Study No: H3B109689

Title : A single blind, placebo-controlled, randomised study in mild to moderate Alzheimer's Disease patients to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK239512, a selective histamine H3 receptor antagonist

Rationale: GSK239512 is an histamine H3 receptor antagonist being developed for the symptomatic treatment of cognitive impairments associated with dementia, schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD) and other disorders such as obesity and hypersomnolence.

Pre-clinical studies show GSK239512 to be a highly potent, selective, orally bioavailable and brain penetrant histamine H3 receptor antagonist which is active in animal models of cognition. The mechanism of action for H3 antagonists in cognitive improvement is not clear, but it is likely to involve local release of histamine and secondary up-regulation of other neurotransmitters such as acetylcholine, noradrenaline, dopamine and/or serotonin. Thus, GSK239512 has the potential to improve cognition in patients with Alzheimer's disease (AD).

The purpose of this single blind (investigator and subject blinded), placebo-controlled, randomised study was to examine the safety and tolerability profile of GSK239512 in patients with AD to identify an optimal dose titration regimen which will allow progression to larger-scale efficacy studies

Phase: I

Study Period: 21 February 2008 to 16 June 2009

Study Design: This study was conducted in two parts: **Part A** was a single blind, placebo run-in, flexible dose titration in four subjects with AD. **Part B** was a single blind, randomised, placebo controlled, parallel group, flexible dose titration study in three cohorts, each consisting of eight subjects.

Centres: Three centres in the United Kingdom, 2 centres in South Korea, 1 centre each in Australia and Czech Republic.

Indication: Alzheimer's Disease

Treatment:

Part A: The first two subjects from Cohort 1, commenced dosing on Day 1 with a 2 μg daily dose of GSK239512 for three days and escalated to 5 μg, according to safety and tolerability review as judged by the investigator. A further two subjects (Cohort 2) commenced dosing with GSK239512 at a dose of 5 μg for three days and escalated to 10 μg for the remaining four days, according to safety and tolerability as judged by the investigator.

Part B: Six subjects were randomised to receive active treatment and two subjects were randomised to receive placebo in each cohort. The dosing period was 4 weeks and subjects followed the titration regimens as outlined in the protocol and described below. The safety and tolerability data were reviewed by the investigators and the GSK study team prior to selecting the dose titration regimen for the next cohort.

Cohort 1: The first cohort (n=8) started at 5 μg /day and was planned to titrate up weekly to a maximum of 40 μg /day (5 μg /10 μg /20 μg /40 μg). Titration was flexible and subjects could remain on the same dose level or step down to a previous dose level if there were safety or tolerability concerns, as judged by the Investigator. Four of the 6 subjects in Cohort 1 titrated up to 40μg of GSK239512 as per the specified regimen. However, one subject received 5 μg/10 μg/5 μg/5 μg and another subject received 5 μg/10 μg/20 μg/10 μg.

Cohort 2: Based on the safety review from Cohort 1, the second cohort (n=8) started at 10 μg /day and was planned to titrate up to a maximum of 80 μg /day (10 μg /20 μg /40 μg /80 μg). Five of the 6 subjects in Cohort 2 titrated up to 80μg of GSK239512 as per the specified regimen. However, one subject received 10 μg / 10 μg / 20 μg /40 μg.

Cohort 3: Based on the safety review from Cohort 2, the final cohort (n=8) started at 20 μg /day and planned to titrate up to a maximum of 150 μg /day (20 μg /40 μg /80 μg /150 μg). Three of the 6 subjects in Cohort 3 titrated up to 150μg of GSK239512 as per the specified regimen. However, 2 subjects received 20 μg /20 μg /40 μg /80 μg and 1 subject received 20 μg /40 μg /80 μg /80 μg.

Objectives: Primary objective of the study was to assess the safety and tolerability of GSK239512 in subjects with mild to moderate Alzheimer's disease on repeat dosing.

Statistical Methods:

Sample Size Considerations: A sufficient number of subjects were to be enrolled such that data from at least four evaluable subjects were available in Part A, prior to initiating Part B. Any subject who had received at least one dose of study medication and had undertaken at least one post dose assessment was evaluable. In Part B a sufficient number of subjects were to be recruited such that at a maximum of 24 evaluable subjects were to be treated with GSK235912; a total of 18 subjects were treated with GSK239512 in Part B. Subjects who completed Part A could not participate in Part B of the study.

Interim Analysis: No formal interim analyses were planned. The decision to proceed to higher dose strengths was made by the investigator and the study team based on assessment of safety, tolerability at the preceding dose.

Final Analyses:

PK/Pharmacodynamic (PD) exploration: A graphical PK/PD exploration was conducted for each CogState task. Individual CogState standardised scores were plotted versus GSK239512 average plasma concentration during CogState battery. As no clear PK/PD relationship was shown, no formal PK/PD modeling was conducted.

PD Analyses (Part B Only): Change from baseline at Day 29 for CogState individual tests, was standardised into effect sizes (i.e. estimate of treatment difference / standard deviation) using the between-subject standard deviation from an analysis of covariance at Day 29 adjusting for baseline. Subjects were grouped according to the dose received at Day 28. Actigraphy data was averaged over each dose titration week for summaries; no statistical analysis was performed. Leeds Sleep Evaluation Questionnaire (LSEQ) domains were averaged over each dose titration week for summaries; no statistical analysis was performed.

Study Population: Male or post-menopausal (i.e. 12 months without menstrual period) or surgically sterile female subjects aged ≥50 years, with a clinical diagnosis of probable Alzheimer's disease in accordance with the NINCDS-ADRDA criteria and a Haschinski ischaemia score ≤4 and a magnetic resonance imaging (MRI) or computed tomography (CT) scan in the last 12 months and with an MMSE score at Screening of 12 to 26 for Part A and 16 to 26 for Part B, were enrolled into this study.

Part A

Number of Subjects:	**Cohort 1 (2/5μg)**	**Cohort 2 (5/10μg)**
Number of subjects planned	2	2
Number of subjects randomised, N:	2	2
Number of subjects included in All subjects' population, n (%):	2 (100)	2 (100)
Number of subjects included in PD population, n (%):	2 (100)	2 (100)
Number of subjects completed as planned, n (%):	2 (100)	2 (100)
Number of subjects withdrawn (any reason), n (%):	0	0
Demographics		
Age in Years, Median (Range)	82.5 (78-87)	71.0 (55-87)
Sex, n (%)		
Female:	1 (50)	0
Male:	1 (50)	2 (100)
BMI, Median (Range)	(22.8) 21.3-24.3	40.6 (40.2-41.1)
Height, Median (Range)	164.0 (156-172)	154.0 (126-182)
Weight, Median (Range)	61.9 (51.8-72)	99.9 (64-136)
Ethnicity, n (%)		
Not Hispanic or Latino:	2 (100)	2 (100)
Race, n (%)		
White – White/Caucasian/European Heritage	2 (100)	2 (100)

Part B

Number of Subjects:	**Cohort 1 (placebo or 5/10/20/40μg)**	**Cohort 2 (placebo or 10/20/40/80μg)**	**Cohort 3 (placebo or 20/40/80/150μg)**
Number of subjects planned	8	8	8
Number of subjects randomised, N:	8	8	8
Number of subjects included in All subjects' population, n (%):	8 (100)	8 (100)	8 (100)
Number of subjects included in PK population, n (%):	8 (100)	8 (100)	8 (100)
Number of subjects included in PD population, n (%):	8 (100)	8 (100)	8 (100)
Number of subjects completed as planned, n (%):	7 (88)	8 (100)	8 (100)
Number of subjects withdrawn (any reason), n (%):	1 (13)	0	0
Number of subjects withdrawn for serious adverse event, n (%):	1 (13)	0	0
Demographics			
Age in Years, Mean (SD)	71.0 (9.94)	72.9 (5.51)	71.4 (6.97)

Sex, n (%)			
Female:	3 (38)	2 (25)	3 (38)
Male:	5 (63)	6 (75)	5 (63)
BMI, Mean (SD)	24.3 (3.7)	24.3 (2.1)	23.2 (4.6)
Height, Mean (SD)	166.4 (19.0)	167.8 (5.8)	164.0 (10.9)
Weight, Mean (SD)	69.2 (23.0)	68.4 (7.1)	62.5 (14.1)
Ethnicity, n (%)			
Not Hispanic or Latino:	8 (100)	8 (100)	8 (100)
Race, n (%)			
Asian- East Asian Heritage	3 (38)	3 (38)	2 (25)
White – White/Caucasian/European Heritage	5 (63)	5 (63)	6 (75)

Pharmacokinetics, pharmacodynamics, PK/PD Endpoints:

Pharmacokinetic (Part B, Day 1): GSK239512 PK parameters were derived from the individual PK profiles on Day 1 Part B. PK parameters in subjects with AD were consistent with those observed in healthy volunteers in the FTIH study on Day 1.

Geometric Mean (CVb%) GSK239512 Pharmacokinetic Parameters in Part B, Day 1

Cohort	Dose	n	Cmax (ng/mL)	tmax (h)[2]	AUC(0-24) (ng·h/mL)	AUC(0-t) (ng·h/mL)	t½ (h)
1[1]	5μg	3[3]	0.01(35)	6.0 (2.0-6.0)	NC	NC	NC
2	10μg	6	0.02 (19)	2.0 (2.0 - 6.0)	0.28 (22)	0.24 (41)	14.1 (34) [4]
3[1]	20μg	6	0.05 (38)	4.0 (1.0 - 6.0)	0.65 (21)	0.77 (35)	13.5 (55)

NC = Not calculable value because most concentrations were below the limit of quantification (LOQ=0.005 ng/mL)

1. GSK239512 concentrations 24h post dose for subjects 300002, 300003 and 300004 were abnormally high and were excluded from the PK parameter analysis
2. Median (range)
3. 3 non quantifiable profiles (subjects 300001, 700001 and 700002)
4. n=5

PK/PD: As no clear trend of a relationship between CogState standardised scores and Cave was shown across all CogState tasks, and given the small number of subjects on each dose, no formal PK/PD analysis was performed.

Geometric Mean (CVb%) GSK239512 Plasma Through Concentration during CogState Across Doses

Statistics	GSK239512					
	5 μg	10 μg	20 μg	40 μg	80 μg	150 μg
N	8[1]	14[2]	19	16[3]	12	3
Geometric Mean (ng/mL)	0.007	0.013	0.03	0.064	0.102	0.229
CV% Geometric Mean (%)	31	31	28	38	43	27

1. Concentrations from 3 subjects were < LOQ (0.005 ng/mL). Cave extrapolated from the rest of the PK profile assuming PK linearity.
2. Concentrations from 2 subjects were < LOQ (0.005 ng/mL). Cave extrapolated from the rest of the PK profile assuming PK linearity.
3. Concentrations from 1 subject was < LOQ (0.005 ng/mL). Cave extrapolated from the rest of the PK profile assuming PK linearity.

PD (Part B): LSEQ and Actigraphy data suggests that there was no consistent worsening in sleep pattern compared to placebo for any dose titration regimen. There were signals of positive effects on both attention and working memory tasks in the CogState battery compared to placebo.

Summary of Day 29 CogState Effect Sizes

	Effect Size Compared to Placebo (95% CI)			
	40 μg	80 μg	150 μg	GSK239512
Detection (Attention)	0.36 (-1.02, 1.73)	0.30 (-0.87, 1.47)	0.27 (-1.24, 1.77)	0.33 (-0.69, 135)
Identification (Attention)	1.37 (-0.13, 2.88)	0.70 (-0.45, 1.84)	2.36 (0.84,3.88)	1.05 (0.02, 2.08)
One-Back (working Memory)	0.03 (-1.38, 1.43)	0.01 (-1.15, 1.16)	-0.75 (-2.25, 0.75)	-0.16 (-1.19, 0.87)
ISL (Episodic Memory)	-0.36 (-1.72, 1.01)	0.90 (-0.25, 2.04)	1.18 (-0.36, 2.72)	0.56 (-0.46, 1.58)
ISL-R	0.80	0.75	0.63	0.78

(Episodic Memory)	(-0.59, 2.19)	(-0.41, 1.90)	(-0.87, 2.13)	(-0.24, 1.79)

Safety results: Time period for collection of adverse events (AEs) and serious adverse events (SAEs) was from the day of Screening until the last visit of Follow-up. No deaths or pregnancies were reported during any part of the study.

Part A: A total 2 AEs: moderate initial insomnia (5 μg during Day 3 to Day 4) and mild pruritus (10 μg during Day 7 to Day 14) were reported by 1 subject during treatment with GSK239512. Of these AEs, only pruritus was reported as related to GSK239512 by the investigator.

Part B: Thirteen subjects (72%) treated with GSK239512 and 4 (67%) with placebo reported AEs in this part of the study. Nausea, headache and fatigue were the most common AEs in this part of the study.

Summary of Adverse Events experienced by more than 1 subject in at least 1 treatment group (Part B)

Cohort 1:

Adverse Events	**GSK239512**				**Total**
	5 μg (N=6)	**10 μg (N=6)**	**20 μg (N=5)**	**40 μg (N=4)**	**(N=6)**
Any Events, n (%)	**4 (67)**	**2 (33)**	**2(40)**	**0**	**5(83)**
Nausea	1 (17)	2 (33)[2]	1 (20)	0	2 (33)

Cohort 2: There were no AE experienced by more than 1 subject in at least 1 treatment group of Cohort 2.

Cohort 3:

Adverse Events	**GSK239512**				**Total**
	20 μg (N=6)	**40 μg (N=6)**	**80 μg (N=6)**	**150 μg (N=3)**	**(N=6)**
Any event, n (%)	**3(50)**	**2(33)**	**3(50)**	**3(100)**	**6(100)**
Fatigue	1(17)[1]	1(17)[1]	2(33)[1]	0	3(50)
Sleep disorder	2(33)[1]	0	0	0	2(33)

Placebo:

Adverse Events	**Total (N=6)**
Any event, n (%)	**4 (67)**
Dizziness	2 (33)[2]

1. Drug related AE
2. Out of two AEs only one AE was described as drug related

Overall tolerability was satisfactory for Cohort 1 with the 5/10/20/40 μg regimen. The 10/20/40/80 μg regimen of Cohort 2 was well-tolerated. Approximately 80% of subjects treated with these regimens were able to titrate up to their highest target dose level in Week 4. The regimen of 20/40/80/150 μg of Cohort 3 showed poorer tolerability than that of Cohorts 1 and 2.

Across all three titration regimens, there was no worsening of clinical global impression, neuropsychiatric features or subjective ratings of sleep. Thus a titration regimen for AD subjects starting at 5 or 10 μg and then doubling the dose every week to a maximum dose of 40 - 80 μg is likely to be a well-tolerated regimen for future clinical trials.

There were no clinically significant changes in vital signs, laboratory parameters and ECG parameters in subjects during treatment with GSK239512.

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: There were no SAEs reported in Part A of the study. In Part B, one subject (Cohort 1) experienced a SAE of spinal compression fracture nine days after completing dosing at 40 μg/day, which was considered to be not related to the investigational product. This subject was withdrawn from the study.