Clinical Study Report Synopsis

Drug Substance	Quetiapine Fumarate XR
Study Code	D1444C00007
Edition Number	1.0
Date	10 Aug 2010

A Randomized, Open-label Trial to Evaluate the Pharmacokinetics of Extended-Release (XR) Quetiapine Fumarate 300 mg, 600 mg and 800 mg in Chinese schizophrenic patients

Study dates: First subject enrolled: 28 June 2009
Last subject last visit: 24 March 2010

Phase of development: Phase I (PK)

Principal Investigator:

Clinical Responsible Unit:

Sponsor's Responsible Medical Officer:

Responsible Statistician:

Drug Registration Applicant:

Registration applicant contact person:

Archive of the original documents:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted in Peking University No.6 Hospital in China.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
to evaluate the pharmacokinetics (PK) of XR quetiapine fumarate (300 mg once daily, 600 mg once daily, and 800 mg once daily) in Chinese schizophrenic patients with respect to the following outcome variables quetiapine and norquetiapine (N-desalkyl quetiapine)	Single dose PK parameters (300 mg only): AUC_{0-24}, C_{max}, T_{max}, MRT and $T_{1/2}$.	Pharmacokinetic
	Steady-state multiple doses PK parameters: AUC_{ss}, $C_{ss,max}$, $C_{ss,min}$, T_{max},$T_{1/2}$, DF_{ss} and CL/F (quetiapine only).	
Secondary	**Secondary**	
to evaluate the safety and tolerability of XR quetiapine fumarate (300 mg once daily, 600 mg once daily, and 800 mg once daily)	Incidence and severity of adverse events (AEs)(AEs, serious AEs, discontinuations of study due to AEs, other significant AEs)	Safety
	Clinical significant change in laboratory tests (clinical chemistry, haematology and urinalysis) from baseline to up to Day 9	
	Clinical significant change in vital signs (blood pressure, pulse rate, body temperature) and ECG from baseline up to Day 9	

Study design

This was a single-center, open-label, single dose and steady-state multiple-dose, randomised study to evaluate the PK profile of 300mg, 600mg and 800mg quetiapine fumarate XR in Chinese schizophrenic patients.

Target subject population and sample size

Chinese male or female, aged 18-60 years (inclusive), with a Chinese Classification and Diagnostic Criteria of Mental Disorder, 3rd edition criteria of schizophrenia, should meet Body Mass Index (BMI) 20-27 kg/m^2 (inclusive).

The total sample size was planned to be 36 evaluable patients, i.e.12 patients per group. This sample size was based on SFDA technical guideline on the PK study for chemical drug products in which 8-12 patients are required for each dosing group.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product: dosage, mode of administration and batch numbers are presented in Table S2.

Table S2 Identity of investigational product

Investigational product	Dosage form, strength,	Manufacturer	Formulation number	Batch number
quetiapine fumarate XR	Tablet, 300 mg	AstraZeneca	F12527	MC4620
quetiapine fumarate XR	Tablet, 200 mg	AstraZeneca	F12840	NL4618

XR quetiapine fumarate 300 mg (one 300 mg tablets per dose), administered once-daily

XR quetiapine fumarate 600 mg (two 300 mg tablet per dose), administered once-daily

XR quetiapine fumarate 800 mg (two 300 mg tablet and one 200 mg tablet per dose), administered once-daily

Patients in 300 mg group were given oral doses of 300 mg/day of quetiapine fumarate XR once daily in the morning of 08:00 from Day 1 to Day 5.

Patients in 600 mg group were given doses of 300 mg/day quetiapine fumarate XR once daily in the morning of 08:00 on Day 1, and 600 mg/day of quetiapine fumarate XR once daily in the morning of 08:00 from Day 2 to Day 6.

Patients in 800 mg group were given doses of 300 mg/day quetiapine fumarate XR once daily in the morning of 08:00 on Day 1, 600 mg/day of quetiapine fumarate XR once daily in the morning of 08:00 on Day 2, and 800 mg/day of quetiapine fumarate XR once daily in the morning of 08:00 from Day 3 to Day 7.

Day 6 to Day 7 will be the follow-up period after the last dose of Day 5 for 300 mg group.
Day 7 to Day 8 will be the follow-up period after the last dose of Day 6 for 600 mg group.
Day 8 to Day 9 will be the follow-up period after the last dose of Day 7 for 800 mg group.

Duration of treatment

The study comprised an up to 7 days enrollment period followed by 7-9 days of quetiapine fumarate XR treatment. Patients had to stay in hospital from randomization to study termination.

Statistical methods

Patients who were evaluable for pharmacokinetic analysis were defined as those who met the patient selection criteria and who completed the study without major protocol violations or deviations. Data for all patients who took at least 1 dose of the study medication and for whom any post-dose data are available were included in the safety analysis.

Plasma concentrations of quetiapine and N-desalkyl quetiapine were summarized by protocol scheduled time point. The primary focus of the statistical analysis was to characterize the single dose (300mg only) and steady-state pharmacokinetics of quetiapine and N-desalkyl quetiapine. Descriptive statistics by dose group, including median and range, were provided for all PK parameters. Additionally, summary statistics of the PK parameters were provided for relevant time points used to determine single dose (300mg only) and steady state estimates.

Analyses of safety data were descriptive only.

Subject population

A total of 55 (75%) of the 73 enrolled patients were randomized. Of the 18 patients who failed enrolment, 13 were withdrawn due to incorrect enrolment (meeting exclusion criteria), 5 were withdrawn due to voluntary discontinuation. 40(73%) of the 55 randomized patients completed the study, with 13 in 300mg group, 13 in 600mg group and 14 in 800mg group. Of the 15 patients who didn't complete the study, 13 were withdrawn due to voluntary discontinuation by not receiving treatment, 2 were withdrawn due to voluntary discontinuation after receiving treatment. All the patients who completed the study were evaluable for PK analysis.

All patients in the PK analysis set were Asian schizophrenia patients with age of 19-55 years and BMI of 20-27 kg/m^2. There were similar males and female patients across dose group in the PK analysis set. There was no obvious difference between the PK analysis set and safety analysis set with respect to demographic and baseline characteristics.

Summary of PK results

PK parameters of quetiapine and N-desalkyl quetiapine are summarized in Table S3, Table S4, Table S5 and Table S6.

Quetiapine Following a single oral dose administration of 300 mg quetiapine fumarate XR on Day 1, quetiapine was absorbed with time to maximum plasma concentrations (t_{max}) ranging from 1 to 10 hours; and following multiple oral dose administrations of quetiapine fumarate XR on Day last ranging from 1 to 10 hours for 300 mg group, from 1 to 8 hours for 600 mg group, and from 1 to 10 hours for 800 mg group, respectively. Geometric mean terminal half-life ($t_{1/2}$) of quetiapine for these group was 7.07 (single dose), 7.92, 7.40, and 7.74 hours, respectively. $C_{ss,max}$ and AUC_{ss} increased with dose within the dose levels tested. Oral clearance of quetiapine at steady state appeared to be comparable across dose group 300 mg group, 600 mg group, and 800 mg [geometric mean (CV%): 59 (29%) L/hr for 300 mg group, 78 (56%) L/hr for 600 mg group, and 60 (43%) L/hr for 800 mg group]. DF_{ss} of quetiapine were 186, 193 and 164 for group of 300 mg group, 600 mg group and 800 mg group, respectively.

N-desalkyl quetiapine. Following either single or multiple oral dose administrations of quetiapine fumarate XR, N-desalkyl quetiapine was formed with time to maximum plasma concentration (t_{max}) ranging from 2 to 23.9 hours for 300 mg post single dose; from 3 to 12 hours, 1.5 to 10 hours, and from 1.5 to 10 hours for group of 300 mg group, 600 mg group and 800 mg group, respectively. Geometric mean terminal half-life ($t_{1/2}$) of N-desalkyl quetiapine for these group was 11.5 (single dose, N=3), 17.9 (N=11), 16.9 (N=10), and 20.1 (N=13) hours, respectively. DF_{ss} of quetiapine were 73, 75 and 68 for group of 300 mg group, 600 mg group and 800 mg group, respectively. The metabolite to parent ratio (N-desalkyl quetiapine to quetiapine), as evaluated by geometric mean AUC_{ss} of N-desalkyl quetiapine to geometric mean AUC_{ss} quetiapine, was 0.448, 0.565 and 0.545 for group 300 mg group, 600 mg groupand 800 mg group, respectively, of which the ratio of 300 mg groupwas different from that observed on Day 1 (ratio=0.203).

Quetiapine was well absorbed and N-desalkyl quetiapine, an active metabolite of quetiapine, was formed with an approximate metabolite to parent ratio of 0.5 (as evaluated by geometric mean AUC_{ss} of N-desalkyl quetiapine to geometric mean AUC_{ss} quetiapine) across 3 dose group. $C_{ss,max}$ and AUC_{ss} increased with dose. The geometric mean terminal half-life ($t_{1/2}$) of quetiapine and N-desalkyl quetiapine was consistent for 3 dosing group (approximately 7 hours for quetiapine and 18 hours for N-desalkyl quetiapine, respectively). Oral clearance of quetiapine at steady state appeared to be comparable across 3 dose group [geometric mean (CV%): 59 (29%) L/hr for 300 mg, 78 (56%) L/hr for 600 mg, and 60 (43%) L/hr for 800 mg, respectively]. The PK properties of quetiapine and N-desalkyl quetiapine were well characterized in the current study in 40 male and female Chinese patients with schizophrenia following single and multiple oral dose (group) administrations with quetiapine fumarate XR at 3 dose levels.

Table S3 PK parameters of quetiapine at single dose period (PK analysis set)

Dose (mg)	Variable	n	Gmean	CV (%)	Mean	SD	Median	Min	Max
300 mg/day arm	AUC 0-24 (ng/mL*hr)	13	3393	47	3717	1723	3160	1350	7760
	Cmax (ng/mL)	13	343	48	376	165	335	141	676
	Tmax (hr)	13	-	-	-	-	3.0	1.0	10.0
	t1/2 (hr)*	12	7.07	41	7.62	3.25	6.99	4.52	15.00
	Kel (1/hr)	12	0.0981	41	0.1048	0.0373	0.0994	0.0463	0.1530
	MRT (hr)	13	8.45	30	8.76	2.25	8.62	4.36	12.00

*: $t_{1/2}$ was not reported for patients who had estimated values * 2 (hour) > time period of PK sample collection.

Table S4 PK parameters of quetiapine at multiple dose period (PK analysis set)

Dose (mg)	Variable	n	Gmean	CV (%)	Mean	SD	Median	Min	Max
300 mg/day arm	AUCss (ng/mL*hr)	13	5094	30	5315	1798	4680	3690	10100
	Css_max (ng/mL)	13	467	27	482	129	499	293	787
	Tmax (hr)	13	-	-	-	-	6.0	1.0	10.0
	t1/2 (hr)	13	7.92	22	8.09	1.80	8.22	6.03	12.10
	DFss	13	186	35	196	64	183	105	306
	CL/Fss (L/hr)	13	59	29	61	15	64	30	81
	Css_av (ng/mL)	13	212	30	221	75	195	154	421
	Kel (1/hr)	13	0.0875	22	0.0893	0.0185	0.0843	0.0572	0.1150
600 mg/day arm	AUCss (ng/mL*hr)	13	7685	56	8462	3254	8190	1760	15100
	Css_max (ng/mL)	13	740	70	851	382	855	140	1390
	Tmax (hr)	13	-	-	-	-	3.0	1.0	8.0
	t1/2 (hr)	13	7.40	29	7.68	2.19	6.63	4.94	11.50

Table S4 PK parameters of quetiapine at multiple dose period (PK analysis set)

Dose (mg)	Variable	n	Gmean	CV (%)	Mean	SD	Median	Min	Max
	DFss	13	193	40	208	90	189	115	404
	CL/Fss (L/hr)	13	78	56	92	77	73	40	341
	Css_av (ng/mL)	13	320	56	353	136	341	73	629
	Kel (1/hr)	13	0.0936	29	0.0970	0.0261	0.1050	0.0601	0.1400
800 mg/day arm	AUCss (ng/mL*hr)	14	13237	43	14257	5635	13400	4690	28000
	Css_max (ng/mL)	14	1126	46	1226	514	1085	549	2030
	Tmax (hr)	14	-	-	-	-	4.0	1.0	8.0
	t1/2 (hr)	14	7.74	23	7.93	1.74	7.99	5.07	10.80
	DFss	14	164	36	173	59	166	90	274
	CL/Fss (L/hr)	14	60	43	66	34	60	29	171
	Css_av (ng/mL)	14	551	43	594	235	559	195	1167
	Kel (1/hr)	14	0.0895	23	0.0918	0.0223	0.0869	0.0642	0.1370

Table S5 PK parameters of N-desalkyl quetiapine at single dose period (PK analysis set)

Dose (mg)	Variable	n	Gmean	CV (%)	Mean	SD	Median	Min	Max
300 mg/day arm	AUC 0-24 (ng/mL*hr)	13	690	56	779	388	659	247	1570
	Cmax (ng/mL)	13	48	60	56	33	40	23	136
	Tmax (hr)	13	-	-	-	-	8.0	2.0	23.9
	t1/2 (hr)*	3	11.50	13	11.57	1.46	11.80	10.00	12.90
	MRT (hr)	13	11.78	16	11.91	1.75	11.70	8.23	14.20

*: t1/2 was not reported for patients who had estimated values * 2 (hour) > time period of PK sample collection.

Table S6 PK parameters of N-desalkyl quetiapine at multiple dose period (PK analysis set)

Dose (mg)	Variable	n	Gmean	CV (%)	Mean	SD	Median	Min	Max
300 mg/day arm	AUCss (ng/mL*hr)	13	2284	22	2338	532	2150	1710	3500
	Css_max (ng/mL)	13	138	28	144	50	133	97	298
	Tmax (hr)	13	-	-	-	-	6.0	3.0	12.0
	t1/2 (hr)*	11	17.92	17	18.15	3.13	17.30	14.50	23.90
	DFss	13	73	38	77	30	74	37	157
	Css_av (ng/mL)	13	95	22	97	22	90	71	146
600 mg/day arm	AUCss (ng/mL*hr)	13	4341	44	4678	1765	4690	1820	7670
	Css_max (ng/mL)	13	262	49	288	121	265	103	491
	Tmax (hr)	13	-	-	-	-	3.0	1.5	10.0
	t1/2 (hr)*	10	16.93	24	17.35	4.05	16.35	11.50	24.00
	DFss	13	75	26	77	21	65	56	118
	Css_av (ng/mL)	13	181	44	195	74	195	76	320
800 mg/day arm	AUCss (ng/mL*hr)	14	7216	23	7394	1703	6795	5020	11000
	Css_max (ng/mL)	14	426	24	438	102	430	301	595
	Tmax (hr)	14	-	-	-	-	6.0	1.5	10.0
	t1/2 (hr)*	13	20.09	14	20.25	2.48	20.70	14.30	23.20
	DFss	14	68	26	70	20	63	49	120
	Css_av (ng/mL)	14	301	23	308	71	284	209	458

*: $t_{1/2}$ was not reported for patients who had estimated values * 2 (hour) > time period of PK sample collection.

Summary of safety results

The most common reported AE were somnolence (92.9% in 300mg group or 600mg group, 71.4% in 800mg group), dizziness (14.3% in 300mg group or 600mg group, 28.6% in 800mg group), and constipation (14.3% in 600mg group and 7.1% in 800mg group), which are within quetiapine XR profile. There were three patients (one in each group) reporting tongue paralysis which was related with concomitant use of risperidone during the study. All the maximum reported intensity was mild. There was no death, no SAE or OAE. Two patients reported DAE, one patient in the 300 mg group was exposed to Day 1 dosage of 300 mg for 4 hours before voluntary discontinuation due to drowsiness and refusing blood sample collection, and one patient in the 600 mg group was exposed to Day 1 dosage of 300 mg for 50 minutes before voluntary discontinuation due to tongue stiffness and drowsiness. There was no clinical important change about hematology test value. But one patient in 600mg group reported clinical abnormally increase of fasting cholesterol 6.43mmol/l, one patient in 800mg group reported clinical abnormally decrease of total thyroxine 3.67ug/dL. Four patients in 300mg group reported clinical abnormally decease of fasting high density lipoprotein-cholesterol, four patients in 600mg group or four patients in 800mg group. One patient in 300mg group(2.68mmol/L), two patients in 600mg group(3.42mmol/L and 2.39mmol/L) and one patient in 800mg group (2.71mmol/L) respectively reported clinical abnormally increase of fasting triglycerides. However, all these clinical abnormal changes in chemical tests were not reported as AE. Seven patients in 300mg group, five patients in 600mg group and six patients in 800mg group reported clinical abnormally decrease of SBP at last follow-up, which were not reported as AE. Three patients had clinical important change of BP together with AE reported dizziness. There were no cases of syncope, orthostatic hypotension or faint reported with clinical important change of BP. Even there were concomitant uses of risperidone or olanzapine, all the reported AEs and above clinical abnormal changes were within quetiapine XR profile.

There were no new safety or tolerability concerns arising from this study.