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.: H3B110651

Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of the H3 receptor antagonist, GSK239512 in subjects with mild to moderate Alzheimer's disease.

Rationale: GSK239512 is a highly potent, selective, orally bioavailable and brain-penetrant histamine H3 receptor antagonist. 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, it is believed that GSK239512 has the potential to improve cognition in patients with Alzheimer's disease (AD).

Preclinically, when dosed orally to rats, GSK239512 has been shown to potently reverse H3 agonist-induced drinking, inhibit cortical *ex vivo* H3 receptor binding and to exhibit activity in three models of cognition. Following three days of oral dosing, GSK239512 (0.3 and 1 mg/kg) significantly enhanced cognitive function in the object-recognition 48-hour delay paradigm in rats. In addition, GSK239512 (1 and 3 mg/kg PO) was able to reverse amnesia induced by scopolamine in a single-trial, step-through, light-dark, passive avoidance paradigm and improve working memory in the delayed-matching-to-sample task in rats. In addition, cognitive and global effects of GSK239512 as a monotherapy have been investigated in subjects with mild-to-moderate AD in one Phase IIa study H3B109689 (a 4-week, dose-titration regimen study).

Phase: Phase IIa

Study Period: 02 November 2009 to 08 November 2010

Study Design: An international, multi-centre, randomized, double-blind, placebo-controlled, parallel group study in subjects with mild to moderate AD (Mini Mental State Examination [MMSE] 16-24) to assess the efficacy, safety and tolerability of oral GSK239512 administered over 16 weeks of treatment. Following a screening period of up to two weeks, subjects entered a two-week placebo run-in period before being randomized (1:1) to receive either GSK239512 or placebo for a period of 16 weeks, which included 4 weeks of titration from 10 µg/day to a target maintenance dose of 80 µg/day for the 12 week maintenance phase. The randomization was stratified by MMSE to ensure that the treatment allocation within stratum was balanced. The aim was to recruit approximately 50% Mild AD subjects (MMSE 20 to 24) and 50% Moderate AD (MMSE 16 to 19) but this was not forced in the randomization. Subjects underwent weekly review for assessment of safety and tolerability before each dose titration. The dose was kept unchanged or decreased if in the Investigator's opinion there were safety or tolerability concerns. Subjects were required to maintain a minimum dose of 20 µg/day to remain in the study.

Centres: 34 centers from 8 countries (Bulgaria, Chile, Czech Republic, Germany, Korea, Russia, Slovakia and United Kingdom).

Indication: Alzheimer's Disease

Treatment: All subjects were allocated single-blind placebo study treatment for the 2-week placebo run-in period. Eligible subjects were then randomized to either GSK239512 or matching placebo in a 1:1 ratio in accordance with the randomization schedule. Further details are provided above (see "Study Design"). GlaxoSmithKline (GSK) provided GSK239512 tablets in 10 µg, 20 µg, 40 µg and 80 µg dose strengths, as well as matching placebo tablets. Subjects were instructed to take one tablet of their assigned medication each morning, by mouth, without regard to food.

Objectives: To assess the efficacy of GSK239512 on cognitive function in subjects with mild to moderate AD after 16 weeks of treatment.

Primary Outcome/Efficacy Variable:

- Change from baseline in the executive function/working memory composite score in the CogState neuropsychological test battery at Week 16.
- Change from baseline in the episodic memory composite score in the CogState neuropsychological test battery at Week 16.

Secondary Outcome/Efficacy Variable(s):

- Change from baseline in the attention composite score in the CogState neuropsychological test battery at Week 16.
- Change from baseline in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) total score at Week 16.
- Change from baseline in the CogState battery total score at Week 16. (Note: not specified as an endpoint in the protocol).

- Clinician's Interview-Based Impression of Change-plus (CIBIC+) score at Week 16.
- Change from baseline in the Disability Assessment for Dementia scale (DAD) total score at Week 16.
- Patient's Global Impression of Change (PGIC) and Caregiver's Global Impression of Change (CrGIC) at Week 16.
- Clinician's Global Impression of Change (CGIC) at Week 16.
- Change from baseline in the Neuropsychiatric Inventory (NPI) at Week 16.
- Change from baseline in MMSE total score at Week 16.
- Change from baseline in the Pittsburgh Sleep Quality Inventory (PSQI) at Week 16.
- Change from baseline in the Epworth Sleepiness Scale (ESS) at Week 16.
- Olfaction tests were included as an exploratory endpoint.
- Plasma concentrations of GSK239512.

Statistical Methods: It was initially planned that a minimum of 152 subjects would be randomised into this study, which would be analysed using Bayesian methodology. Subjects were randomised to receive GSK239512 or placebo with equal probability, to ensure 138 evaluable subjects given the expected dropout rate of 10%, which was assumed. The maximum planned number of subjects to be recruited to the study stated in the protocol was 200. An internal decision was made prior to unblinding the study to change to a Frequentist methodology-based analysis. In this study, 196 subjects were randomized. Assuming a 10% rate of attrition on the 196 recruited subjects this was considered to equate to around 176 evaluable subjects, roughly 88 subjects per arm. The nominal alpha level for all statistical tests was set to be 0.10. The target effect size for the study was 0.4. Assuming a Normal distribution with mean of 0 and variance of 1 for the effect size, the assumed total sample size of 176 provided 84% power to detect an effect size of 0.4 at the 10% level of significance. No adjustment was made for multiple testing due to the exploratory nature of the study.

The primary population for the efficacy analysis was the intent-to-treat (ITT) population, which consisted of all subjects randomized to treatment, who took at least one dose of study medication and who had at least one post-baseline efficacy or health outcomes assessment. All CogState neuropsychological test battery endpoints (NTB), ADAS-Cog, DAD, NPI, MMSE, PSQI and ESS endpoints were analyzed using a mixed model for repeated measures (MMRM), which included terms for treatment, visit, treatment by visit, baseline, baseline by visit, baseline MMSE, baseline body mass index (BMI), duration of AD and Country group as fixed effects and subject as a random effect. CIBIC+ and Clinician, Patient and Caregiver Global Impressions of Change were analysed using non-parametric analysis techniques (stratified Wilcoxon Rank Sum Test). The primary population for safety analyses was the safety population, which consisted of all subjects who were randomized and took at least one dose of study medication. No formal statistical testing was performed on the safety data.

Study Population: Eligible subjects were aged ≥50 years with a clinical diagnosis of probable AD with symptoms of AD for at least the last 3 months in accordance with National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. A screening MMSE score of 16 to 24 inclusive, a Haschinski ischaemia score ≤4 and a magnetic resonance imaging (MRI) computed tomography (CT) scan in the last 12 months were required. Cohabitation (or regular contact) with a caregiver along with written informed consent by both the subject and caregiver and no other likely causes of dementia were required inclusion criteria. Concurrent medical conditions, concomitant medications, and abnormal test/laboratory findings that would preclude participation were specified.

Number of Subjects:	**Placebo**	**GSK239512**
Planned, N	76	76
Randomised, N	99	97
Safety Population, N	99	97
Completed, n (%)	92 (93)	82 (85)
Total Number Subjects Withdrawn, N (%)	8 (8)	15 (15)
Withdrawn due to Adverse Events, n (%)	4 (4)	3 (3)
Withdrawn for other reasons, n (%)	4 (4)	12 (12)
Titrated to highest dose level at Week 4, n (%)	82 (85)	66 (73)
Note: All completed and withdrawn subject percentages are based on the Safety Population.		
Demographics	**Placebo**	**GSK239512**
N (ITT)	98	96
Females: Males	69:29	57:39
Mean Age, years (Standard Deviation (SD))	72.0 (8.59)	71.6 (8.79)
White, n (%)	93 (95)	93 (97)

Co-Primary Efficacy Endpoint Results:		
	Placebo (N=98)	**GSK239512 (N=96)**
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in CogState Executive Function / Working Memory Composite Score at Week 16		
n	87	79
Adjusted Mean Change from baseline (Standard Error (SE))	0.172 (0.0510)	0.247 (0.0689)
Difference between treatments (GSK239512 minus placebo)		0.075
90% Confidence Interval (CI)		(-0.066, 0.216)
p-value		0.3804
Effect Size		0.16
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in CogState Episodic Memory Composite Score at Week 16		
n	84	78
Adjusted Mean Change from baseline (SE)	-0.027 (0.0692)	0.166 (0.0691)
Difference between treatments (GSK239512 minus placebo)		0.192
90% (CI)		(0.032, 0.353)
p-value		0.0495
Effect Size		0.35
Secondary Efficacy Endpoint Results:		
	Placebo (N=98)	**GSK239512 (N=96)**
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in ADAS-Cog Score at Week 16		
n	92	81
Adjusted Mean Change from baseline (SE)	-1.2 (0.50)	-1.6 (0.55)
Difference between treatments (GSK239512 minus placebo)		-0.4
90% (CI)		(-1.7, 0.8)
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in CogState Attention Composite Score at Week 16		
n	82	69
Adjusted Mean Change from baseline (SE)	-0.096 (0.0619)	0.059 (0.0615)
Difference between treatments (GSK239512 minus placebo)		0.156
90% (CI)		(0.012, 0.299)
Effect Size		0.28
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in CogState Total Composite Score at Week 16		
n	74	61
Adjusted Mean Change from baseline (SE)	0.047 (0.0419)	0.148 (0.0517)
Difference between treatments (GSK239512 minus placebo)		0.100
90% (CI)		(-0.010, 0.210)
Effect Size		0.30
Summary of Non-parametric Analysis of Change from Baseline in CIBIC+ Score at Week 16		
n	90	81
Difference between treatments (GSK239512 minus placebo)		0
90% (CI)		(0.0)
Summary of Non-parametric Analysis of Change from Baseline in PGIC at Week 16		
n	93	82
Difference between treatments (GSK239512 minus placebo)		0
90% (CI)		(0.0)
Summary of Non-parametric Analysis of Change from Baseline in CrGIC at Week 16		
n	93	82
Difference between treatments (GSK239512 minus placebo)		0
90% (CI)		(0.0)

Summary of Non-parametric Analysis of Change from Baseline in CGIC at Week 16		
n	94	83
Difference between treatments (GSK239512 minus placebo)		0
90% (CI)		(0.0)
Summary of Parametric Analysis of Change from Baseline in DAD Total Score at Week 16		
n	89	81
Adjusted Mean Change from baseline (SE)	1.9 (1.12)	0.9 (0.98)
Difference between treatments (GSK239512 minus placebo)		-1.0
90% (CI)		(-3.5, 1.5)
Summary of Parametric Analysis of Change from Baseline in MMSE Total Score at Week 16		
n	94	83
Adjusted Mean Change from baseline (SE)	0.2 (0.29)	0.6 (0.28)
Difference between treatments (GSK239512 minus placebo)		0.4
90% (CI)		(-0.2, 1.1)
Summary of Parametric Analysis of Change from Baseline in NPI Total Score at Week 16		
n	92	81
Adjusted Mean Change from baseline (SE)	-1.6 (0.46)	-2.1 (0.62)
Difference between treatments (GSK239512 minus placebo)		-0.5
90% (CI)		(-1.8, 0.8)
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in Pittsburgh Seep Quality Index at Week 16		
n	91	80
Adjusted Mean Change from baseline (SE)	-0.0 (0.18)	0.4 (0.26)
Difference between treatments (GSK239512 minus placebo)		0.4
90% (CI)		(-0.1, 1.0)
Summary of Mixed-Model Repeated Measures Analysis of Change from Baseline in Epworth Sleepiness Scale at Week 16		
n	87	76
Adjusted Mean Change from baseline (SE)	0.2 (0.32)	-0.0 (0.36)
Difference between treatments (GSK239512 minus placebo)		-0.3
90% (CI)		(-1.1, 0.5)
Olfaction tests were not formally analyzed due to their exploratory nature.		
Note: CogState Executive Function/Working Memory, Episodic Memory, Attention and Total Scores, DAD, MMSE and NPI scores: A positive difference represents benefit over placebo. ADAS-Cog, CIBIC+, PGIC, CrGIC and CGIC scores: A negative difference represents benefit over placebo.		
Plasma Concentrations of GSK239512: The table below illustrates the distribution of the CcogState values across doses and shows a dose-proportional increase in the geometric mean of CcogState between 10 µg and 80 µg doses.		

CcogState values across doses, titration and maintenance visits

	10 µg	**20 µg**	**40 µg**	**80 µg**
n*	93	125	119	223
Geometric mean ng/mL	0.02	0.04	0.09	0.17
Coefficient of Variation %	72	78	69	88
[5th-95th percentiles] ng/mL	[0.01-0.06]	[0.01-0.11]	[0.03-0.2]	[0.05-045]
[min-max] ng/mL	[0.01-0.09]	[0.01-0.33]	[0.02-0.39]	[0.01-0.68]

*: n is the number of pairs of GSK239512 concentrations at each visit (pre and post CogState battery)
Note: a subject will have contributed to more than one dose and to a dose more than once in the analysis.

An on-treatment adverse event (AE) was defined as an AE with onset on or after the start date of double-blind randomized investigational product but not later than 2 days after the last date of investigational product, or an event with onset date missing and a stop date after the first day of investigational product. An on-treatment serious adverse event (SAE) was defined as a SAE with onset on or after the start date of double-blind randomized investigational product and up to 2 days after the last dose of investigational product.

Week 16 Analysis (Safety Population)	**Placebo (N=99) n (%)**	**GSK239512 (N=97) n (%)**
Subjects with any on-treatment AE	43 (43)	50 (52)
Most frequent on-treatment AEs		
Headache	8 (8)	11 (11)
Dizziness	4 (4)	6 (6)
Diarrhoea	4 (4)	4 (4)
Nausea	4 (4)	3 (3)
Vomiting	4 (4)	3 (3)
Insomnia	0	5 (5)
Bronchitis	2 (2)	2 (2)
Nasopharyngitis	1 (1)	3 (3)
Urinary tract infection	3 (3)	1 (1)
Abdominal pain upper	1 (1)	2 (2)

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

Week 16 Analysis (Safety Population)	**Placebo (N=99)**	**GSK239512 (N=97)**
	n (%) [related]	**n (%) [related]**
Subjects with any SAEs (includes both fatal and non-fatal events)	2 (2) [0]	1 (1) [0]
Subjects with non-fatal SAEs, n (%)		
Pneumothorax traumatic, Rib Fracture	0	1 (1) [0]
Sick Sinus Syndrome	1 (1) [0]	0
Subjects with fatal SAEs, n (%)		
Ischaemic stroke	1 (1) [0]	0

Note: An SAE of femur fracture occurred during the placebo run-in phase; the subject withdrew from study prior to randomization and receiving any double-blind study medication.
The SAE of ischaemic stroke occurred during the follow-up phase of the study (investigational product stopped as planned 8 days prior to event).

Conclusions:

- GSK239512, at doses up to 80 mcg administered orally once each morning, demonstrated mild to moderate efficacy on some measures of the CogState neuropsychological test battery.
- Other efficacy measures utilized in this study, such as the ADAS-Cog, showed no separation at Week 16.
- In this study, headache was the most frequent adverse event, with an incidence of 11% on GSK239512 and 8% on placebo.