The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: PKI113009

Title: A six week randomized, double-blind, multi-center, placebo-controlled, exploratory, adaptive design study to explore the antidepressant properties of the p38 MAP kinase inhibitor GW856553 compared to placebo in adult subjects with Major Depressive Disorder

Rationale: The traditional understanding of the pathophysiology of Major Depressive Disorder (MDD) includes a dysregulation of central neurotransmitters, in particular the monoamines serotonin and noradrenaline. The relevance of other mechanisms has been recently proposed, in particular involving pro inflammatory cytokines. Increased circulating levels of pro-inflammatory cytokines, acute phase proteins and chemokines are known to be associated with symptoms of depression and fatigue in humans and preclinical animal models. At the same time, treatment of depressive symptoms by tricyclic antidepressants and selective serotonin re-uptake inhibitors has been associated with reduction in the levels of circulating cytokines such as TNFα. GW856553 is a potent inhibitor of the p38α mitogen-activated protein kinase (MAPK). Inactivation of p38 kinase using GW856553 has been shown preclinically to suppress the production of TNFα, IL-1β, IL-6 and other cytokines. Additionally, data from a prematurely terminated GSK study with GW856553 in subjects diagnosed with MDD (Study PKI108574) has suggested potentially beneficial effects of treatment with GW856553.
The study population was selected on the basis of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition – TR diagnosis of MDD, and exhibiting symptoms of decreased energy and interest, and psychomotor retardation, all potentially related to cytokine effects in humans.

Phase: II

Study Period: 25 Sep 2009]- 07 Jul 2010

Study Design: A randomized, multi center, double blind, parallel group, placebo controlled, exploratory and adaptive design study

Centres: 21 centers in 5 countries (Bulgaria [4 centers], Estonia [1 centers], Germany [7 centers], Russia [5 centers], US [4 centers])

Indication: Major Depressive Disorder

Treatment: Subjects were randomized (1:1) to receive: Placebo (matching GW856553) (1 tablet twice daily [BID] - 2 tablets) or GW856553 15 mg (1 tablet twice daily – 2 x 7.5 mg tablets).

Objectives: The primary objective of the study was to evaluate the clinical antidepressant effects of GW856553 versus placebo treatment at Week 6 in adult subjects diagnosed with MDD with symptoms of decreased energy and interest, and with psychomotor retardation.

Primary Outcome/Efficacy Variable: The primary endpoint was change from Randomization (Week 0) associated with GW856553 versus placebo at Week 6 in the Bech (6-item Hamilton Depression Rating Scale (HAMD-17) score.

Secondary Outcome/Efficacy Variable(s): The secondary endpoints were: Global depressive symptoms - Changes associated with GW856553 versus placebo from Week 0 to Weeks 1, 2, 3, 4, 5, 6 and Follow–up in the scores of the following clinical scales: Bech (6-item HAMD-17) score (excluding Week 6, since covered in the primary endpoint); HAMD-17 total score; Inventory of Depressive Symptomatology – Clinician Rated (IDS-C) total score; Inventory of Depressive Symptomatology – Self Reported (IDS-SR) total score (only at Weeks 0, 2, 4 and 6); The Quick Inventory of Depressive Symptomatology (16-item) – Self Report (QIDS-SR16) total score derived from the IDS-SR (only at Weeks 0, 2, 4 and 6).
Changes from Randomization (Week 0) associated with GW856553 versus placebo at Week 1 and Week 6 in the morning plasma levels of the following pro-inflammatory biomarkers adjusted for age, gender, body mass index (BMI), and smoking status: IL-6; TNFα.
Percentage of IDS-C responders (subjects with a reduction in total score of $\geq$50% from Randomization at Week 6/study exit).
Percentage of IDS-C remitters (subjects whose total score was $\leq$15 at Week 6/study exit).
Percentage of IDS-SR responders (subjects with a reduction in total score of $\geq$50% from Randomization at Week 6/study exit).
Percentage of IDS-SR remitters (subjects whose total score was $\leq$15 at Week 6/study exit).
Percentage of QIDS-SR16 responders (subjects with a reduction in total score of $\geq$50% from Randomization at Week 6/study exit).
Percentage of QIDS-SR16 remitters (subjects whose total score was $\leq$5 at Week 6/study exit).
Percentage of Bech responders (subjects with a reduction in total score of $\geq$ 50% from Randomization at Week

6/study exit).
Percentage of Bech remitters (subjects whose total score was ≤4 at Week 6/study exit).
Percentage of subjects with a Clinical Global Impression Global Improvement (CGI-I)score of 1 ("very much improved") or 2 ("much improved") at Weeks 1, 2, 3, 4, 5, 6 and at Follow-up.
Changes from Randomization (Week 0) associated with GW856553 versus placebo at Weeks 1,2,3,4, 5, 6 and at Follow-up in the Clinical Global Impression Severity of Illness (CGI-S) score.

Statistical Methods: The change from Randomisation in the Bech subscale of the HAMD-17 was analysed using Bayesian mixed-effects model repeated measures (BMMRM) assuming missing at random (MAR). The estimate of treatment difference and corresponding 95% credible intervals (Cr I) were constructed for the difference between placebo and GW856553 for each week, with the primary inference being the change at Week 6. The primary analysis was performed on the Intent To Treat (ITT) population which was defined as all subjects with at least one post dose efficacy assessment.
Primary inference was based on an informative prior distribution obtained from the previous GSK study PKI108574. The prior distribution, for the estimate of treatment difference between GW856553 7.5 mg BID and placebo for Week 6 from study PKI108574 is $N(4.1, 1.27^2)$, however to introduce some scepticism around these observed results, a prior of $N(4.1, 2.53^2)$ was used. A non-informative normal prior, N(0, 1e6), for the difference between treatments at other timepoints and all covariates were used.
A maximum of 180 subjects with MDD were planned to be recruited to ensure that approximately 46 subjects per arm complete at least 4 weeks of treatment. Based on the results from the interim analysis a decision whether to add an additional arm of GW865553 2.5 mg were made.
It was considered that the minimum clinically meaningful difference of some relevance is 1.6 points on the Bech, as obtained from the aggregated GSK Paroxetine database. The decision to add a new dose would be made if at an official interim analysis there was more than 80% probability that the true treatment difference was greater than 1.6 (symbolically this is expressed as $Pr(\theta>1.6)>80\%$). Conversely the decision to stop the study for lack of sufficient benefit would be made if there was less than a 5% probability that the true treatment difference was greater than 1.6 (symbolically this is expressed as $Pr(\theta>1.6)<5\%$). If the posterior probability of the true treatment difference being 1.6 fell between these two probabilities, $5\% \leq Pr(\theta>1.6) \leq 80\%$, then the study would continue with just two treatment arms (GW856553 7.5mg BID and placebo).

Study Population: Male or female subjects aged 18 to 60 years, suffering from MDD (without psychotic features). Females of non-child bearing potential (post- menopausal or surgically sterile) were eligible, and females of child bearing potential were eligible provided they were not pregnant and using adequate contraception from first dose to Follow-up visit. Male subjects eligible for the study had to use adequate contraception from first dose to Follow-up visit. Subjects had to meet DSM IV-TR criteria for their current MDD for at least 4 weeks and had at least one previous major depressive episode with a diagnosis of MDD in his/her history. Subjects exhibited moderate to severe levels of depression as defined by IDS-SR measured at the Screening and Randomisation visits:

- a total score ≥38, and
- a score ≥1 for each of the items representing mood (item 5; feeling sad), interest (item 19; general interest), energy (item 20; energy level) and psychomotor retardation (item 23; feeling slowed down).

IDS-C when measured at the Screening visit and at the Randomization visit (Week 0)

- a total score of ≥36, and
- a score ≥ 1 on Items representing mood (item 5), interest (item 19), energy (item 20), **and** psychomotor retardation (item 23).
- A change (either increase or decrease) in total score at Randomization of no more than 25% from Screening.

Subjects were not eligible for inclusion in the study if had any history of liver disease, a positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening, a history of elevated liver function tests on more than one occasion (ALT, AST, and total bilirubin > 2 x ULN or ALP > 3 x ULN) in the past 7 months.

Number of Subjects:	**Placebo**	**GW856553 7.5 mg**
Planned, N	60	60
Randomised, N	64	64
Completed, n (%)	50 (78)	51 (80)
Total Number Subjects Withdrawn, N (%)	14 (22)	13 (20)
Withdrawn due to Adverse Events, n (%)	5 (8)	5 (8)
Withdrawn due to Lack of Efficacy, n (%)	3 (5)	5 (8)
Protocol deviation, n (%)	1 (2)	0
Lost to follow-up, n (%)	1 (2)	0
Investigator discretion, n (%)	2 (3)	0

Withdrew consent, n (%)	2 (3)	3 (5)
Demographics	**Total**	
N (All Subjects)	128	
Females: Males	76:52	
Mean Age, years (SD)	43.1 (11.50)	
White, n (%)	122 (95)	
Height, cm (SD)	170.3 (9.70)	
Weight, kg (SD)	75.17 (16.502)	
BMI, kg/m^2 (SD)	25.78 (4.516)	

Primary Efficacy Results:

Summary of Bayesian Analysis of Bech Total Score ITT Population

		Posterior means				Posterior probability Trt Diff<X		
Comparison	Estimate	GW856553	Placebo	95% HPD (Lower, Upper)	SD	0	-1.6	-2
GW856553 7.5 mg BID – Placebo (Week1)	-0.29	10.81	11.09	(-1.08, 0.49)	0.399	76.38	0.07	0.00
GW856553 7.5 mg BID – Placebo (Week2)	0.38	10.16	9.78	(-0.58, 1.34)	0.490	21.90	0.01	0.00
GW856553 7.5 mg BID – Placebo (Week3)	0.51	8.98	8.46	(-0.61, 1.59)	0.561	17.92	0.01	0.00
GW856553 7.5 mg BID – Placebo (Week4)	1.15	8.34	7.19	(0.04, 2.25)	0.563	2.02	0.00	0.00
GW856553 7.5 mg BID – Placebo (Week5)	1.26	7.48	6.22	(-0.03, 2.54)	0.659	2.80	0.00	0.00
GW856553 7.5 mg BID – Placebo (Week6)	1.11	7.05	5.94	(-0.22, 2.50)	0.693	5.55	0.01	0.00

Secondary Outcome Variable(s):
Summary Statistics of Change from Randomisation of Bech(6-items), HAMD-17, IDS-C, IDS-SR, QIDS-SR (ITT Population)

Visit	Treatment group	Bech (6-item)	HAMD-17	IDS-C	IDS-SR	QIDS-SR16
Week 1	Placebo	-1.2	-2.8	-5.4		
	GW856553	-1.6	-3.2	-6.1		
Week 2	Placebo	-2.5	-5.6	-9.9	-12.9	-5.0
	GW856553	-2.2	-4.6	-9.1	-10.5	-3.7
Week 3	Placebo	-3.9	-7.8	-13.9		
	GW856553	-3.4	-6.4	-12.6		
Week 4	Placebo	-5.1	-10.3	-18.1	-17.9	-7.3
	GW856553	-4.1	-7.6	-14.1	-15.7	-5.8
Week 5	Placebo	-6.2	-11.9	-21.7		
	GW856553	-5.0	-9.6	-18.2		

Week 6	Placebo	-6.5	-12.6	-23.0	-22.2	-8.5
	GW856553	-5.6	-10.6	-19.4	-20.7	-7.6

Percentage of Responders and Remitters by Week 6 (ITT Population)

Primary clinical scales	Treatment	Responders n/N (%)	Remitters n/N (%)
Bech (6-item HAMD-17) score	Placebo	31/50 (62)	19/50 (38)
	GW856553	25/51(49)	10/51 (20)
HAMD-17 total score	Placebo	29/50 (58)	14/50(28)
	GW856553	23/51 (45)	8/51(16)
IDS-C score	Placebo	21/51 (50)	9/51 (38)
	GW856553	25/50 (41)	19/50 (17)
IDS-SR score	Placebo	25/51 (49)	19/51 (37)
	GW856553	25/53 (47)	10/53 (19)
QIDS-SR16 total score	Placebo	28/51 (55)	16/51 (31)
	GW856553	24/53 (45)	7/53 (13)

Pharmacokinetic

Schedule Time	**Week**	**N**	**GW856553 Plasma Concentration (ng/mL)**		
			Mean (SD)	**Median**	**Range**
3 Hrs Post-Dose	0	62	26.37 (13.87)	26.57	0.00 to 61.27
Pre-Dose	1	62	9.69 (7.87)	7.29	0.00 to 48.31
3 Hrs Post-Dose	1	62	34.17 (18.84)	33.07	0.00 to 91.38
Pre-Dose	6	50	9.27 (9.04)	8.23	0.00 to 53.59
3 Hrs Post-Dose	6	50	33.82 (13.69)	34.13	0.00 to 68.75

Safety Results: All adverse events (AE) occurring after administration of the first dose of study medication and on or before the final Follow-up contact were reported as AEs or serious adverse events (SAEs), as applicable. From the time a subject consented to participate in the study until he or she completed the study (including any Follow-up period), any SAEs assessed as related to study participation were recorded. Any SAE reported after the final Follow-up visit and considered related to the investigational product by the Investigator were also reported. There were no pregnancies reported in the study.

	Placebo	**GW856553 7.5 mg**
Adverse Events	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	28 (44)	26 (41)
Headache	9 (14)	12 (19)
Diarrhoea	7 (11)	1 (2)
Fatigue	4 (6)	0
Dyspepsia	3 (5)	3 (5)
Nausea	3 (5)	3 (5)
Abdominal pain upper	3 (5)	1 (2)
Nasopharyngitis	3 (5)	2 (3)
Anxiety	2 (3)	4 (6)
Somnolence	1 (2)	3 (5)
Constipation	1(2)	2(3)

Serious Adverse Events - On-Therapy, n (%) [n considered by the investigator to be related to study medication]

Serious Adverse Events	**Placebo n (%)**	**GW856553 7.5 mg n (%)**
Subjects with any SAE(s) n(%)	1 (2)	1(2)
Suicidal ideation	1 (2)	1 (2)

There were no deaths and fatal SAEs reported.

Conclusion: There was no statistical different between GW856553 and placebo for the primary efficacy variable. In the group of GW856553, 26 subjects reported AEs with most frequently reported being headache. In the placebo group, 28 subjects reported AEs with the most frequently reported being headache. Two SAEs were reported, one in the placebo group and one in the GW856553 group. Both SAEs were suicidal ideation and were not considered to be related to study medication. There were no fatalities reported in either group.