Synopsis

Identifier: HH2008/00419/00 **Study Number:** PKI108574

Title: A randomised, double-blind, placebo-controlled study to explore the antidepressant properties of the P38a kinase inhibitor GW856553X 15mg compared to placebo in subjects with Major Depressive Disorder exhibiting symptoms of loss of energy and interest, and psychomotor retardation, for a six week treatment period.

Investigators: Multicentre study

Study centres: 11 centres in 3 countries (Estonia, India and Russia).

Publication: None as of April 2009

Study Period: 27Dec2007 - 25Jun2008

Phase of Development: II

Objectives: Primary: To evaluate the clinical antidepressant effects of GW856553X versus placebo treatment at Week 6 in adult subjects diagnosed with Major Depressive Disorder (MDD) with symptoms of loss of energy / interest and with psychomotor retardation. To measure the decrease of circulating serum cytokines (either tumour necrosis factor alpha [TNFα] or interleukin (IL)-6) associated with GW856553X versus placebo treatment in adult subjects diagnosed with MDD in the whole population sample, in a sample of subjects with elevated cytokine levels at baseline or at screening and in a sample of subjects that responded to the treatment versus non-responders at Week 6, according to the various clinical scores.

Secondary: To evaluate safety and tolerability of GW856553X in subjects with MDD. To evaluate the antidepressant effects of GW856553X versus placebo treatment at Weeks 1, 2, 3, 4 and 5 in adult subjects diagnosed with MDD including symptoms of loss of energy / interest and with psychomotor retardation. To evaluate the antidepressant effects of GW856553X versus placebo treatment in the sample of adult subjects diagnosed with MDD with abnormally elevated cytokine level at randomisation (Week 0). To evaluate the effects of GW856553X versus placebo treatment on specific clusters of symptoms possibly associated with pro-inflammatory cytokine effects (putative cytokine-related intermediate phenotypes) in the same adult subjects diagnosed with MDD, in particular: psychomotor retardation, fatigue & daytime sleepiness. To assess the relationship between cytokine levels (IL-6 or TNFα), other inflammatory blood biomarkers, and clinical or behavioural effects (i.e., primary and secondary efficacy endpoints) in the same adult subjects diagnosed with MDD, with attention to responders. To evaluate the pharmacokinetic (PK)–pharmacodynamic (PD) relationship between GW856553X exposure and clinical, behavioural and biomarker levels (i.e., primary and secondary efficacy endpoints), or safety and tolerability outcomes in the same adult subjects diagnosed with MDD. To characterise population PK of GW856553X and its primary metabolite GSK198602 in subjects with MDD. To assess the difference of cytokine levels and other exploratory biomarkers between healthy subjects recruited in the same centres and subjects with MDD when assessed at randomisation.

Methodology: Randomised, multicentre, double-blind, parallel group, placebo-controlled study to compare the antidepressant effects of GW856553X 15 mg/day versus placebo treatment in adult subjects diagnosed with MDD exhibiting symptoms of loss of energy / interest and psychomotor retardation. Screening visit was followed by six weeks treatment and follow-up. Healthy subjects were included for serum cytokine assessments only.

All primary efficacy parameters were examined as per protocol. However, as a result of study termination several aspects of the study were revised or not conducted according to protocol or the planned statistical analysis

Number of subjects: Approximately 120 subjects with MDD were to be recruited to ensure 45 evaluable subjects per arm for PD evaluation; 20 healthy subjects per country to be recruited for cytokine assessments only.

n (%)	GW856553X 15 mg	Placebo	Healthy subjects	Total
Number planned	60	60	40	160
Number randomised	12	12	5	29
Completed Study	8 (67)	7 (58)	5 (100)	20 (69)
Withdrawn	4 (33)	5 (42)	0	9 (31)
Reason for withdrawal				
Adverse event	0	1 (8)	0	1 (3)
Protocol violation	1 (8)	0	0	1 (3)
Subject decision	3 (25)	4 (33)	0	7 (24)

Insufficient evidence for the mechanism of cytokine elevations in MDD and data from a completed negative proof-of-concept trial in rheumatoid arthritis suggested that further progression of GW856553X in depression was scientifically and ethically not justified. The trial was therefore terminated before all subjects had been recruited.

Diagnosis and main criteria for inclusion: Male or female subjects with MDD aged 18 to 60 years, body mass index within the range 18.5 to 35.0 kg/m^2 inclusive and with normal liver function, current major depressive episode for at least 4 weeks but for no greater than 24 months, a minimum score at screening of 17 on the quick inventory of depressive symptomatology 16 Item Self Report (QIDS-SR16) and of 36 on the inventory for depressive symptomatology clinician rated (IDS-C) scale (with a score of at least 1 on items representing depression, interest, energy & psychomotor retardation). Healthy subjects matched the group of subjects with MDD in demographic profile.

Treatment administration: Subjects with MDD were randomised (1:1) to receive GW856553X 7.5 mg (as one 5 mg and one 2.5 mg tablet) or placebo twice a day for six weeks. Healthy subjects received no treatment. Batch numbers were: 061122845

(GW856553X 2.5 mg), 061122846 (GW856553X 5 mg) and 061122712 (matching placebo).

Criteria for evaluation: Primary clinical endpoints were changes from randomisation (Week 0) produced by GW856553X versus placebo at Week 6 in Bech (6-item Hamilton depression rating scale [HAMD-17]) score, IDS-C total score, QIDS-SR16 total score and HAMD-17 total score. Other primary endpoints were changes at Week 6 in morning serum levels of pro-inflammatory biomarkers IL-6, TNFα, IL-10 and interleukin-2 receptor alpha (IL-2ra).

Statistical methods: Sample size was estimated on the basis of the change from randomisation in the Bech subscale of the HAMD-17 scale. Based on a GlaxoSmithKline aggregated paroxetine database, the average effect size observed was 0.37 units with a standard deviation of 4.32. This translated to an average treatment difference (active - placebo) in change from randomisation of -1.6. A maximum of 120 subjects with MDD was planned to be recruited to ensure 45 subjects with MDD per arm. In addition, up to 20 healthy subjects were to be recruited in each country. However, following study termination, the number of subjects with MDD and healthy subjects was 24 (12 per arm) and 5, respectively.

The primary efficacy analyses of change from randomisation at Week 6 in the Bech subscale of the HAMD-17 and other key endpoints (IDS-C, HAMD-17 and QIDS-SR16 total scores) was done by using mixed-effects model for repeated measures (MMRM). Initially the MMRM included terms for country, baseline (score at randomisation), treatment, week, treatment*week, treatment *country, and treatment*baseline. Country, treatment by country, baseline by week and treatment by baseline interaction were not found to be statistically significant and therefore excluded from the final model. The result of the analysis was presented as point estimates and 95% confidence intervals for the adjusted mean differences between GW856553X and placebo. Corresponding effect size was also calculated.

Secondary efficacy (clinical/behavioural scales) and PD (IL-6, TNFα, IL-10, IL-2ra, TNFα/IL-10 ratio and high sensitivity-C reactive protein) endpoints were summarized.

To check the robustness of the primary efficacy analysis, missing scores were estimated by a last-observation carried-forward approach on all primary outcome measures for the planned analyses.

Summary:

Efficacy-PD: GW856553X administration resulted in greater changes in subjects with MDD at Week 6 on the Bech (6-item HAMD-17) score, IDS-C total score, HAMD-17 total score and QIDS-SR16 total score when compared to placebo. The treatment difference of 4.1 points at Week 6 was statistically significant for the Bech scale ($p=0.017$). Even though no statistically significant difference was observed between GW856553X and placebo on other scales, the differences were marked, showing a benefit of GW856553X when compared to placebo.

Subjects assigned to placebo experienced substantial symptom reduction, although not of the magnitude experienced by those assigned to GW856553X. The percentage of remitters and responders on Bech (6-item HAMD-17) score, IDS-C and QIDS-SR16 total scores demonstrated marked improvement in depression symptoms in both groups but it was greater in GW856553X treated subjects.

The biomarker TNFα showed a trend to decrease from baseline at Week 6 following GW856553X administration. No other biomarker showed a clear change from baseline.

An increase was observed at Week 6 following GW856553X administration when compared to placebo for the visual analogue scale (VAS) scores for daytime sleepiness and tiredness.

Safety: Adverse events (AEs) occurring in more than one subject are included below; there was no time of event recorded so an event on "Day 1" is classed as treatment emergent.

Adverse event : Preferred term	GW856553X 15 mg N=12	Placebo N=12	Total N=24
Number (%) of subjects with any AE	6 (50)	4 (33)	10 (42)
Number of AEs	*9*	*10*	*19*
Headache	2 (17))	0	2 (8)
Nasopharyngitis	2 (17)	0	2 (8)
Nausea	0	2 (17)	2 (8)
Anxiety	0	2 (17)	2 (8)
Insomnia	1 (8)	1 (8)	2 (8)

One event of nausea (in a placebo subject) led to subject withdrawal. Occasional changes in vital signs, electrocardiograms or laboratory parameters were considered to be of no clinical significance and there was no difference between treatment groups.

PK: There was evidence for a small increase in steady state plasma concentrations of GW856553X over the 6 week dosing period. Plasma concentrations of the metabolite GSK198602 exceeded those of parent compound, suggesting it was eliminated more slowly.

Conclusions:

- GW856553X produced a marked change in the Bech (6-item HAMD-17) score, IDS-C total score, HAMD-17 total score and QIDS-SR16 total score as compared to placebo at Week 6 in subjects with MDD. The low numbers of subjects meant that, only for the Bech scale was the treatment difference at Week 6 found to be statistically significant.
- Subjects with MDD who were assigned to placebo treatment experienced substantial symptom reduction, although not of the magnitude experienced by those assigned to GW856553X.
- The percentage of subjects on GW856553X who were remitters and responders on Bech (6-item HAMD-17) score, IDS-C and QIDS-SR16 total scores demonstrated significant improvement in depressive symptoms, when compared to subjects treated with placebo.
- A trend for reduction from baseline was observed for TNFα following 6 weeks treatment with GW856553X 15 mg.
- No conclusive evidence for treatment differences could be derived from the multiplex protein panel of exploratory biomarkers due to the limited samples available.
- An improvement was observed with GW856553X compared to placebo at Week 6 for both the VAS Scores (fatigue and daytime sleepiness).
- There was evidence for a small increase in steady state plasma concentration of GW856553X over the 6 week dosing period. Plasma concentrations of the metabolite GSK198602 exceeded those of parent compound.
- In this MDD study population GW856553X was well tolerated. The AE profile was similar to that in the placebo treated subjects. There was only one withdrawal due to an AE of nausea and this was in a placebo treated subject.

Date of Report: April 2009