- In Study A3921032, HAQ-DI decreased from baseline to a greater extent in the active treatment groups: -0.43 in the 5 mg group (p<0.0001), -0.46 in the 10 mg (p<0.0001) and -0.18 in the placebo

- In Study A3921044, for HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 groups: LS mean change -0.40 for 5 mg, -0.54 for 10 mg and -0.15 for placebo (p<0.0001)

- In Study A3821064, for HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 and adalimumab groups compared to placebo: LS mean change -0.55 for 5 mg, -0.61 for 10 mg, -0.49 for adalimumab and -0.24 for placebo (p<0.0001)

For DAS-4(ESR) <2.6:

- In Study A3921032 the proportion of subjects with DAS28-4(ESR) <2.6 was greater in the active treatment groups 6.72% in the 5 mg (p=0.0496), 8.80% in the 10 mg (p=0.0105) and 1.67% in the placebo

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[16] Erratum: correct LS mean value is 0.06 for the 10 mg group

- In Study A3921044, the proportion of subjects achieving DAS28-4(ESR) was greater in the CP-690,550 groups: 7.17% for 5 mg (p<0.0034), 15.95% for 10 mg (p<0.0001) compared with 1.55% for placebo

- In Study A3821064, the proportion of subjects achieving DAS28-4(ESR) <2.6 at Month 6 was greater in the CP-690,550 and adalimumab groups relative to placebo: 6.21% for 5 mg (p=0.0151), 11.41% for 10 mg (p<0.0001), 6.74% for adalimumab (p=0.0091) and 1.09% for placebo

In Study A3921032, Study A3921044 and Study A3821064 there was no significant difference in efficacy between the two dosing levels[17]. In Study A3821064 there was no significant difference in response between the CP-690,550 and adalimumab in efficacy outcome measures. Efficacy was not influenced by prior treatment with TNFα inhibitors. Efficacy was maintained for up to 12 months. The secondary outcome measures were supportive of efficacy.

Efficacy for both dose levels (5 mg twice daily and 10 mg twice daily) was demonstrated in monotherapy in Study A3921045:

- For ACR20 response at Month 3, there were 59.75% responders in the 5 mg group, 65.70% in the 10 mg and 26.67% in the placebo (p<0.0001)

- For HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 groups: LS mean change -0.50 for 5 mg, -0.57 for 10 mg and -0.19 for placebo (p<0.0001)

- There was no significant difference between CP-690,550 and placebo in the proportion of subjects achieving DAS28-4(ESR) <2.6 at Month 3: 5.60% for 5 mg, 8.73% for 10 mg, and 4.39% for placebo

Efficacy was maintained for up to 6 months. There was no significant difference in response between the 5 mg and 10 mg dose levels in efficacy outcome measures[17]. The secondary outcome measures supported efficacy.

Efficacy was demonstrated as concurrent treatment with DMARDs in Study A3921046:

- For ACR20 response at Month 6, there were 52.73% responders in the 5 mg group, 58.25% in the 10 mg and 31.21% in the placebo (p<0.0001)

- For HAQ-DI the change (improvement) from baseline was greater in the CP-690,550 groups: LS mean change -0.46 for 5 mg, -0.56 for 10 mg and -0.21 for placebo (p<0.0001)

- The proportion of subjects achieving DAS28-4(ESR) <2.6 at Month 6 was greater in the CP-690,550 groups relative to placebo: 9.13% for 5 mg (p=0.0038), 13.33% for 10 mg (p<0.0001), and 2.70% for placebo

Efficacy was maintained for up to 12 months. There was no significant difference in response between the 5 mg and 10 mg dose levels in efficacy outcome measures[17]. Efficacy response was not influenced by the type of background DMARD. The secondary outcome measures supported efficacy.

In Study A3921024 / A3921041 (an open-label study) efficacy (as measured by ACR20, ACR50 and ACR70) appeared to be maintained for up to 3 years.

The outcomes used in the efficacy studies were clinically relevant. The outcomes included symptom scores, measures of disease progression and also measures of wellbeing. The statistical analyses were appropriate.

The populations included in the efficacy studies were consistent with the indication that is being applied for:

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[17] There was no statistical comparison between tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

"JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate"

The recommended dosing regimen in the Product Information document is supported by the efficacy data: "The recommended dosage is 5 mg administered twice daily. Some patients may benefit from an increase to 10 mg administered twice daily, based on clinical response."

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

· AEs, SAEs and DAEs

· AEs of particular interest, including serious infections and cardiovascular events

· Laboratory tests, including serum lipids, CK, Creatinine, CRCL, ALT, AST and FBC

8.1.2. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

· AEs, SAEs and DAEs

· Laboratory tests, including serum lipids, CK, Creatinine, CRCL, ALT, AST and FBC

8.1.3. Other studies evaluable for safety only

· Study A3921024 is an ongoing, open label, long term, follow-on safety study. It includes subjects that have completed randomised Phase 2 and Phase 3 studies. Study A3921041 is also an ongoing long term safety study.

· Study A3921061 is an **[ongoing]** open label long-term safety study in subjects with plaque psoriasis. Limited data listings were provided.

· A3921069 is an ongoing Phase 3, randomised, 24-month, double-blind, parallel group study comparing CP-690,550 with MTX. Some adverse event data were provided, but were blinded to treatment allocation.

8.1.4. Other studies with limited safety data

Study A3921009 was a Phase 2 study of CP-690,550 (15 mg and 30 mg twice daily) as an immunosuppressant in the prevention of graft rejection in renal transplant recipients. There were 61 subjects in the study. Efficacy and safety results were similar to those for tacrolimus. Study A321021 was a follow-on study to Study A3021009. Data listings were provided for Study A3921021 but were blinded for treatment allocation.

Study A3921030 was a Phase 2 study of CP-690,550 (15 mg twice daily, followed by 10 mg twice daily) as an immunosuppressant in the prevention of graft rejection in renal transplant recipients. A total of 322 subjects received treatment. To Month 6, there were higher rates of infection with CP-390,550 than cyclosporine: around 35% subjects compared with 18%. Study A3921050 is an open-label extension study of Study A3921030. Data listings were provided but were blinded to treatment allocation.

Study A3921043 was a Phase 2 study of CP-690,550 (1 mg, 5 mg or 15 mg twice daily) in the treatment of Crohn's disease. There was a higher than expected placebo response in this study and although the 5 mg dose appeared to have greater efficacy than placebo, the 1 mg and 15 mg doses did not. The adverse event profile for CP-690,550 was similar to that for placebo.

Study A3921047 was a Phase 2 study of CP-690,550 (2 mg, 5 mg and 15 mg) compared with placebo in subjects with chronic plaque psoriasis over a 12 week period. A total of 197 subjects were randomized to treatment, 49 in each of the CP-690,550 dose groups. CP-690,550 was superior to placebo in the proportions of subjects with PASI75 response. The rates of AEs in the CP-690,550 groups were similar to those in the placebo.

Study A3921063 was a Phase 2 study of CP-690,550 (0.5 mg, 3 mg, 10 mg and 15 mg twice daily) compared to placebo in the treatment of ulcerative colitis over 8 weeks. A total of 194 subjects received study treatment. Clinical response was recorded in a greater proportion of subjects in the 10 mg and 15 mg groups than in the placebo. The AE rates were similar in the CP-690,550 groups to placebo.

Study A3921073 is an ongoing study of CP-690,550 that aims to explore the effect of CP-690,550 10 mg BID on blood and synovial tissue biomarkers in subjects with active rheumatoid arthritis. AE data were provided but were blinded to treatment allocation.

Study A3921080 is an ongoing Phase 3 study comparing CP-690,550 with etanercept in the treatment of severe chronic plaque psoriasis. Listings of AEs were provided but were blinded to treatment allocation.

Study A3921111 is an ongoing Phase 3 study of treatment withdrawal / re-treatment with CP-690,550 in subjects with moderate severe chronic plaque psoriasis. Listings of AEs were provided but were blinded to treatment allocation.

A study protocol but no data were provided for Study A3921068.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no studies where safety was the primary outcome.

8.3. Patient exposure

The total number of subjects (patient years) exposed to CP-690,550 is stated in the Clinical Summary of Safety to be 1369 (419.95) in Phase 2 studies, 3030 (2210.97) in Phase 3, 3227 (3085.13) in long-term extension studies and 4816 (5716.03) in all of these studies combined.

8.3.1. Patient exposure in phase 2 studies

In Study A3921019 there were 61 subjects exposed to 5 mg, 69 to 15 mg, and 69 to 30 mg CP690,550 for up to 6 weeks.

In Study A3921025 there were 71 subjects exposed to 1 mg CP-690,550, 68 to 3 mg, 71 to 5 mg, 75 to 10 mg, 75 to 15 mg, all twice daily, and 80 to 20 mg once daily, for up to 24 weeks.

In Study A3921035 subjects were treated with 1 mg, 51 with 3 mg, 49 with 5 mg, 61 with 10 mg, and 57 with 15 mg for up to 24 weeks. A further 53 subjects were treated with adalimumab for 12 weeks followed by 5 mg twice daily for a further 12 weeks.

In Study A3921039 there were 28 subjects exposed to 1 mg twice daily, 27 to 3 mg, 27 to 5 mg and 26 to 10 mg, for up to 12 weeks.

In Study A3921040 there were 53 subjects treated with 1 mg CP-690,550 twice daily, 53 with 3 mg, 52 with 5 mg, 53 with 10 mg, and 54 with 15 mg for up to 12 weeks.

8.3.2. Pivotal studies

In Study A3921032 a total of 133 subjects were exposed to 5 mg twice daily and 134 to 10 mg for 6 months, with a further 66 subjects in the placebo/5 mg group exposed to the 5 mg dose for 3 months and 66 in the placebo/10 mg to 10 mg for 3 months.

In Study A3921044 there were 321 subjects exposed to 5 mg twice daily, 316 to 10 mg twice daily, 81 to placebo/5 mg and 79 to placebo/10 mg. Subjects exposed to more than one year of treatment included: 232 in the 5 mg group, 237 in the 10 mg, 56 in the placebo/5 mg and 52 in the placebo/10 mg.

In Study A3921064 there were 204 subjects exposed to 5 mg twice daily, 201 to 10 mg twice daily, 56 to placebo/5 mg, 52 to placebo/10 mg and 204 to adalimumab (all in combination with MTX). Subjects exposed to more than one year of treatment included: 32 in the 5 mg group, 28 in the 10 mg, seven in the placebo/5 mg, ten in the placebo/10 mg and 40 in the adalimumab.

In Study A3921045, there were 243 subjects exposed to 5 mg twice daily, 245 to 10 mg, 61 to placebo/5 mg and 61 to placebo/10 mg for up to 6 months.

In Study A3921046 there were 315 subjects exposed to 5 mg twice daily, 318 to 10 mg twice daily, 79 to placebo/5 mg and 80 to placebo/10 mg. Subjects exposed to more than one year of treatment included: 50 in the 5 mg group, 49 in the 10 mg, 15 in the placebo/5 mg and 12 in the placebo/10 mg.

8.3.3. Open-label follow-on studies

In Study A3921024 / A3921041 a total of 3227 subjects were included: 1321 treated with CP-690,550 5 mg twice daily and 1906 treated with 10 mg twice daily. There were 970 subjects treated for more than 12 months, 659 for more than 24 months and 62 for more than 36 months.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Adverse events in general

8.4.1.1.1. Pivotal studies

In Study A3921032, up to Month 3, 145 TEAEs were reported in 71 (53.4%) subjects in the 5 mg group, 165 in 76 (56.7%) in the 10 mg and 167 in 75 (56.8%) in the placebo. From Month 3 to Month 6, there were 96 TEAEs in 57 (42.9%) subjects in the 5 mg group, 123 in 58 (43.3%) in the 10 mg, 57 in 24 (36.4%) in the placebo/5 mg and 59 in 28 (42.4%) in the placebo/10 mg.

In Study A3921044, to Month 3 there were 308 TEAEs reported in 157 (48.9%) subjects in the 5 mg group, 331 in 171 (54.1%) in the 10 mg and 131 in 73 (45.6%) in the placebo. From Month 3 to Month 6, there were 270 TEAEs reported in 145 (45.2%) subjects in the 5 mg group, 199 in 111 (35.1%) in the 10 mg group, 33 in 21 (25.9%) in those subjects remaining on placebo, 32 in 18 (42.9%) of those subjects switched from placebo to 5 mg and 28 in 15 (40.5%) of those subjects switched from placebo to 10 mg. From Month 6 to Month 12, 249[18] TEAEs were reported in 166 (51.7%) subjects in the 5 mg group, 384 in 174 (55.1%) in the 10 mg, 73 in 34 (42.0%) in the placebo/5 mg and 75 in 35 (44.3%) in the placebo/10 mg. The overall incidence rate (95% CI) for TEAEs was 164.849 (147.014 to 184.848) per 100,000 patient years exposure for 5 mg, 171.562 (152.911 to 192.489) per 100,000 patient years exposure for 10 mg, and 208.293 (167.755 to 258.628) per 100,000 patient years exposure for placebo.[19]

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[18] Erratum: number of TEASs was 349

[19] Erratum: rates indicated in this paragraph are per 100 patient-years, not per 100,000 patient years.

In Study A3921045, to Month 3 there were 279 TEAEs in 124 (51.0%) subjects in the 5 mg group, 295 in 139 (56.7%) in the 10 mg and 127 in 67 (54.9%) in the placebo. The most common TEAE was headache, occurring in 13 (5.3%) subjects in the 5 mg group, 11 (4.5%) in the 10 mg and three (2.5%) in the placebo. From Month 3 to Month 6, there were 170 TEAEs in 97 (39.9%) subjects in the 5 mg group, 207 in 101 (41.2%) in the 10 mg, 40 in 22 (36.1%) in the placebo/5 mg and 54 in 24 (39.3%) in the placebo/10 mg.

In Study A3921046, to Month 3 there were 400 TEAEs reported in 166 (52.7%) subjects in the 5 mg group, 373 in 173 (54.4%) in the 10 mg and 179 in 97 (61.0%) in the placebo. From Month 3 to Month 6, there were 211 TEAEs reported in 121 (38.4%) subjects in the 5 mg group, 238 in 124 (39.0%) in the 10 mg group, 39 in 21 (25.9%) in those subjects remaining on placebo, 32 in 18 (42.1%) of those subjects switched from placebo to 5 mg and 39 in 18 (45.0%) of those subjects switched from placebo to 10 mg. From Month 6 to Month 12, there were 208 TEAEs reported in 104 (33.0%) subjects in the 5 mg group, 272 in 135 (45.2%) in the 10 mg, 57 in 34 (43.0%) in the placebo/5 mg and 61 in 29 (36.3%) in the placebo/10 mg. After Month 3, respiratory tract infections were the most common TEAEs.

In Study A3921064, to Month 3 there were 189 TEAEs reported in 106 (52.0%) subjects in the 5 mg group, 184 in 94 (46.8%) in the 10 mg, 86 in 51 (47.2%) in the placebo and 182 in 105 (51.5%) in the adalimumab. Infections, particularly upper respiratory tract infections, were more common in the active treatment groups. From Month 3 to Month 6, there were 119 TEAEs reported in 67 (32.8%) subjects in the 5 mg group, 94 in 62 (30.8%) in the 10 mg group, 25 in 16 (27.1%) in those subjects remaining on placebo, 15 in seven (25.0%) of those subjects switched from placebo to 5 mg, ten in nine (42.9%) of those subjects switched from placebo to 10 mg, and 120 in 68 (33.3%) in the adalimumab. Infections and laboratory test abnormalities were more common in the active treatment groups. From Month 6 to Month 12, there were 162 TEAEs reported in 89 (43.6%) subjects in the 5 mg group, 160 in 84 (41.8%) in the 10 mg, 34 in 18 (32.1%) in the placebo/5 mg, 49 in 21 (40.4%) in the placebo/10 mg, and 142 in 83 (40.7%) in the adalimumab.

8.4.1.1.2. Other studies

· **Phase 1 studies**

In Study A3921002 there was a higher rate of TEAEs in the higher dose levels, particularly headache and nausea were at the 60 mg and 100 mg dose levels. There were no clinically significant changes in laboratory test parameters or vital signs. There were no deaths, SAEs or DAEs.

In Study A3921003 there were 16 TEAEs in eleven subjects. The most frequently reported TEAEs were headache (5) and nausea (3). There were no deaths or DAEs. There was one SAE: atrial fibrillation. The frequency of abnormalities in vital signs or ECGs was not increased in the treatments groups relative to the placebo.

In Study A3921028, following a single dose of 100 mg CP-690,550 there were 59 AEs reported in 32 subjects, the most common being headache in 17 (28.3%) subjects, nausea in 17 (28.3%) and vomiting in six (10.0%). There were no deaths, SAEs or DAEs. There were no clinically significant abnormalities in laboratory test results.

During Study A3921109, in the open label period 82 AEs were reported in 52 subjects. The most frequent AEs were herpes zoster in five (4.5%) subjects, nausea in four (3.6%), headache in three (2.7%), and diarrhoea in three (2.7%). In the double blind period there were 36 TEAEs in 21 (42%) subjects in the atorvastation group and 36 in 19 (40.4%) in the placebo.

· **Phase 2 studies**

In Study A3921019 there were 107 TEAEs reported in 36 (59.0%) subjects in the 5 mg group, 155 in 52 (75.4%) in the 15 mg, 169 in 53 (76.8%) in the 30 mg and 107 in 38 (58.5%) in the

placebo. The risk of headache, nausea, leukopenia and infection increased with increasing dose of CP-690,550.

For Study A3921025 the analysis of TEAEs is complex because of the complicated dosing regimens over the 24 weeks of the study. However, the group with the largest number of TEAEs was the 10 mg twice daily group, and the group with the greatest proportion of affected subjects was the 15 mg twice daily group with 57 (76.0%) subjects. There was a higher rate of infections in the CP-690,550 groups compared to placebo but this did not appear to be dose related.

In Study A3921035, the proportion of subjects reporting AEs increased with dose for the CP-690,550 groups, but was similar for the 5 to 15 mg dose ranges, at around 50% of subjects, and also for adalimumab. Following reassignment, there was a higher proportion of subjects reporting AEs in the adalimumab/ 5 mg group than in those groups that were simply continuing on CP-690,550. The rate of TEAEs increased with increasing dose in the CP-690,550 groups.

In Study A3921039, the frequency of TEAEs increased with CP-690,550 dose, with the highest proportion of subjects reporting TEAEs in the 10 mg group: 20 (76.9%) subjects. The most commonly reported TEAEs in the 10 mg group were infections: eleven (42.3%) subjects.

In Study A3921040 there were 37 TEAEs reported in 21 (39.6%) subjects treated with the 1 mg dose level, 31 in 23 (43.4%) with 3 mg, 42 in 29 (55.8%) with 5 mg, 62 in 32 (60.4%) with 10 mg, 50 in 28 (51.9%) with 15 mg and 41 in 23 (44.2%) with placebo. The rate of infections was increased in the 5 mg, 10 mg and 15 mg dose groups. Hyperlipidaemia was reported in six (11.3%) subjects in the 10 mg dose group.

· **Open-label follow-on studies**

In Study A3921024 / A3921041 the rates of subjects reporting TEAEs was between 38 and 60%, and did not appear to be related to dose or duration of treatment. The most common TEAEs were: nasopharyngitis (10%), upper respiratory tract infection (7.3%), urinary tract infection (4.6%), hypertension (4.2%), bronchitis (4.5%), back pain (3.3%), influenza (3.3%), herpes zoster (4.1%), headache (3.7%), diarrhoea (3.4%), sinusitis (2.8%), and RA (2.4%).

· **Studies of pooled data of AEs**

Study PMAR-00188 combined data from four Phase 2 studies (Study A3921025, Study A3921035, Study A3921039 and Study A3921040) and two long-term open-label extension studies (Study A3921024 and Study A3921041) to examine long-term risk for serious infections and malignancy. In these studies there were 37 (4.66%) subjects with serious infections (incidence rate 2.39 per 100 patient years) and 21 (2.64%) with malignancy (incidence rate 1.36 per 100 patient years). The risk of serious infections increased with dose: the 10 mg twice daily dose was estimated to have 1.3 to 1.9 times greater likelihood of serious infections compared to 5 mg twice daily with the 90% CI excluding ≥2.9 relative risk. There was no apparent association between CP-690,550 exposure and malignancy risk.

8.4.2.   Adverse events of special interest

8.4.2.1.   *Infection*

In Study A3921019 the rates of infection, particularly urinary tract infection, increased with increasing dose. In Study A3921025, Study A3921035, Study A3921039 and Study A3921040, overall the rate of infections increased with increasing CP-690,550 dose.

In Study A3921040, herpes zoster or simplex infections were reported in four subjects in the 10 mg group and three in the 15 mg.

For Study A3921025, EBV DNA levels reached or exceeded the level of potential concern (>500 copies/500 ng DNA) in four subjects: two in the 5 mg group, one in the 20 mg once daily group, and one in the 15 mg group.

In Study A3921032, rates of treated-infection AEs were higher in the 5 mg group (26 treated infections) and the placebo group (24) compared with the 10 mg group (17).

In Study A3921044, the incidence (95% CI) of serious infections was 4.168 (2.553 to 6.803) per 100,000 patient years exposure in the 5 mg group, 2.319 (1.207 to 4.457) per 100,000 patient years in the 10 mg and 3.679 (0.920 to 14.710) per 100,000 patient years in the placebo[20].

In Study A3921045 [through Month 6], there was one (0.4%) subject in the 5 mg group with serious infection, four (1.6%) in the 10 mg, one (1.6%) in the placebo/5 mg (during the 5 mg phase) and none in the placebo/10 mg.

In Study A3921064, serious infections were reported in seven (3.4%) subjects in the 5 mg group, eight (4.0%) in the 10 mg, 0ne (1.8%) in the placebo/5 mg, one (1.9%) in the placebo/10 mg and three (1.5%) in the adalimumab.

8.4.2.2. *Dyslipidaemia*

In Study A3921035, proportion of subjects with dislipidaemia peaked at the 10 mg dose level, at 8.2%.

In Study A3921039, there was a higher proportion of subjects in the CP-690,550 groups with elevated LDL-C (around 20%), but this was observable from the lowest dose level: 1 mg twice daily.

In Study A3921032, during the placebo controlled phase, there was one subject in each of the 5 mg and 10 mg groups with hypertriglyceridaemia. In Study A3921032, there was one subject in the 10 mg group with acute myocardial infarction.

In Study A3921044 to Month 3, dyslipidaemia was reported in nine (2.8%) subjects in the 5 mg group, 16 (5.1%) in the 10 mg and three (1.9%) in the placebo; myocardial infarction/ ischemic heart disease was reported in three subjects in the 10 mg group, and hypertension was reported in 13 (4.0%) subjects in the 5 mg group, five (1.6%) in the 10 mg and two (1.3%) in the placebo.

In Study A3921045, to Month 3, dyslipidaemia was reported in eight (3.3%) subjects in the 5 mg group, ten (4.1%) in the 10 mg and one (0.8%) in the placebo. To Month 3, hypertension was reported in two (0.8%) subjects in the 5 mg group, eleven (4.5%) in the 10 mg and three (2.5%) in the placebo; congestive heart failure was reported in eight (3.3%) subjects in the 5 mg group, five (2.0%) in the 10 mg and three (2.5%) in the placebo; and acute myocardial infarction was reported in three (1.2%) subjects in the 5 mg group, ten (4.1%) in the 10 mg and one (0.8%) in the placebo.

In Study A3921046, to Month 3 dyslipidaemia as an AE was reported in nine (2.9%) subjects in the 5 mg group, twelve (3.8%) in the 10 mg and one (0.6%) in the placebo; hypertension as an AE was reported in five (1.6%) subjects in the 5 mg group, nine (2.8%) in the 10 mg and two (1.3%) in the placebo; acute myocardial infarction was reported in five (1.6%) subjects in the 5 mg group, six (1.9%) in the 10 mg and one (0.6%) in the placebo. From Month 3 to Month 6, acute myocardial infarction was reported in a further one (1.0%) subject in the 5 mg group, and five (1.6%) in the 10 mg, but none in those subjects continuing on placebo.

In Study A3921064, to Month 3, hypercholesterolaemia was reported in two (1.0%) subjects in the 5 mg group, two (1.0%) in the 10 mg and one (0.5%) in the adalimumab; myocardial infarction was reported in one subject in the 10 mg group and one in the adalimumab; hypertension as an AE was reported in four (2.0%) subjects in the 10 mg group, seven (3.5%) in the 5 mg, two (1.9%) in the placebo and none in the adalimumab.

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[20] Erratum: rates indicated in this paragraph are per 100 patient-years, not per 100,000 patient years.

8.4.2.3. Treatment comparisons for adverse events of special interest

The Integrated Summary of Safety performed comparisons between CP-690,550, placebo and adalimumab and also incorporated literature reports for drugs used to treat RA. CP-690,550 had a similar rate of serious infections, but a higher rate of Herpes Zoster infections, and resulted in higher serum LDL, in comparison with placebo and other anti-rheumatic drugs.

8.4.3. Treatment-related adverse events (adverse drug reactions)

8.4.3.1. Pivotal studies

In Study A3921032, up to Month 3, there were 57 treatment related AEs reported in 34 (25.6%) subjects in the 5 mg group, 73 in 44 (32.8%) in the 10 mg and 37 in 26 (19.7%) in the placebo (Table 6). There was no clear pattern to the treatment related AEs. From Month 3 to Month 6, there were 37 TEAEs in 25 (18.8%) subjects in the 5 mg group, 48 in 29 (21.6%) in the 10 mg, 17 in twelve (18.2%) in the placebo/5 mg and 14 in nine (13.6%) in the placebo/10 mg.

Table 6: Most Frequent Treatment-Emergent (Treatment-Related) AEs by System Organ Class and Preferred Term (≥2% of Patients in Any Treatment Group, Baseline to Month 3) (Study A3921032)

System Organ Class[a] Preferred Term[a]	CP-690,550 5 mg BID (N=133) n (%)	CP-690,550 10 mg BID (N=134) N (%)	Placebo (N=132) n (%)
No. patients with an event	34 (25.6)	44 (32.8)	26 (19.7)
Gastrointestinal disorders			
Abdominal pain upper	3 (2.3)	1 (0.7)	0
Diarrhea	5 (3.8)	5 (3.7)	2 (1.5)
Infections and infestations			
Nasopharyngitis	1 (0.8)	4 (3.0)	2 (1.5)
Upper respiratory tract infection	1 (0.8)	1 (0.7)	3 (2.3)
Urinary tract infection	1 (0.8)	3 (2.2)	1 (0.8)
Nervous system disorders			
Headache	1 (0.5)	6 (4.5)	1 (0.8)
Skin and subcutaneous tissue disorders			
Skin lesion	0	3 (2.2)	0

Source: Tables 14.3.1.3.1.1 and 14.3.1.3.6.1.1
Abbreviations: AE = adverse event, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities.
N = number of patients, n = number of patients meeting prespecified criteria, v = version, No. = number
[a]MedDRA (v13.1) coding dictionary applied.

In Study A3921044, to Month 3 there were 161 treatment related AEs reported in 98 (30.5%) subjects in the 5 mg group, 157 in 105 (33.2%) in the 10 mg and 72 in 41 (25.6%) in the placebo (Table 7). The only treatment related AEs occurring in ≥2% of any treatment group were headache (14 [4.4%] subjects in the 5 mg group, one [0.3%] in the 10 mg and two [0.6%[21]] in the placebo) and nasopharyngitis (eight [2.5%] subjects in the 5 mg group, seven [1.3%] in the 10 mg and one [0.6%] in the placebo). From Month 3 to Month 6, there were 143 treatment related AEs reported in 88 (27.4%) subjects in the 5 mg group, 98 in 61 (19.3%) in the 10 mg group, 16 in ten (12.3%) in those subjects remaining on placebo, 20 in 14 (33.3%) of those subjects switched from placebo to 5 mg and 18 in eleven (29.7%) of those subjects switched from placebo to 10 mg. From Month 6 to Month 12, 167 TEAEs were reported in 100 (31.2%) subjects in the 5 mg group, 177 in 101 (32.0%) in the 10 mg, 42 in 22 (27.2%) in the placebo/5 mg and 43 in 25 (31.6%) in the placebo/10 mg.

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[21] Erratum: correct value is 1.3%

Table 7: Most Frequent Treatment-Emergent (Treatment-Related) AEs by System Organ Class and Preferred Term (≥2% of Patients in Any Treatment Group, Months 6 to 12, 1-Year Analysis) (Study A3921044)

System Organ Class Preferred Term No. (%) of Patients	CP-690,550 5 mg BID (N=321)	CP-690,550 10 mg BID (N=316)	Placebo → CP-690,550 5 mg BID (N=81)	Placebo → CP-690,550 10 mg BID (N=79)
No. patients with an event	100 (31.2)	101 (32.0)	22 (27.2)	25 (31.6)
Gastrointestinal disorders				
Constipation	3 (0.9)	1 (0.3)	2 (2.5)	0
Infections and infestations				
Bronchitis	4 (1.2)	4 (1.3)	1 (1.2)	2 (2.5)
Herpes zoster	6 (1.9)	9 (2.8)	3 (3.7)	2 (2.5)
Nasopharyngitis	15 (4.7)	13 (4.1)	2 (2.5)	3 (3.8)
Upper respiratory tract infection	6 (1.9)	9 (2.8)	3 (3.7)	3 (3.8)
Urinary tract infection	5 (1.6)	8 (2.5)	2 (2.5)	1 (1.3)
Investigations				
Hepatic enzyme increased	0	0	0	2 (2.5)
Metabolism and nutrition disorders				
Hypercholesterolemia	4 (1.2)	2 (0.6)	1 (1.2)	2 (2.5)
Skin and subcutaneous tissue disorders				
Rash	4 (1.2)	5 (1.6)	2 (2.5)	1 (1.3)

In Study A3921045, to Month 3 there were 108 treatment related AEs in 63 (25.9%) subjects in the 5 mg group, 134 in 77 (31.3%) in the 10 mg and 54 in 33 (27.0%) in the placebo (Table 8). Headache was the most common treatment related AE, occurring in eight (3.3%) subjects in the 5 mg group, eight (3.3%) in the 10 mg and two (1.6%) in the placebo. From Month 3 to Month 6, there were 54 treatment related AEs in 39 (16.0%) subjects in the 5 mg group, 79 in 55 (22.4%) in the 10 mg, 15 in 13 (21.3%) in the placebo/5 mg and 26 in 11 (18.0%) in the placebo/10 mg.

Table 8: Most Frequent Treatment-Emergent (Treatment-Related) AEs by System Organ Class and Preferred Term (≥2% of Patients in Any Treatment Group, Baseline to Month 3) (Study A3921045)

System Organ Class[a] Preferred Term[a]	CP-690,550 5 mg BID (N=243) n (%)	CP-690,550 10 mg BID (N=245) N (%)	Placebo (N=122) n (%)
No. patients with an event	63 (25.9)	77 (31.4)	33 (27.0)
Gastrointestinal disorders			
Diarrhea	6 (2.5)	3 (1.2)	1 (0.8)
Constipation	5 (2.1)	5 (2.0)	1 (0.8)
Nausea	4 (1.6)	6 (2.4)	3 (2.5)
Gastritis	1 (0.4)	1 (0.4)	3 (2.5)
Nervous system disorders			
Headache	8 (3.3)	8 (3.3)	2 (1.6)
Dizziness	2 (0.8)	2 (0.8)	4 (3.3)
Infections and infestations			
Upper respiratory tract infection	5 (2.1)	3 (1.2)	3 (2.5)
Investigations			
Blood creatine phosphokinase increased	2 (0.8)	10 (4.1)	1 (0.8)
Vascular disorders			
Hypertension	1 (0.4)	6 (2.4)	1 (0.8)

In Study A3921046, to Month 3 there were 230 treatment related AEs reported in 111 (35.2%) subjects in the 5 mg group, 187 in 114 (35.8%) in the 10 mg and 90 in 50 (31.4%) in the placebo (Table 9). The pattern of treatment related AEs was similar for the three groups. From Month 3

to Month 6, there were 89 treatment related AEs reported in 64 (20.3%) subjects in the 5 mg group, 107 in 64 (20.1%) in the 10 mg group, 14 in nine (11.1%) in those subjects remaining on placebo, 15 in nine (23.7%) of those subjects switched from placebo to 5 mg and 17 in 13 (32.5%) of those subjects switched from placebo to 10 mg. From Month 6 to Month 12, there were 83 TEAEs reported in 53 (16.8%) subjects in the 5 mg group, 124 in 73 (23.0%) in the 10 mg, 27 in 18 (22.8%) in the placebo/5 mg and 31 in 18 (22.5%) in the placebo/10 mg.

Table 9: Most Frequent Treatment-Emergent (Treatment-Related) AEs by System Organ Class and Preferred Term (≥2% of Patients in Any Treatment Group, Baseline to Month 3) (Study A3921046)

System Organ Class[a] Preferred Term[a]	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo
No. patients with an event	315	318	159
Gastrointestinal disorders			
Diarrhea	12 (3.8)	5 (1.6)	5 (3.1)
Dyspepsia	2 (0.6)	7 (2.2)	2 (1.3)
Nausea	9 (2.9)	5 (1.6)	2 (1.3)
Infections and infestations			
Nasopharyngitis	5 (1.6)	1 (0.3)	5 (3.1)
Upper respiratory tract infection	12 (3.8)	16 (5.0)	5 (3.1)
Investigations			
Alanine aminotransferase increased	6 (1.9)	5 (1.6)	4 (2.5)
Nervous system disorders			
Headache	8 (2.5)	7 (2.2)	2 (1.3)

In Study A3921064, to Month 3 there were 100 treatment related AEs reported in 66 (32.4%) subjects in the 5 mg group, 94 in 53 (26.4%) in the 10 mg, 27 in 19 (17.6%) in the placebo and 82 in 54 (26.5%) in the adalimumab (Table 10). From Month 3 to Month 6, there were 46 treatment related AEs reported in 30 (14.7%) subjects in the 5 mg group, 35 in 26 (12.9%) in the 10 mg group, six in six (10.2%) in those subjects remaining on placebo, seven in four (14.3%) of those subjects switched from placebo to 5 mg, five in four (19.0%) of those subjects switched from placebo to 10 mg and 53 in 35 (17.2%) in the adalimumab. From Month 6 to Month 12, there were 70 TEAEs reported in 45 (22.1%) subjects in the 5 mg group, 48 in 35 (17.4%) in the 10 mg, seven in six (10.7%) in the placebo/5 mg, 18 in eleven (21.2%) in the placebo/10 mg and 34 in 29 (14.2%) in the adalimumab. The most frequently reported treatment related AEs were upper respiratory tract infections.

Table 10: Most Frequent Treatment-Emergent AEs by System Organ Class (≥5% of Patients in Any Treatment Group) and Preferred Term (≥2% of Patients in Any Treatment Group) Baseline to Month 3 (Treatment-Related) (Study A3921064)

System Organ Class[a] Preferred Term, n (%)[a]	CP-690,550 BID		Placebo	Adalimumab 40 mg SC q 2 weeks
	5 mg	10 mg		
Number of patients evaluated	204	201	108	204
Gastrointestinal disorders	18 (8.8)	16 (8.0)	6 (5.6)	11 (5.4)
Abdominal pain upper	4 (2.0)	2 (1.0)	1 (0.9)	2 (1.0)
Diarrhea	4 (2.0)	1 (0.5)	0	1 (0.5)
Infections and infestations	19 (9.3)	22 (10.9)	3 (2.8)	16 (7.8)
Herpes zoster	0	4 (2.0)	0	0
Nasopharyngitis	1 (0.5)	4 (2.0)	0	3 (1.5)
Upper respiratory tract infection	4 (2.0)	4 (2.0)	0	3 (1.5)

8.4.3.2. Other studies

In Study A3921025, there was a higher rate of infections attributed to treatment in the CP-690,550 groups.

In Study A3921035, the proportion of subjects reporting treatment related TEAEs appear to increase with increasing dose, the highest proportion being 39% with the 10 mg dose.

In Study A3921039, there were 16 treatment related AEs reported in twelve (42.9%) subjects in the 1 mg group, 24 in eleven (40.7%) in the 3 mg, 32 in 17 (63%) in the 5 mg, 32 in 19 (73.1%) in the 10 mg, and 17 in eight (28.6%) in the placebo. These were most commonly abnormalities in laboratory investigations.

In Study A3921040 there were 20 treatment related TEAEs reported in 18 (34.0%) subjects treated with the 1 mg dose level, 26 in 19 (35.8%) with 3 mg, 31 in 24 (46.2%) with 5 mg, 46 in 28 (52.8%) with 10 mg, 38 in 25 (46.3%) with 15 mg and 29 in 30 (38.5%) with placebo.

8.4.4. Deaths and other serious adverse events

8.4.4.1. Pivotal studies

In Study A3921032 there was one death due to pulmonary embolism in the placebo/10 mg group, whilst taking 10 mg twice daily.

In Study A3921044, there were seven deaths reported. One occurred prior to receiving study treatment. Two subjects died while on treatment (one in the 5 mg group [pneumonia] one in the 10 mg [aspiration]). Three additional patients in the 5 mg group died after withdrawing due to AEs considered related to treatment (one from ARDS/ pneumonia viral, one from lung cancer metastatic, and one due to multi-organ failure). One subject who only received placebo withdrew due to several AEs (renal failure acute/ cardiac arrest) and subsequently died.

In Study A3921045, there was one death in the 10 mg group from diarrhoea/ hyperkalaemia/ cardiac arrest.

In Study A3921046 there were four deaths reported: two in the 5 mg group (traumatic brain injury and interstitial lung disease) and two in the 10 mg group (bronchopneumonia and valvular heart disease).

In Study A3921064 there were two deaths reported during the study: one in the 5 mg group (apical pneumonia) and one in the adalimumab (cardiac arrest).

In Study A3921032, up to Month 3, SAEs were reported in two (1.5%) subjects in the 5 mg group, two (1.5%) in the 10 mg and six (4.5%) in the placebo. From Month 3 to Month 6, SAEs were reported in 5 (3.8%) subjects in the 5 mg group, six (4.5%) in the 10 mg, three (4.5%) in the placebo/5 mg and two (3.0%) in the placebo/10 mg. There was no apparent pattern to the SAEs.

In Study A3921044, up to Month 3 SAEs were reported in twelve (3.7%) subjects in the 5 mg group, ten (3.2%) in the 5 mg and five (3.1%) in the placebo. From Month 3 to Month 6, SAEs were reported in 17 (5.3%) subjects in the 5 mg group, seven (2.2%) in the 10 mg group, five (6.2%) in those subjects remaining on placebo, one (2.4%) of those subjects switched from placebo to 5 mg and one (2.7%) of those subjects switched from placebo to 10 mg. From Month 6 to Month 12, SAEs occurred for 13 (4.0%) subjects in the 5 mg group, nine (2.6%) in the 10 mg, one (1.2%) in the placebo/5 mg and four (5.1%) in the placebo/10 mg. There was no apparent pattern to the SAEs.

In Study A3921045, to Month 3, SAEs were reported in one (0.4%) subject in the 5 mg group, five (2.0%) in the 10 mg and six (4.9%) in the placebo. From Month 3 to Month 6, SAEs were reported in five (2.1%) subjects in the 5 mg group, six (2.4%) in the 10 mg, one (1.6%) in the placebo/5 mg and none in the placebo/10 mg. There was no apparent pattern to the SAEs.

In Study A3921046, up to Month 3, SAEs were reported in nine (2.9%) subjects in the 5 mg group, eight (2.5%) in the 5 mg and six (3.8%) in the placebo. From Month 3 to Month 6, SAEs were reported in five (1.6%) subjects in the 5 mg group, seven (2.2%) in the 10 mg group, and none in the placebo, placebo/5 mg and placebo/10 mg. From Month 6 to Month 12, SAEs

occurred for seven (2.2%) subjects in the 5 mg group, nine (2.8%) in the 10 mg, one (1.3%) in the placebo/5 mg and none in the placebo/10 mg. There was no apparent pattern to the SAEs.

In Study A3921064, up to Month 3, SAEs were reported in twelve (5.9%) subjects in the 5 mg group, ten (5.0%) in the 5 mg, two (1.9%) in the placebo and five (2.5%) in the adalimumab. From Month 3 to Month 6, SAEs were reported in ten (4.9%) subjects in the 5 mg group, seven (3.5%) in the 10 mg group, two (3.4%) in the placebo, none in the placebo/5 mg, none in the placebo/10 mg and six (2.9%) in the adalimumab. From Month 6 to Month 12, SAEs occurred for ten (4.9%) subjects in the 5 mg group, six (3.0%) in the 10 mg, one (1.8%) in the placebo/5 mg, four (7.7%) in the placebo/10 mg and seven (3.4%) in the adalimumab. There was no apparent pattern to the SAEs.

8.4.4.2.   Other studies

There were no deaths reported during the Phase I studies. In Study A3921109, Study A3921019, Study A3921039, Study A3921040 there were no deaths.

In Study A3921025, there were two deaths reported, but one occurred prior to randomization. The on-treatment death was due to pneumonia, respiratory failure and cardiac failure. In Study A3921035 there was one death due to cerebrovascular accident in the 15 mg twice daily group. In Study A3921019, SAEs were reported in one (1.6%) subject in the 5 mg group, five (7.2%) in the 15 mg, three (4.3%) in the 30 mg and one (1.5%) in the placebo. SAEs were mostly considered to be unrelated to treatment.

In Study A3921025, SAEs were reported only in the CP-690,550 groups and not in the placebo group. The highest rate of SAEs was in the highest dose group (15 mg twice daily) with six (8.0%) subjects affected.

In Study A3921035, SAEs were most common in the 15 mg group and the adalimumab group. SAEs were reported in two subjects in the 1 mg group, one in the 3 mg, one in the 10 mg, four in the 15 mg and four in the adalimimab.

In Study A3921039, there was one subject with SAE in each of the 1 mg (foot deformity), 3 mg (osteoarthritis) and 5 mg (femur fracture) groups, two in the 10 mg group (cardiac failure and dyspnoea), and none in the placebo.

In Study A3921040, SAEs were reported in no subjects at the 1 mg dose level, three (5.7%) at the 3 mg (elevated CPK/AST/ALT, gastric ulcer perforation, rheumatoid vasculitis), two (3.8%) at the 5 mg (tibia/fibula fracture, paralysis/herpes zoster), two (3.8%) at the 10 mg (tendon rupture and herpes zoster), one (1.9%) at the 15 mg (herpes zoster oticus/ lumbar vertebral fracture) and one (1.9%) with placebo (atalectasis).

· **Phase 1 Studies**

In Study A3921109 there were three subjects with SAEs: pneumonia (2) and arthritis (1).

· **Open label follow-on studies**

In Study A3921024 / A3921041 there were 20 deaths reported. The mortality rate (95% CI) for the 5 mg dose was 0.760 (0.473 to 1.223) per 100 patient years, and for the 10 mg dose was 0.340 (0.110 to 1.055) per 100 patient years.

In Study A3921024 / A3921041 the rates of subjects reporting SAEs were 153 (15.8%) subjects in the 5 mg group and 98 (5.1%) in the 10 mg group. For the combined CP-690,550 population, more than five SAE events were recorded for: urinary tract infection, herpes zoster, cholelithiasis, tendon rupture, fall, cellulitis, diverticulitis, and deep vein thrombosis. The incidence rate (95% CI) for SAEs was 10.279 (8.999 to 11.742) per 100 patient years for the 5 mg dose and 13.958 (11.671 to 16.692) per 100 patient years for the 10 mg dose. Myocardial infarction was recorded for 34 (2.6%) subjects in the 5 mg dose group and 21 (1.1%) in the 10 mg. The exposure adjusted event rate for myocardial infarction was 1.53 per 100 patient years

for the 5 mg dose and 2.41 for the 10 mg dose. (The calculation of exposure adjusted event rates included all time on study, whereas duration of exposure for incidence rates excluded time after the event). There were three cases of TB. The incidence rate (95% CI) for serious infection was 2.250 (1.706 to 2.969) per 100 patient years for the 5 mg dose and 4.892 (3.628 to 6.597) per 100 patient years, indicating increased risk with increasing dose. The incidence rate (95% CI) for herpes zoster was 4.253 (3.463 to 5.223) per 100 patient years for the 5 mg dose and 4.453 (3.760 to 5.275) per 100 patient years for the 10 mg. There were 35 subjects with malignancies excluding non-melanoma skin cancer, 13 subjects with basal cell carcinoma of the skin and three with squamous cell carcinoma of the skin. Hepatobiliary disorders were reported in 20 (1.5%) subjects in the 5 mg dose group and 14 (0.7%) in the 10 mg. The exposure adjusted event rate for hepatobiliary disorders was 0.90 per 100 patient years for the 5 mg dose level and 1.60 per 100 patient years for the 10 mg dose level.

In Study A3921024 / A3921041 there was one subject with hepatic failure. This subject was in the 5 mg twice daily group, was a 65 year old Hispanic female and died as a consequence of the adverse event. The event occurred on Day 487 of treatment. In the Integrated Safety Summary Hepatic the Sponsor states "There were no Hy's law cases in the CP-690,550 RA program" but this particular case of hepatic failure cannot be identified in the report.

8.4.5. Discontinuation due to adverse events

8.4.5.1. Pivotal studies

In Study A3921032, up to Month 3, DAE occurred for eight (6.0%) subjects in the 5 mg group, six (4.5%) in the 10 mg and seven (5.3%) in in the placebo. From Month 3 to Month 6, DAE occurred for four (3.0%) subjects in the 5 mg group, six (4.5%) in the 10 mg, one (1.5%) in the placebo/5 mg and two (3.0%) in the placebo/10 mg. There was no clear pattern to the DAEs.

In Study A3921044 to Month 3, DAE occurred for 15 (4.7%) subjects in the 5 mg group, 14 (4.4%) in the 10 mg and five (3.1%) in the placebo. Infections and abnormal liver enzymes were more common causes of DAE in the CP-690,550 groups. From Month 3 to Month 6, DAE occurred for 16 (5.0%) subjects in the 5 mg group, eight (2.5%) in the 10 mg group, three (3.7%) in those subjects remaining on placebo, two (4.8%) of those subjects switched from placebo to 5 mg and two (5.4%) of those subjects switched from placebo to 10 mg. There were two subjects in the 5 mg group who discontinued due to cellulitis and two due to herpes zoster. From Month 6 to Month 12, DAE occurred for nine (2.8%) subjects in the 5 mg group, seven (2.2%) in the 10 mg, two (2.5%) in the placebo/5 mg and two (2.5%) in the placebo/10 mg. No preferred term was reported in more than one subject in each group.

In Study A3921045, to Month 3, DAEs occurred for two (0.8%) subjects in the 5 mg group, six (2.4%) in the 10 mg and five (4.1%) in the placebo. From Month 3 to Month 6, DAEs were reported in one (0.4%) subjects in the 5 mg group, five (2.0%) in the 10 mg, none in the placebo/5 mg and none in the placebo/10 mg. There was no apparent pattern to the DAEs.

In Study A3921046 to Month 3, DAE occurred for 13 (4.1%) subjects in the 5 mg group, 13 (4.1%) in the 10 mg and two (1.3%) in the placebo. From Month 3 to Month 6, DAE occurred for six (1.9%) subjects in the 5 mg group, eight (2.5%) in the 10 mg group, one (1.2%) in those subjects remaining on placebo, none of those subjects switched from placebo to 5 mg and one (2.5%) of those subjects switched from placebo to 10 mg. From Month 6 to Month 12 DAE occurred for one (0.3%) subjects in the 5 mg group, nine (2.8%) in the 10 mg, none in the placebo/5 mg and one (1.3%) in the placebo/10 mg. There were no apparent differences between the groups in the pattern of DAE, and overall most common reasons for DAE were infection and laboratory test abnormalities.

In Study A3921064 to Month 3, DAE occurred for 14 (6.9%) subjects in the 5 mg group, ten (5.0%) in the 10 mg, two (1.9%) in the placebo and ten (4.9%) in the adalimumab. From Month 3 to Month 6, DAE occurred for five (2.5%) subjects in the 5 mg group, eleven (5.5%) in the 10 mg group, none in those subjects remaining on placebo, one (3.6%) of the subjects that had

been switched from placebo to 5 mg, none of subjects that had been switched from placebo to 10 mg, and nine (4.4%) in the adalimumab group. From Month 6 to Month 12, DAE occurred for six (2.9%) subjects in the 5 mg group, three (1.5%) in the 10 mg, none in the placebo/5 mg, two (3.8%) in the placebo/10 mg and four (2.0%) in the adalimumab. The most common reasons for DAE were infections and elevations in liver enzymes.

8.4.5.2. Other studies

In Study A3921019, DAE occurred for one (1.6%) subject in the 5 mg group, six (8.7%) in the 15 mg, ten (14.5%) in the 30 mg and four (6.2%) in the placebo. The risk of leukopenia and neutropenia leading to discontinuation increased with CP-690,550 dose.

For Study A3921025, the rate of DAE increased with increasing dose. The highest rate was in the 15 mg twice daily group, with the excess being attributable to abnormalities in ALT and AST.

In Study A3921035, DAE was uncommon and there did not appear to be a dose related increase, or pattern in the DAEs.

In Study A3921039, DAE occurred for no subjects in the 1 mg group, two in the 3 mg, four in each of the 5 mg and 10 mg groups and two in the placebo. For four subjects in the CP-690,550 groups DAE was due to elevations in ALT and AST.

In Study A3921040, DAE occurred for no subjects at the 1 mg dose level, one (1.9%) at the 3 mg (rheumatoid vasculitis), two (3.8%) at the 5 mg (tibia/fibula fracture and herpes zoster), three (5.7%) at the 10 mg (tendon rupture, herpes zoster and ecchynosis), none at the 15 mg and two (3.8%) with placebo (two subjects with elevated ALT and AST).

In Study A3921109, 15 subjects discontinued due to AEs: three due to elevated hepatic enzymes.

In Study A3921024 / A3921041 the rates of subjects reporting with DAE were 148 (11.6%) subjects in the 5 mg group and 75 (3.9%) in the 10 mg group. The most common reason for DAE was elevated ALT (ten subjects). The incidence rate (95% CI) for DAE was 3.815 (3.085 to 4.719) per 100 patient years for the 5 mg dose and 3.978 (2.856 to 5.540) for the 10 mg.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

In Study A3921032, elevations in AST and ALT were more common with CP-690,550. Elevated AST occurred in 14% of the 5 mg group and elevated ALT occurred in 20% of the 10 mg group.

In Study A3921044 to Month 3, possible drug related hepatic disorders were reported in seven (2.2%) subjects in the 5 mg group, eleven (3.5%) in the 10 mg and three (1.9%) in the placebo. Mild elevation of AST and ALT occurred in over 20% of subjects in the CP-690,550 groups, and around 15% in the placebo, but there were similar proportions of subjects with marked elevation in AST and ALT.

In Study A3921045 to Month 3, possible drug related hepatic disorders were reported in three (1.2%) subjects in the 5 mg group, two (0.8%) in the 10 mg and three (2.5%) in the placebo. Elevations in AST were more common with increasing CP-690,550 dose: 23 (9.47%) subjects in the 5 mg group, 29 (11.84%) in the 10 mg and seven (5.79%) in the placebo; but the incidence of elevations in ALT was similar for the three groups.

In Study A3921046, to Month 3 possible drug related hepatic disorders were reported in twelve (3.8%) subjects in the 5 mg group, 15 (4.7%) in the 10 mg and six (3.8%) in the placebo. There was a dose dependent mild elevation in AST and ALT in the CP-690,550 groups at Month 3,

which persisted at around 20% of the treated population throughout the study. Elevation of transaminases, including significant elevation, was more common with concurrent MTX.

In Study A3921064, to Month 3, hepatobiliary disorders as an AE were only reported in two (1.0%) subjects in the 5 mg group. To Month 3, elevations in AST were reported in 48 (23.6%) subjects in the 5 mg group, 48 (23.9%) in the 10 mg, eleven (10.5%) in the placebo and 36 (17.6%) in the adalimumab. To Month 3, elevations in ALT were reported in 58 (28.6%) subjects in the 5 mg group, 49 (24.4%) in the 10 mg, 18 (17.1%) in the placebo and 48 (23.5%) in the adalimumab. In the CP-690,550 groups, around 20% of subjects had mild elevations in AST and/or ALT through to Month 12.

8.5.1.2. Other studies

In Study A3921019 there were no treatment emergent, clinically significant abnormalities in ALT or AST.

In Study A3921025, post-baseline elevation of ALT and ALT were more common in the 15 mg group with 37% and 39% of subjects affected respectively.

In Study A3921035, abnormalities in ALT and AST reported as TEAEs were uncommon and did not appear to be related to dose. In the listings of laboratory test abnormalities, elevations in AST and ALT were more common with increasing CP-690,550 dose.

In Study A3921039, at Week 12, There was a significant increase from baseline in ALT in the 10 mg groups of 7.92 U/L (p<0.05). There was a significant increase from baseline in AST in the 5 mg and 10 mg groups of 11.70 U/L and 18.95 U/L respectively (p<0.05).

In Study A3921040, there was no trend in mean ALT or AST concentrations but serum bilirubin concentrations increased with CP-690,550 dose.

Although in Study A3921024 / A3921041 there was a report of hepatic failure the results for ALT and AST were not reported.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

In Study A3921032 there was no apparent difference between the treatment groups in serum creatinine or creatinine clearance. In Study A3921044 mean serum creatinine concentrations increased by around 0.075 mg/dL to Month 12.

In Study A3921045, in the 10 mg group to Month 3 there were two (0.8%) subjects reported with renal failure, and two (0.8%) in the same group from Month 3 to Month 6. It is not clear if these were the same two subjects. Mean CRCL decreased by around 5 mL/min in the CP-690,550 groups.

In Study A3921046, to Month 3 acute renal failure as an AE was reported in one (0.3%) subject in the 5 mg group, four (1.3%) in the 10 mg and none in the placebo. There was an increase in mean serum creatinine of 0.08 mg/dL during the study. To Month 3, CRCL decreased by a mean of 2.967 mL/min in the 5 mg group, 5.713 mL/min in the 10 mg group and 0.831 mL/min in the placebo.

In Study A3921064, acute renal failure as an AE was reported in one (0.5%) subject in the 5 mg group and two (1.0%) in the adalimumab. Serum creatinine concentrations increased in the CP-690,550 groups relative to placebo and adalimumab through to Month 12.

To Month 3, CRCL decreased by a mean of 3.76 mL/min in the 5 mg group, 4.86 mL/min in the 10 mg group, 0.89 mL/min in the placebo/5 mg, 0.95 in the placebo/10 mg and 1.52 in the adalimumab.

8.5.2.2. Other studies

In Study A3921003, urine calcium excretion was increased, and creatinine clearance reduced, for some subjects in the treatments groups, but also in the placebo group. In Study A3921025, there was a significant decrease in CRCL in the 10 mg group of 9.30 mL/min (p=0.0047). In Study A3921035, disordered renal function was uncommon and did not appear to be related to dose or treatment. However, there was a significant increase in mean serum creatinine, and also a change in CRCL, although it is not clear from the study report whether this represents an increase or a decrease.

In Study A3921040, there was a dose dependent reduction in mean CRCL of up to 6.67 mL/min as calculated by the Cockroft-Gault method.

8.5.3. Other clinical chemistry

8.5.3.1. Creatinine kinase

In Study A3921032, two subjects in the 10 mg group had treatment emergent elevation of CK, compared with none in the other groups. In Study A3921044, to Month 3 treatment emergent elevation in CK occurred in five (1.6%) subjects in the 5 mg group, ten (3.3%) in the 10 mg and none in the placebo. In Study A3921045, treatment emergent elevations in CK occurred in six (2.5%) subjects in the 5 mg group, 19 (8.1%) in the 10 mg, none in the placebo/5 mg and three (5.3%) in the placebo/10 mg. In Study A3921046, to Month 3 elevations in CK were reported in two (0.6%) subjects in the 5 mg group, five (1.7%) in the 10 mg and none in the placebo. In Study A3921064, to Month 3, post-baseline elevations in CK were reported in one (0.5%) subjects in the 5 mg group, three (1.6%) in the 10 mg group, and none in the placebo and adalimumab groups.

8.5.3.2. Serum lipids

In Study A3921019 mean serum total, HDL and LDL cholesterol levels all increased in a dose-dependent manner.

In Study A3921025, HDL-C was increased in the CP-690,550 groups, but the effect plateaued from the 5 mg dose level. There was also an increase in LDL-C but this peaked with the 10 mg dose level. There was a similar increase in total cholesterol.

In Study A3921035, there were increases in serum HDL-C and LDL-C that were significant at the 10 mg and 15 mg dose levels.

In Study A3921040, serum HDL-C, LDL-C and total cholesterol were all increased in the CP-690,550 groups in a dose dependent manner.

In Study A3921032, HDL-C, LDL-C and cholesterol were elevated in the CP-690,550 groups relative to placebo and the elevation persisted to 6 months. There was no significant difference in LDL/HDL ratio.

In Study A3921044, HDL-C, LDL-C and cholesterol were elevated in the CP-690,550 groups relative to placebo and the elevation persisted to 12 months. There was no significant difference in LDL/HDL ratio.

In Study A3921045, mean HDL-C, LDL-C and cholesterol were elevated in the CP-690,550 groups by approximately 15% and this elevation persisted to 6 months.

In Study A3921046, mean HDL-C, LDL-C and cholesterol were elevated in the CP-690,550 groups by approximately 15% and this elevation persisted to 12 months.

In Study A3921064, mean HDL-C, LDL-C and cholesterol were elevated in the CP-690,550 groups by approximately 15% and this elevation persisted to 12 months. Although HDL increased by approximately 5%, both LDL and total cholesterol were stable during the study in the adalimumab group.

Submission PM-2012-00788-3-3 Extract from the Clinical Evaluation Report for Xeljanz Tofacitinib citrate: First and second rounds

Page 65 of 72

8.5.4. Haematology

8.5.4.1. Pivotal studies

In Study A3921032, mean neutrophil count decreased slightly in all the treatment groups. Two subjects (one in each of the 5 mg and 10 mg groups) were reported with thrombocytopenia.

In Study A3921044, the incidence (95% CI) of neutropenia as an AE was 1.041 (0.391 to 2.774) per 100,000 patient years in the 5 mg group, 0.516 (0.129 to 2.064) per 100,000 patient years in the 10 mg and 0.0 per 100,000 patient years in the placebo. Thrombocytopenia was reported in one subject in the 5 mg group, two in the 10 mg and none in the placebo[22].

In Study A3921045, there was an increase in mean haemoglobin at Month 3 of 0.28 g/dL in the 5 mg group and 0.03 g/dL in the 10 mg; and at Month [6] 0.25 g/dL and 0.15 g/dL, respectively. Mean neutrophil count at Month 3 decreased by 0.92 x 10^3/mm^3 in the 5 mg group and 1.36 x 10^3/mm^3 in the 10 mg, and at Month 6 by 0.86 x 10^3/mm^3 and 1.15 x 10^3/mm^3 respectively. Two subjects in the 5 mg group were reported with thrombocytopenia. Mean platelet counts in the CP-690,550 groups decreased by around 40 x 10^3/mm^3.

In Study A3921046, mean neutrophil count decreased with CP-690,550 treatment, and this effect was greater with concurrent MTX and leflunomide treatment. Three subjects were reported with thrombocytopenia, all during treatment with 10 mg CP-690,550 twice daily.

In Study A3921064, mean neutrophil counts decreased in the CP-690,550 groups and in the adalimumab group by around 1 x 10^3/mm^3 from early in treatment through to Month 12.

8.5.4.2. Other studies

In Study A3921109 there was no difference between the groups in mean haematology parameters.

In Study A3921019 there was an increase in the rate of anaemia, leukopenia, neutropenia and thrombocytopenia with increasing dose.

In Study A3921025, platelet and neutrophil counts decreased in the treatment groups relative to placebo. The greatest effect on neutrophils was in the 15 mg group: mean decrease of 1.13 x 10^3/μL. The greatest decrease in platelet count was in the 5 mg group: 31.17 x 10^3/μL.

In Study A3921035, mean platelet count was decreased at all CP-690,550 doses by 20 to 40 x 10^3/mm^3.

In Study A3921039, there was a dose-dependent decrease in neutrophil and platelet counts. There was a higher proportion of subjects in the 5 mg and 10 mg groups with decreased lymphocyte count (around 40%). There were small decreases in CD16+/56+ NK-cell counts in the 3 mg, 5 mg and 10 mg treatment groups. IgG levels were decreased by around 20% in the 3mg, 5 mg and 10 mg treatment groups.

In Study A3921040, there was no difference between the active treatment groups in the proportion of subjects reported with anaemia. Neutrophil count and platelet count decreased in a dose dependent manner. Mean changes in lymphocyte counts did not indicate any dose dependent effects or significant difference from placebo. Decreases in IgG were <15%.

8.5.5. Other laboratory tests

In Study A3921019 there were no clinically significant changes in the levels of EBV DNA over Baseline.

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[22] Erratum: rates indicated in this paragraph are per 100 patient-years, not per 100,000 patient years.

In Study A3921025, EBV DNA levels reached or exceeded the level of potential concern (>500 copies/500 ng DNA) in four subjects: two in the 5 mg group, one in the 20 mg once daily group, and one in the 15 mg group.

In Study A3921035, there were significant increases in the expression of EBV DNA in both the 10 mg and 15 mg treatment groups, but no apparent change in the adalimumab or placebo groups. In Study A3921035, expression of EBV DNA increased in a dose-dependent manner.

8.5.5.1. Other studies

In Study A3921019 there was one subject in each of the 5 mg, 30 mg and placebo groups with an increase in QTcB from baseline ≥60 ms, but no subject had a QTcB ≥500 ms. In Study A3921025, Study A3921035, and Study A3921039 there were no significant changes in ECGs. In Study A3921040 there were no trends in ECG parameters.

8.5.6. Vital signs

8.5.6.1. Pivotal studies

In Study A3921044, Study A3921046 and Study A3921064 there was an average 2 kg weight gain over 12 months of treatment with CP-690,550. In Study A3921045 there was also mean increase in weight with CP-690,550 of 2 kg over the 6 months of the study. In Study A3921064, there was an average 1 kg weight gain in the adalimumab group over 6 months.

8.6. Post-marketing experience

There were no post-marketing data included in the submission.

8.7. Evaluator's overall conclusions on clinical safety

In the Pivotal studies, the overall rates of TEAEs were similar for the CP-690,550 5 mg and 10 mg dose levels and placebo for up to 3 Months of treatment. Beyond 3 months comparisons between CP690,550 and placebo were not possible due to the complicated design of the efficacy studies, and the low numbers of subjects in the placebo groups after 3 months. Where incidence rates for TEAEs were provided, the rates of TEAEs were similar for both of the CP-690,550 dose levels and for placebo. For example, in Study A3921044 the overall incidence rate (95% CI) for TEAEs was 164.849 (147.014 to 184.848) per 100,000 patient years exposure for 5 mg, 171.562 (152.911 to 192.489) per 100,000 patient years exposure for 10 mg, and 208.293 (167.755 to 258.628) per 100,000 patient years exposure for placebo. The most common TEAEs were infections and abnormal laboratory tests[23].

In Phase 1 studies doses up to 100 mg were evaluated, which represents 10 times the higher recommended dose level. Headache and nausea were more common at these very high dose levels. In the Phase 2 studies, doses of 15 mg twice daily and above results in higher rates of TEAEs than placebo. In the pooled study, Study PMAR-00188, the risk of serious infections increased with dose: the 10 mg twice daily dose was estimated to have 1.3 to 1.9 times greater likelihood of serious infections compared to 5 mg twice daily with the 90% CI excluding ≥2.9 relative risk. There was no apparent association between CP-690,550 exposure and malignancy risk.

Dyslipidaemia was more common in the CP-690,550 treatment groups than placebo. However, possibly due to the follow-up time being too short, there did not appear to be an increased rate of ischaemic heart disease.

Deaths were uncommon and did not appear to be attributable to CP-690,550. The rates of SAE with CP-690,550 did not appear to be greater than for either placebo or adalimumab.

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[23] Erratum: rates indicated in this paragraph are per 100 patient-years, not per 100,000 patient years.

The rates of DAE were similar for the two CP-690,550 dose levels and for CP-690,550 in comparison with placebo and adalimumab. The most common reasons for DAE were infection and elevated ALT or AST.

Mild elevations in ALT and AST were more common in the CP-690,550 groups than with placebo or adalimumab. Over 20% of subjects treated with CP-690,550 in the studies of 3 Months or longer duration had mild elevations in ALT or AST. However, liver disease and/or marked elevations of ALT or AST were not more common with CP-690,550. Elevation of transaminases, including significant elevation, was more common with concurrent MTX. There was one case of hepatic failure leading to death reported during the development program.

In the Pivotal studies there were small, but statistically significant, increases in serum creatinine and decreases in CRCL (as measure by the Cockroft-Gault method. However, it is not clear whether this represents a decrease in renal function or interference with the active transport of creatinine. There was no increase in reports of acute renal failure in the CP-690,550 groups.

There were consistent elevations in HDL, LDL and total cholesterol in the CP-690,550 groups. The elevations were in the order of 15% of baseline values. Reports of elevations in CK were also more common in the CP-690,550. These findings may indicate an increase in cardiovascular risk.

Neutrophil and platelet counts decreased in a dose dependent manner with CP-690,550. However, neutropenia and thrombocytopenia were uncommon.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

CP-690,550 in combination with MTX at both the 5 mg and 10 mg twice daily dose levels results in a clinically and statistically significant improvement in the symptoms of RA. At the 10 mg dose level there was a clinically and statistically significant decrease in disease progression. At both dose levels there was an improvement in wellbeing. These effects were demonstrated in comparison with placebo.

In monotherapy, CP-690,550 at both the 5 mg and 10 mg twice daily dose levels results in a clinically and statistically significant improvement in the symptoms of RA and an improvement in wellbeing.

In combination with DMARDs, CP-690,550 at both the 5 mg and 10 mg twice daily dose levels there was a clinically and statistically significant improvement in the symptoms of RA and an improvement in wellbeing.

Efficacy was maintained for up to 3 years with ongoing treatment.

9.2. First round assessment of risks

The overall rates of TEAEs were similar for CP-690,550 and placebo as monotherapy, in combination with MTX and in combination with DMARDs. As would be expected with an immunomodulatory agent, infections were common. At higher than recommended doses, headache and nausea are common. The likelihood of serious infection increases with CP-690,550 dose.

Dyslipidaemia was more common in the CP-690,550 treatment groups than placebo. There were consistent elevations in HDL, LDL and total cholesterol in the CP-690,550 groups. The elevations were in the order of 15% of baseline values. Reports of elevations in CK were also more common in the CP-690,550. These findings may indicate an increase in cardiovascular

risk. However, possibly due to the follow-up time being too short, there did not appear to be an increased rate of ischaemic heart disease.

Deaths were uncommon and did not appear to be attributable to CP-690,550. The rates of SAE with CP-690,550 did not appear to be greater than for either placebo or adalimumab.

Mild elevations in ALT and AST were more common in the CP-690,550 groups than with placebo or adalimumab. Over 20% of subjects treated with CP-690,550 in the studies of 3 Months or longer duration had mild elevations in ALT or AST. However, liver disease and/or marked elevations of ALT or AST were not more common with CP-690,550. Elevation of transaminases, including significant elevation, was more common with concurrent MTX. There was one case of hepatic failure leading to death reported during the development program.

In the Pivotal studies there were small, but statistically significant, increases in serum creatinine and decreases in CRCL (as measure by the Cockroft-Gault method). However, it is not clear whether this represents a decrease in renal function or interference with the active transport of creatinine. There was no increase in reports of acute renal failure in the CP-690,550 groups.

Neutrophil and platelet counts decreased in a dose dependent manner with CP-690,550. However, neutropenia and thrombocytopenia were uncommon.

9.2.1. First round assessment of benefit-risk balance

The benefit-risk balance of CP-690,550, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Tofacitinib (CP-690,550) should be approved for the following indication:

> *JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate.*

11. Clinical questions

11.1. Pharmacokinetics

What data does the Sponsor have to support pharmacokinetics in the elderly population? Can the Sponsor provide a summary of the data of the available data with regard to clearance of CP-690,550 in the older age groupings (i.e. age ≥65 years and age ≥75 years)?

Does the Sponsor have any data with regard to the effects of CP-690,550 on glucuronidation of other drugs? Has the Sponsor investigated the potential interaction of CP-690,550 with paracetamol?

Does the Sponsor have further data with regard to the mechanism for active renal secretion of CP-690,550? What are the possible consequences of interactions at the level of renal transporters with regard to the pharmacokinetics of CP-690,550? How does the Sponsor plan to manage these risks should CP-690,550 be approved for marketing?

11.2. Safety

What is the mechanism for the increase in serum creatinine and decrease in CRCL observed with long-term CP-690,550 treatment?

Can the Sponsor provide further details regarding the case of hepatic failure leading to death reported in Study A3921024 / A3921041? Are there any cases potentially fulfilling the three components of Hy's Law that have not been included in the Integrated Safety Summary Hepatic?

12. Second round evaluation of clinical data submitted in response to questions

With regard the PK of CP-690,550 in subjects ≥65 years and ≥75 years the Sponsor has provided an updated analysis based on PK data comprising 1710 subjects in total, with 263 patients ≥65 years and 21 patients ≥75 years. The PK parameters did not appear to be altered in the elderly. The geometric mean ratio (90% CI) for CL/F for elderly subjects/non-elderly subjects was 0.939 (0.923 to 0.957) for subjects ≥65 years and 0.971 (0.917 to 1.03) for subjects ≥75 years. This indicates no decrease in clearance in the elderly. These conclusions are limited in subjects ≥75 years of age by the small numbers in that subgroup, but the findings for subjects ≥65 years are reassuring.

With regard the effect of CP-690,550 on glucuronidation, the Sponsor has performed an in-vitro study (Study CP-6905500) to assess the in-vitro inhibition profiles of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 by tofacitinib in human liver microsomes with and without 2% bovine serum albumin. The substrates used for each UGT isoform were:

- UGT1A1: β-Estradiol
- UGT1A4: Trifluoperazine
- UGT1A6: 5-Hydroxytrytophol
- UGT1A9: Propofol
- UGT2B7: Zidovudine

For each UGT isoform positive controls were also used. Concentrations of CP-690550 up to 100 μM were used. The experiments indicate that CP-690550 did not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 at concentrations up to and including 100 μM. Hence it is unlikely that CP-690550 would inhibit the glucuronidation of paracetamol in normal therapeutic use.

With regard the potential for drug interactions involving transporters, the Sponsor states that the proportion of the clearance accounted for by active renal secretion is 11%, and that there are unlikely to be significant interactions as a result of inhibition of transporters. Although the Sponsor has not identified the transporter involved in the active renal secretion of CP-690550, the Sponsor has performed additional in-vitro studies of OCT1 and OCT2. These studies indicate that CP-690550 is not a substrate of either OCT1 or OCT2. Based on the clinical interaction studies CSR A3921013 (methotrexate) and CSR A3921143 (Metformin) the Sponsor argues that it is unlikely that there are clinically significant interactions involving breast cancer resistant peptide (BCRP), organic anion transporter (OAT) 1/2/3, organic anion transporting polypeptide (OATP) 1B1/1B3, multidrug resistance protein (MDR) 1, multidrug resistance associated protein (MRP) 2/3/4, OCT1/2/3 and the multidrug and toxic compound extrusion (MATE) transporter. In the opinion of the Evaluator, based on this information, it is unlikely that there are clinically significant interactions at the level of renal drug transporters involving CP-690550.

With regard the mechanism for the increase in serum creatinine and decrease in CRCL observed with long-term CP-690,550 treatment, the Sponsor states that a measured GFR study in RA patients treated with tofacitinib 10 mg twice daily is ongoing (Protocol A3921152). At this stage the Sponsor does not have a satisfactory explanation for the phenomenon. However, as the Sponsor states, there was no other evidence of nephrotoxicity in the clinical development

program and no increase in reports of acute renal failure in the CP-690,550 groups. The Sponsor has clearly identified nephrotoxicity as a potential risk, as indicated by the need to perform Study A3921152, and in the opinion of the Evaluator it should be included in the RMP.

With regard further details regarding the case of hepatic failure leading to death reported in Study A3921024 / A3921041, the Sponsor states the subject died one month after terminating study treatment. The hepatic failure was considered to be secondary to sepsis following bacterial (septic) arthritis.

With regard cases potentially fulfilling the three components of Hy's Law that have not been included in the Integrated Safety Summary Hepatic, the Sponsor has identified six cases that satisfied the biochemical criteria of Hy's Law. However, the Sponsor proposes alternative explanations for five of these cases. The potential for drug induced liver injury is already included as a Potential Risk in the RMP.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of CP-690,550 in the proposed usage are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of CP-690,550 in the proposed usage are unchanged from those identified in Section 9.2.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Tofacitinib (CP-690,550), given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

Tofacitinib (CP-690,550) should be approved for the following indication:

JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate.

Therapeutic Goods Administration