Synopsis

Identifier: HM2008/00265/00 **Study Number:** H3A106104

Title: An open label, dose escalation study with a double blind randomised placebo controlled withdrawal to examine the effects of the histamine H3 antagonist GSK189254 in subjects with narcolepsy.

Investigators: Multi-centre study.

Study centres: There were four centres in Germany, three centres in the United Kingdom, two centres in Spain, two centres in Austria, one centre in Australia and one centre in the Netherlands who enrolled subjects. One centre in Denmark and one centre in Finland were initiated but did not enroll any subjects.

Publications: None at the time of this report.

Study period:

Initiation Date:	21 Aug 2006
Completion Date:	07 Feb 2008
Early Termination Date:	10 Dec 2007

Phase of development: II

Objectives: The primary objective was to assess the efficacy of GSK189254 to improve daytime hypersomnolence in subjects with narcolepsy.

The secondary objectives were:

- To assess the safety, tolerability and pharmacokinetics of GSK189254 in subjects with narcolepsy.
- To investigate any relationship between efficacy and systemic exposure to GSK189254.

Methodology: A multi-centre study consisting of a 29-day open-label, dose-escalation phase (OLP) and a 13-day double-blind, randomised, placebo-controlled phase (DBP) to explore the treatment potential of GSK189254 in subjects with narcolepsy. Eligible subjects were stabilised on their current cataplexy treatments for a minimum of one month. Subjects were required to wash-out from any medication used to control hypersomnolence (including modafinil, methylphenidate, dexamphetamine, permoline) for at least 48 hours prior to assessment of baseline hypersomnolence using the Maintenance of Wakefulness Test (MWT). Treatment with GSK189254 was started in all subjects at 10 μg daily. During the OLP, the subject's dose level was reviewed on a weekly basis and increased unless there were safety or tolerability reasons (e.g. night-time sleep disruption) not to do so. Treatment response in this study was defined as a 2-minute increase in sleep latency in the 40-minute MWT, from baseline (Day -1) to Day 28 (end of OLP), and a sleep latency of at least 5 minutes on Day 28. Subjects who responded to treatment in the OLP were randomised to either placebo or GSK189254

(1:1) for the DBP; non-responders were withdrawn from further treatment. Randomised subjects maintained their dose level at the end of OLP during DBP.

Number of subjects: A sufficient number of eligible subjects were to be dosed in the OLP in order to obtain 46 subjects to be randomized into the DBP. Forty-six randomised subjects were required to detect a 6-minute treatment difference between GSK189254 and placebo in sleep latency as measured by MWT at the end of the DBP (Day 42) with 90% power using a two-sided t-test at an alpha level of 0.05, assuming an underlying standard deviation of 6.0. Assuming a 15% dropout rate during the OLP, and that at least 80% of subjects enrolled in the OLP would meet the requirements to be randomised into the DBP, a sample size of 70 subjects was expected to be enrolled to obtain 46 randomised subjects. In fact, 69 subjects were enrolled in the OLP. Due to slow enrollment, it was decided to conduct an interim analysis to assess for futility. The interim analysis was based on 55 subjects who had completed the OLP and 25 subjects who had completed the DBP (Placebo, 13 subjects: GSK189254, 12 subjects). The study was terminated based on the results of the futility analysis and, when the final analyses were performed, 31 subjects had entered the DBP (29 completed and 2 were withdrawn).

Subject Disposition and Demographics:

Number of Subjects	Open-label phase
Number of subjects planned, N:	70
Number of subjects enrolled, N:	69
Number of subjects included in All subjects (safety) population, n (%):	69 (100)
Demographics	
Age in Years, Mean (Range)	38.3 (19 – 63)
Sex, n (%) Female : Male	33 (48) : 36 (52)
BMI, Mean (Range), kg/m^2	27.1 (18.0 – 35.9)
Height, Mean (Range), cm	172.6 (153 – 191)
Weight, Mean (Range), kg	80.8 (50.5 – 113.0)
Ethnicity, n (%) Hispanic or Latino:	6 (9)
Not Hispanic or Latino:	63 (91)
Race, n (%) , African American/African Heritage	2 (2.9)
White – White/Caucasian/European Heritage	66 (95.7)
Not recorded	1 (1.4)
Number of subjects completed as planned, n (%):	56 (81)
Number of subjects withdrawn (any reason), n (%):	13 (19)
Reasons for subject withdrawal, n (%)	
Adverse events	1 (1)
Subject decided to withdraw from study	6 (9)
Sponsor terminated study	3 (4)
Other: MWT at Day -1 met exclusion criteria	1 (1)
Other: non-responder	2 (3)*
Baseline MWT, Mean (Range), minutes	10.84 (0.5 – 40.0)
Subjects with Cataplexy Attacks at Baseline, n (%)	36/60 (60)

* These two subjects should not have been flagged as withdrawn from the OLP as they completed Day 28. They were not randomised into the DBP because they were non-responders in the OLP but this was as per protocol and as per the other 25 non-responders in the OLP. They did not withdraw due to their own subjective perception of lack of efficacy.

	Double-blind phase	
Number of Subjects	GSK189254	Placebo
Number of subjects planned, N:	23	23
Number of subjects enrolled, N:	16	15
Number of subjects included in All subjects (safety) population, n (%):	16 (100)	15 (100)
Demographics		
Age in Years, Mean (Range)	41.6 (25 – 63)	39.9 (20 – 62)
Sex, n (%) Female : Male	3 (19) : 13 (81)	11 (73) : 4 (27)
BMI, Mean (Range), kg/m^2	27.55 (22.1 – 35.5)	27.44 (21.9 – 35.9)
Height, Mean (Range), cm	172.4 (166 – 183)	170.6 (153 – 185)
Weight, Mean (Range), kg	81.99 (63.0 – 105.0)	79.47 (64.0 – 96.5)
Ethnicity, n (%) Hispanic or Latino:	4 (25)	0
Not Hispanic or Latino:	12 (75)	15 (100)
Race, n (%) Not recorded	1 (6)	0
White – White/Caucasian/European Heritage	15 (94)	15 (100)
Number of subjects completed as planned, n (%):	15 (94)	14 (93)
Number of subjects withdrawn (any reason), n (%):	1 (6)	1 (7)
Reasons for subject withdrawal, n (%)		
Adverse events	0	0
Subject decided to withdraw from study	1 (6)	0
Sponsor terminated study	0	1 (7)
Baseline MWT, Mean (Range), minutes	10.78 (1.3 – 34.5)	8.87 (0.9 – 28.1)
Subjects with Cataplexy Attacks at baseline, n (%)	9/13 (69)	8/15 (53)

Source data: Table 9.1, Table 9.2, Table 9.3, Table 9.9, Table 9.10, Table 9.11, Table 9.12, Table 9.15 and Table 9.16 and Listing 7

Diagnosis and main criteria for inclusion: Male or female subjects aged 18 to 65 years with documentary evidence of having been diagnosed with narcolepsy, conforming to the International Classification of Sleep Disorder (ICSD-2) criteria for either narcolepsy with cataplexy or narcolepsy without cataplexy, and a body mass index (BMI) between 18 and 36 kg/m^2 inclusive were enrolled. Subjects with a BMI >32 kg/m^2 were required either to have narcolepsy confirmed by polysomnography / Multiple Sleep Latency Test (PSG / MSLT) at screening, or documented PSG / MSLT previously performed, and an apnea-hypopnea index (AHI) no higher than 10.

Treatment administration: The starting dose level of the OLP was initially 10 µg GSK189254. Depending upon the safety and tolerability, as reported by the subjects, the dose was adjusted each week to a maximum of 500 µg. To account for potential doses of 10, 20, 50, 100, 250 and 500 µg, GSK189254 was supplied as 6.0 mm white, round, aqueous film-coated tablets containing 10, 50 or 250 µg of GSK189254 as the monohydrochloride salt for oral administration. During the DBP subjects were administered GSK189254 or placebo.

Criteria for evaluation: The study endpoints were:

Primary: Sleep latency (in minutes), as measured by the MWT, at the end of the DBP.

Secondary: The following efficacy endpoints were assessed at each visit during the OLP, in terms of change from baseline, and at the end of the DBP phase (Day 42) in terms of change from Day 28;

- Sleep latency (minutes), as measured by the MWT,
- Frequency (number) and severity (as measured by Visual Analogue Scale (VAS)) of cataplexy attacks per week,
- Severity (as measured by VAS) of nocturnal symptoms (night terrors, dreams, hallucinations) per week,
- Epworth Sleepiness Scale (ESS),
- Leeds Sleep Evaluation Questionnaire (LSEQ),
- Actigraphy (frequency and duration of daytime naps per week),
- The proportion of subjects who responded to open-label treatment on Day 28,
- Time (in minutes) to sleep onset rapid eye movement (SOREM) as measured on overnight PSG,
- The proportion of subjects with an improved assessment of illness on Day 14 and 28 and proportion of subjects with a stable or improved assessment of illness on Day 42, as measured by the Clinician Global Impression of Change (CGIC) and the Patient Global Impression of Change (PGIC),
- Time required (in minutes) to complete Digit Vigilance Test (DVT) at each visit,
- Safety and tolerability of GSK189254, as measured by change from baseline in vital signs, electrocardiogram (ECG), profile of mood state scales-brief (POMS-B), actigraphy, nocturnal sleep architecture (PSG), and laboratory safety data (haematology, clinical chemistry and urinalysis) and the incidence of adverse events,
- Pharmacokinetics (PK) of GSK189254.

Statistical methods: The primary inference for efficacy was based on the double-blind Intent-to-Treat (ITT) Population which comprised all subjects who were randomized and received at least one dose of double-blind study drug. All summaries of safety data were based on the Safety Population which comprised all subjects who received at least one dose of open-label study drug.

The primary endpoint was sleep latency (in minutes) as measured by the MWT at the end of DBP (Day 42). Analysis of covariance (ANCOVA) was used to test the null hypothesis of no difference between GSK189254 and placebo, versus the alternative hypothesis that there is a difference. In this analysis, sleep latency at baseline (Day -1, prior to the OLP) and sleep latency at the end of the OLP (Day 28) were included as covariates. All statistical tests were two-sided and performed at the 5% significance level. The robustness of the model was assessed by checking the usual assumptions (normality and parallelism for ANCOVA).

In addition, the treatment groups were compared with respect to PGIC and CGIC using Fisher's exact test. The other efficacy parameters were analyzed using the ANCOVA model adjusting for baseline and Day 28 scores. The adverse event rates, the Profile of Mood States-Brief (POMS-B) domain scores and other safety endpoints were summarized by treatment group.

A post study power calculation was done. The post study power was computed to be approximately 36%.

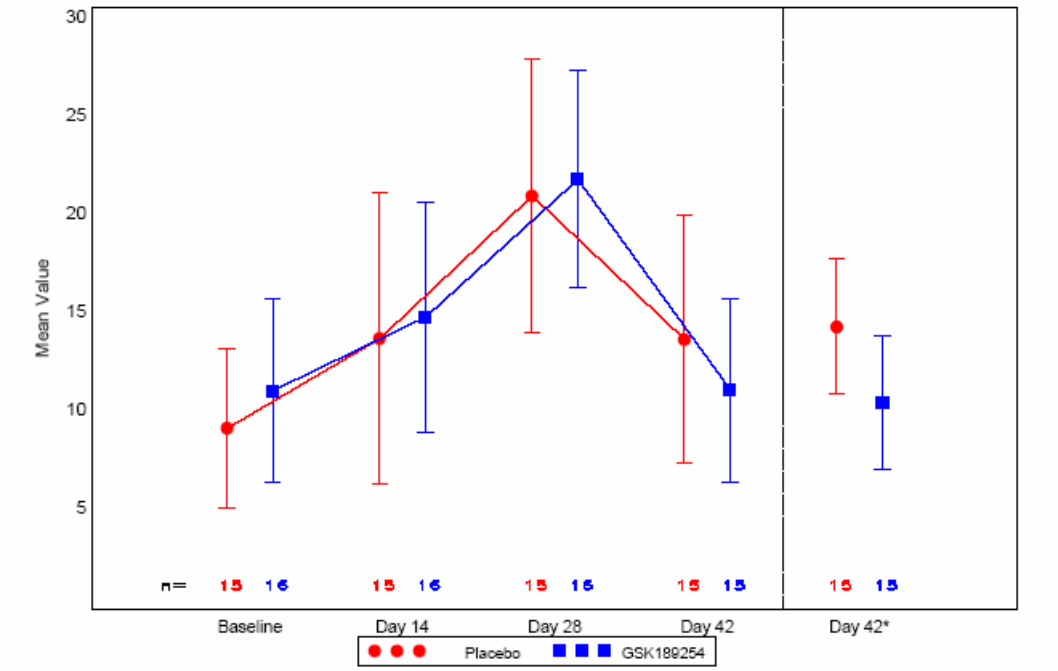
Summary: Sixty-nine subjects were exposed to GSK189254 during the OLP. Forty-eight (81%) subjects in the OLP were able to titrate up to a dose of 250 µg. The maximum dose achieved by subjects in the OLP is summarised in the table below:

	Last Day of Treatment in OLP											
	Day 28				**Day 26**	**Day 20**	**Day 19**	**Day 15***	**Day 13**	**Day 12**	**Day 7**	**Day 2**
Highest dose taken (µg)	250	100	50	20	50	50	50	50	20	20	20	10
Number of subjects	48	7	3	1	1	1	2	1	1	2	1	1

* Subject withdrawn due to adverse event
Source data: Listing 7

Thirty-one subjects met the responder criteria at the end of the OLP and were randomised into the DBP. During the DBP, 15 (48%) subjects took placebo, 12 (39%) subjects took GSK189254 250 µg, 3 (10%) subjects took GSK189254 100 µg and 1 (3%) subject took GSK189254 50 µg.

Maintenance of Wakefulness (MWT) Scores: The mean and 95% confidence intervals (CIs) for the primary endpoint, sleep latency on the MWT at the end of the DBP, are shown by randomised treatment in the DBP in the following figure.



Mean (95% CI) are shown for Baseline, Days 14 and 28 visits during OLP and Day 42 visit during DBP.
Adjusted mean (95% CI) for Day 42 is shown as Day 42*
Source data: Figure 15.1

An increase in sleep latency was seen for subjects in both treatment groups at the end of the OLP (in which all subjects received GSK189254). Analysis of the MWT at the end of the DBP (Day 42) resulted in a treatment difference (95% CI) of -3.85 (-8.75, 1.04) with a 2-sided p-value of 0.1174, between subjects treated with GSK189254 and those treated with placebo.

Endpoint	Placebo (N = 15) Adj. Mean (SE)	GSK189254 (N = 16) Adj. Mean (SE)	Difference (95% CI)	p-value
Adjusted Mean Sleep Latency by MWT at Day 42 (minutes)	14.03 (1.674)	10.18 (1.674)	-3.85 (-8.75, 1.04)	0.1174

Using ANCOVA with baseline MWT and Day 28 MWT scores as covariates
Source data: Table 15.2

Global Impression of Change (PGIC/CGIC): The PGIC and CGIC rated the disease state at the end of the OLP (Day 28) relative to baseline (Day -1), and at the end of the DBP (Day 42) relative to the status at the end of the OLP (Day 28). The PGIC and CGIC ratings are summarised in the following table:

Parameter - outcome, n (%)	Day 28 (end of OLP) (N = 69)[a]	Day 42 (end of DBP)[b]		
		Placebo (N = 15)	GSK189254 (N = 16)	p-value for difference
PGIC – improved	44/59 (75)	10/15 (67)	7/15 (47)	-
PGIC – improved or stable	-	12/15 (80)	12/15 (80)	> 0.999
CGIC – improved	48/59 (81)	11/15 (73)	7/15 (47)	-
CGIC – improved or stable	-	13/15 (87)	12/15 (80)	> 0.999

a. relative to baseline (Day -1)
b. relative to end of OLP (Day 28)
Source data: Listing 21 and Listing 22

There was no statistically significant difference between GSK189254 group and Placebo group in the proportion of subjects with a stable or improved disease state from end of OLP (Day 28) to end of DBP (Day 42) for PGIC or CGIC (p-value for both PGIC and CGIC >0.9999).

Other efficacy parameters: The frequency and severity of cataplexy attacks; severity of nocturnal symptoms (measured by VAS); Epworth sleepiness scale; domains in the LSEQ (Getting to sleep, Quality of sleep, Awakening from sleep and Behaviour following waking); frequency and duration of daytime naps (based on actigraphy); time required to complete the digit vigilance test; and, time until sleep onset rapid eye movement were summarised and analysed. The results of the analysis of change from end of OLP (Day 28) to end of DBP (Day 42) and Days 36-42 (last week of DBP) are summarised in the following table.

Endpoint (placebo n, GSK189254 n)[a]	Placebo (N = 15) Adj. Mean (SE)	GSK189254 (N = 16) Adj. Mean (SE)	Difference (95% CI)	p-value
Change from End of OLP (Day 28) to Days 36-42 (last week of DBP)				
Frequency of cataplexy attacks (14, 12)	0.46 (0.160)	0.41 (0.174)	-0.05 (-0.56, 0.46)	0.837
Severity of cataplexy attacks (14, 14)	3.10 (2.431)	-0.39 (2.431)	-3.49 (-10.91, 3.93)	0.341
Severity of nocturnal symptoms (14, 16)	-9.11 (3.896)	4.40 (3.636)	13.51 (2.38, 24.65)	0.019
Getting to sleep (14, 16)	-7.79 (3.471)	-4.16 (3.226)	3.64 (-6.57, 13.84)	0.470
Quality of sleep (14, 16)	-9.26 (3.367)	-2.52 (3.139)	6.74 (-2.94, 16.43)	0.164
Awakening from sleep (14, 16)	-2.84 (3.592)	5.16 (3.350)	8.01 (-2.30, 18.31)	0.123
Behaviour following waking (14, 16)	-0.40 (2.663)	3.69 (2.488)	4.09 (-3.45, 11.63)	0.275
Frequency of daytime naps (14, 10)	0.37 (0.333)	-0.30 (0.333)	-0.67 (-1.77, 0.43)	0.215
Duration of daytime naps (14, 10)	0.55 (1.702)	-0.40 (1.702)	-0.95 (-6.22, 4.31)	0.703
Change from End of OLP (Day 28) to End of DBP (Day 42)				
Epworth sleepiness scale (14, 15)	1.51 (0.643)	0.69 (0.621)	-0.82 (-2.66, 1.01)	0.365
Time required to complete DVT (15, 15)	0.72 (0.662)	-0.46 (0.662)	-1.18 (-3.19, 0.82)	0.237
Time until sleep onset REM (14, 14)	6.32 (21.268)	21.21 (21.268)	14.89 (-47.39, 77.17)	0.626

a: number of patients in each treatment group included in the analysis REM: Random Eye Movement
SE: Standard error CI: Confidence interval(s) DVT: Digit Vigilance Test
Source data: Table 15.20, Table 15.22, Table 15.23, Table 15.25, Table 15.27, Table 15.29, Table 15.31, Table 15.35 and Table 15.37

The data show that there was no statistically significant difference between GSK189254 group and placebo group in any of these efficacy parameters, except the severity of nocturnal symptoms ($p < 0.05$).

POMS-B: The mean changes from baseline (Day -1) to end of DBP (Day 42) in POMS-B domains for the Safety Population are summarized in the following table:

POMS-B Domain	Placebo (N = 15), (n = 15)		GSK189254 (N = 16), (n = 14)	
	n, Mean (SD) (n = 15)	95% CI for Mean	n, Mean (SD) (n = 14)	95% CI for Mean
Tension/ Anxiety	-0.2 (2.37)	(-1.5, 1.1)	-0.4 (4.33)	(-2.9, 2.1)
Depression/Dejection	-0.2 (2.01)	(-1.3, 0.9)	-2.0 (3.16)	(-3.8, -0.2)
Anger/Hostility	0.1 (3.20)	(-1.6, 1.9)	-0.3 (4.01)	(-2.6, 2.0)
Vigor/Activity	0.5 (4.82)	(-2.2, 3.1)	2.4 (3.59)	(0.4, 4.5)
Fatigue/Inertia	-3.5 (4.72)	(-6.1, -0.9)	-1.9 (5.68)	(-5.2, 1.3)
Confusion/Bewilderment	-0.5 (2.45)	(-1.8, 0.9)	-0.5 (2.53)	(-2.0, 1.0)

SD: Standard deviation
CI: Confidence interval
Source data: Table 10.63

These data show a possible trend towards improvement, from baseline to the end of the DBP in Vigor/Activity and Depression/Dejection on GSK18924 and in Fatigue/Inertia on placebo.

Safety:

Most Frequent Adverse Events, n (%)	Open-label phase N = 69	Double-blind phase	
		GSK189254 N = 16	Placebo N = 15
Any AE	52 (75)	4 (25)	5 (33)
Any AE related to investigational product	32 (46)	2 (13)	2 (13)
Most Common AEs (≥ 10% in any treatment group):			
Headache	29 (42)	2 (13)	2 (13)
Nasopharyngitis	10 (14)	0	0
Diarrhoea	8 (12)	0	0
Nausea	7 (10)	0	0

Source data: Table 10.9, Table 10.10, Table 10.11 and Table 10.12

No subject experienced a serious adverse event or became pregnant during this study.

In the OLP, 167 adverse events (AEs) were reported by 52 (75%) subjects. The most common AEs were headache (42% of subjects), nasopharyngitis (14%), diarrhoea (12%) and nausea (10%). Adverse events related to sleep included hypnagogic hallucinations (reported by 7% of subjects), abnormal dreams (6%), sleep disorder (6%), insomnia (4%) and nightmare (1%). The incidence of these sleep-related AEs appeared to be lower than reported in the first time in humans study, in which healthy young subjects treated with 100 μg for 8 days reported sleep disturbance (100%) and abnormal dreams (50%). Hypnagogic hallucinations are amongst the clinical features in narcolepsy and all the subjects who reported hypnagogic hallucinations as AEs had such symptoms in their history of narcolepsy. One subject (1%) who suffered from cataplexy as part of her narcolepsy reported a worsening of cataplexy during the OLP.

Other AEs reported in the OLP, which were also reported during phase 1 studies, included hot flush (9%), hyperhydrosis (1%), dysgeusia (1%) and anorexia (1%). There were no AEs of anxiety or depression but two subjects reported agitation (3%). Two subjects (3%) reported erectile abnormalities which were not reported previously. One subject was reported to have prolonged QTc. This subject's baseline QTc was 420 ms, and it increased to 456 ms on Day 7 when he was being treated with 20 μg GSK189254. This was reported as an AE because the QTc was greater than 450 ms but the QTc interval returned to baseline despite continued treatment with higher doses of GSK189254 and there was no further increase of QTc to greater than 450 ms. This AE was not considered by the investigator to be related to GSK182954. Two subjects (3%) reported tachycardia as an AE. One of these subjects reported tachycardia for three days, while he was being treated with 100 μg GSK189154, which resolved without treatment or dose reduction, and the investigator did not regard it as related to GSK189254. This subject's ECGs taken on the last day of this AE (Day 28) showed normal heart rate in the range of 52 to 68 beats/min. Another subject reported tachycardia, while she was on 50 μg GSK189254, which lasted 5 min. Her ECG readings at each visit throughout the study showed normal heart rate, between 56 and 83 beats/min.

There was a similar incidence of mild, moderate and severe AEs. Severe AEs were reported by 25% of subjects, and commonly were headache (7%), gastrointestinal disturbances (diarrhoea [6%], nausea, vomiting, upper abdominal pain [each 3%]), and sleep-related AEs, such as hypnagogic hallucinations (4%), abnormal dreams, sleep disorder and insomnia (each 3%). In the OLP, the majority (approximately three-quarters) of subjects who experienced severe AEs were nevertheless able to titrate their dose of GSK189254 to 250 μg. Approximately two-thirds of subjects who experienced severe AEs were non-responders.

There was no clear relation between the incidence of each kind of AE and the increasing dose level at each step of the titration. The overall incidence of AEs showed a trend to decline as the dose level was escalated (48% during the 1st week, on 10 μg, and 17% during the 4th week, on 100 μg). Despite the length of exposure to the lower dose levels being the same as or less than the length of exposure to the higher doses, there were no AEs which showed a trend of increasing incidence with dose escalation. It appeared that many AEs resolved despite continued dose escalation, suggesting that tolerance might have developed. The incidence of AEs on 100 μg and 250 μg GSK189254 in the DBP was comparable, although only 3 subjects received GSK189254 at 100 μg. There were no withdrawals during the DBP due to AEs. Overall, tolerability of GSK189254 during the DBP was satisfactory with a comparable AE profile to placebo.

The overall incidence of AEs was similar between responders and non-responders who completed the OLP. Responders reported more hypnagogic hallucinations (10%), sleep disorder (10%) and nausea (16%) than non-responders (5%, 3% and 5% respectively). Non-responders reported more upper abdominal pain (11%), vomiting (8%) and headache (47%) than responders (3%, 3%, 35%) respectively.

Ten subjects discontinued before reaching Day 28. Only one of these subjects (1%) who discontinued before the end of the OLP was due to an AE which was sleep fragmentation while she was on 20 μg GSK189254. This AE persisted as her dose was increased to 50

μg. The investigator considered this to be related to GSK189254. The AE resolved one day after her last dose of 50 μg of GSK189254.

Twenty-one (30%) subjects in the OLP were not able to dose escalate to 250 μg on Day 28. Eleven of these subjects received a lower dose up to Day 28 (7 on 100 μg, 3 on 50 μg and 1 on 20 μg). Common AEs in the subjects who completed the OLP but did not achieve 250 μg were; headache (9/11 subjects; 82%), hot flush/feeling hot (4/11; 36%), abnormal dreams and insomnia (both 3/11 subjects; 27%) and nausea, vomiting, muscle twitching, nasopharyngitis and agitation (2/11; 18%). These subjects who could not dose escalate to 250 μg experienced similar types of AEs as the whole group in the OLP, but the frequency of their common AEs appeared to be higher than the overall group's frequency.

In the DBP, 7 AEs developed in 4 (25%) subjects randomised to GSK189254, compared to 7 AEs in 5 (33%) subjects randomised to placebo. The most common AE in the GSK189254 group was headache (13% vs. 13% on placebo). Cataplexy, insomnia and upper abdominal pain were each reported by one subject (6%) on GSK189254 vs. 0% on placebo. The subject who reported cataplexy suffered from cataplexy as part of his pre-existing narcolepsy symptoms, and he reported a worsening of cataplexy during treatment with GSK189254 in the DBP. Three subjects in each treatment arm reported severe AEs (19% on GSK189254, 20% on placebo). The severe AEs in GSK189254-treated subjects were cataplexy, insomnia and upper abdominal pain. There were no AEs of hallucinations or mood disturbance which developed during the DBP.

Some subjects who were responders at the end of the OLP and were therefore randomised into the DBP phase continued to experience some of the GSK189254-related AEs which developed in the OLP, during the DBP phase. This occurred in 4 subjects (25%) randomised to GSK189254 and 2 subjects (13%) randomised to placebo. The GSK189254-related AEs which persisted from the OLP into the DBP, in the GSK189254 treatment group, were sleep disorder, insomnia, hallucinations, headache, hot flushes, gastritis, muscle (facial) twitching, increased erections and nausea. In the subjects randomised to placebo, GSK189254-related AEs which persisted from the OLP to the DBP were heartburn and agitation.

There were no subjects in the OLP or DBP who had AEs suggestive of CNS hyperstimulation, including subjects who were on anti-cataplexy medications.

The following table shows the proportion of subjects who had normal baseline laboratory values but developed treatment-emergent abnormal values of potential clinical importance (PCI) during the OLP.

Laboratory test	Number (%) of subjects with a value of Potential Clinical Importance in the OLP			
	Day 7 (N = 67)	Day 14 (N = 63)	Day 21 (N = 60)	Day 28 (N = 59)
Haemoglobin low (<138 g/L)	0	0	0	1 (2%)
Haematocrit low (<0.41 L)	1 (2%)	0	0	1 (2%)
Aspartate aminotransferase elevated (>42 IU/L)	0	0	0	1 (2%)
Bilirubin elevated (>22 µmol/L)	0	1 (2%)	1 (2%)	1 (2%)
Creatinine elevated (>124 µmol/L)	0	1 (2%)	0	0
Glucose elevated (>6.4 mmol/L)	0	1 (2%)	1 (2%)	1 (2%)

Source data: Listing 12 and Listing 13

The following table shows the frequency of laboratory abnormalities of PCI which occurred during the DBP and which were treatment emergent (normal at baseline).

Laboratory test	Number (%) of subjects with a value of Potential Clinical Importance in the DBP	
	Placebo (N = 13)	GSK189254 (N = 14)
Haematocrit low (<0.41 L)	0	1 (7%)
Bilirubin elevated (>22 µmol/L)	1 (8%)	0
Glucose elevated (>6.4 mmol/L)	1 (8%)	0

Source data: Listing 12 and Listing 13

- One subject developed a low haemoglobin (127 g/L) and low haematocrit (0.378 L) on Day 28 of the OLP, with previously normal values (including baseline). The subject continued with GSK189254 during the DBP and the low PCI values had returned to normal on Day 42.
- One subject showed an increase in bilirubin (35 – 36 µmol/L) on Days 14 and 21 after a normal baseline. The subject's bilirubin returned to normal by Day 28 without other abnormalities of liver function tests. He subsequently showed an elevated bilirubin (35 µmol/L) again on Day 42 after placebo treatment in the DBP. It was unlikely that this subject's bilirubin elevation was related to GSK189254 and it was not reported as an AE.
- One subject showed elevation in bilirubin (51 µmol/L) and aspartate aminotransferase (101 IU/L) on Day 28 after normal baseline values. He was a non-responder to treatment. His elevated liver chemistry values returned to normal on follow-up after stopping GSK189254.

None of the changes in laboratory values were considered clinically significant by the investigator or were reported as AEs. The values of urinalysis during the OLP were similar to those at baseline, and during the DBP they were comparable between the two treatment arms. Overall there was no evidence to suggest GSK189254 caused abnormalities in safety laboratory blood tests which were clinically significant.

The mean vital signs during the OLP and the DBP were similar to values at baseline. The following table shows the incidence of treatment-emergent vital signs of PCI during the OLP.

Vital sign	Number (%) of subjects with a value of Potential Clinical Importance in the OLP				
	Day 1 (N = 68)	Day 7 (N = 68)	Day 14 (N = 64)	Day 21 (N = 59)	Day 28 (N = 60)
Systolic BP >160 mmHg	0	0	0	1 (2%)	0
Systolic BP < 85 mmHg	0	1 (2%)	0	0	1 (2%)
Diastolic high	0	1 (2%)	1 (1%)	0	1 (2%)
Diastolic low	1 (2%)	0	0	0	0
Heart rate high	1 (1%)	0	0	0	0
Heart rate low	0	0	1 (2%)	0	0

Source data: Table 10.48 and Listing 15

There were no subjects with vital signs of PCI during the DBP in either treatment arm.

The mean vital signs during the OLP and the DBP were similar to values at baseline. These PCI changes in vital signs were sporadic occurrences in subjects who otherwise had normal values the majority of the time during the treatment period. These changes were probably due to physiological fluctuations. There were no vital signs of PCI which were considered clinically significant by the investigator and none were reported as AEs. Overall, there was no evidence to suggest that GSK189254 altered vital signs.

The following table shows the incidence of treatment-emergent ECG parameters of PCI (in which the affected subjects had normal baseline values) during the OLP.

ECG parameter	Number (%) of subjects with a value of Potential Clinical Importance in the OLP				
	Day 1 (N = 68)	Day 7 (N = 68)	Day 14 (N = 64)	Day 21 (N = 59)	Day 28 (N = 60)
QT-interval >450 msec	1 (1%)	2 (3%)	1 (2%)	1 (2%)	2 (3%)
PR-interval >220 msec	0	0	0	1 (2%)	0
PR-interval <110 msec	1 (1%)	1 (1%)	0	2 (3%)	1 (2%)
QRS duration (>110 msec)	1 (1%)	0	0	0	1 (2%)
QRS duration (<75 msec)	2 (3%)	2 (3%)	0	4 (7%)	1 (2%)

Source data: Table 10.58 and Listing 16

The table below shows the incidence of treatment-emergent ECG parameter changes of PCI during the DBP:

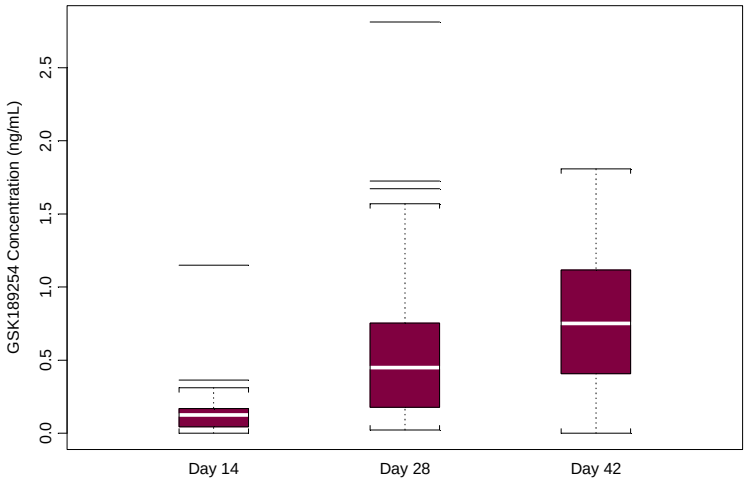
ECG parameter of PCI	Placebo (N = 15)	GSK189254 (N = 15)
PR interval low	0	1 (7%)
PR interval high	0	0
QRS duration low	0	1 (7%)
QRS duration high	0	0
QTc >450 ms	0	0

Source data: Table 10.59 and Listing 16

The mean ECG parameters during the OLP and DBP were similar to values at baseline. The PCI changes in ECG parameters were sporadic occurrences during the OLP and DBP in subjects who otherwise had normal values for the majority of the time during the treatment period. With regard to the QTc interval, 6 (9%) subjects developed values of PCI in the OLP having had normal values at baseline (excluding one subject who had a Day 14 ECG QTc of 507 ms due to an erroneous reading). These QTc intervals of PCI were sporadic occurrences in subjects who otherwise had normal values the majority of the time during their treatment period. The highest QTc value of PCI was 475 ms. No subjects in the DBP developed a QTc interval of PCI. One of the 6 subjects who developed QTc > 450 ms during the OLP was randomised to GSK189254 in the DBP. This subject's QTc returned to normal in the DBP. The investigator reported this QTc prolongation as an AE, although did not consider it to be related to GSK189254. These QTc values of PCI were probably due to physiological variations and there was no evidence to suggest GSK189254 prolonged the QTc interval. Overall, there was no evidence to suggest that GSK189254 altered ECG parameters.

The mean weight of subjects during the OLP and the DBP was similar to baseline.

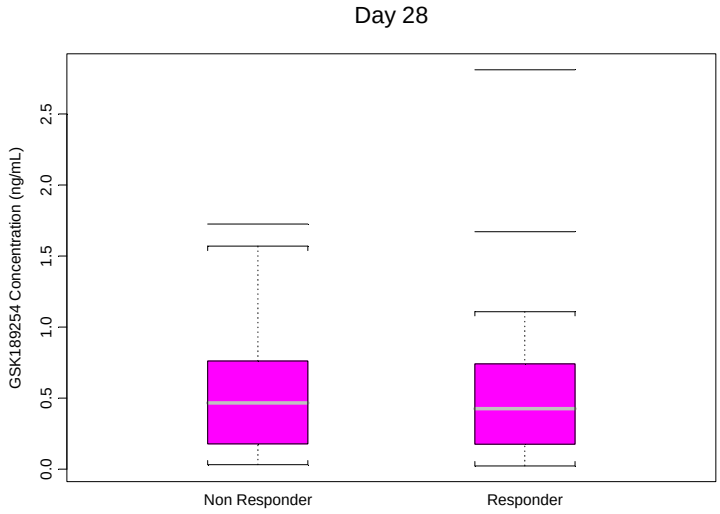
Pharmacokinetics: The observed GSK189254 concentrations on Day 14, Day 28 and Day 42 from all subjects with PK samples are shown in the following figure.



The line within the box plot represents the median (50th percentile), the ends of the box represent the 1st quartile and 3rd quartile and the caps represent 95% CI

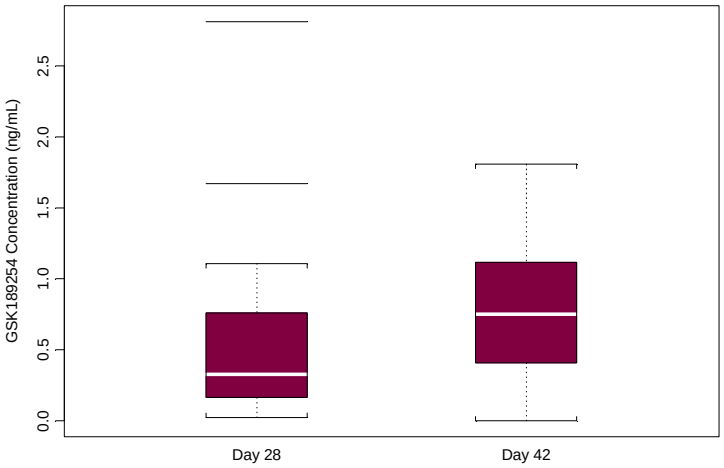
The concentrations on Day 28 (end of OLP) were derived from all subjects (responders who entered the DBP and non-responders who did not). The concentrations on Day 42 (end of DBP) were derived only from responders at Day 28 who were randomised to GSK189254. The majority of subjects with PK samples received 50 µg on Day 14 (57/62), 250 µg on Day 28 (48/58) and 250 µg on Day 42 (12/14). The dose levels in the current study were not studied in the previous repeat-dose study, H3A103127. However, linear interpolation of Cmax values between the dose groups in H3A103127 are consistent with the upper end of the concentration range observed in the current study.

There was no apparent difference in the GSK189254 concentrations on Day 28 (end of OLP) in those subjects that were classified as responders and those classified as non-responders.



The line within the box plot represents the median (50th percentile), the ends of the box represent the 1st quartile and 3rd quartile and the caps represent 95% CI

In those subjects who received GSK189254 in the DBP, GSK189254 concentrations were generally higher at the end of the DBP (Day 42) than when the subjects were randomised into the DBP (Day 28) because Day 28 was the first day of administration of the 250 µg dose and Day 42 was at steady-state.



Conclusions: Since this study was terminated early, it lacks statistical power to make definitive statistical inferences.

- During the OLP, the MWT sleep latency showed improvement from baseline to the end of the OLP (Day 28). However, after randomization into the DBP, both treatment arms showed a drop in sleep latency on the MWT. The results for the MWT sleep latency at the end of the DBP (Day 42) did not provide evidence of a statistically significant difference between GSK189254 and placebo in the treatment of excessive daytime sleepiness caused by narcolepsy, in subjects who were responders at the end of OLP.
- During the OLP, the PGIC/CGIC results showed improvement from baseline to the end of the OLP (Day 28). However, after randomization into the DBP, the PGIC and CGIC did not provide evidence of a statistically significant difference between GSK189254 and placebo in overall clinical status of their narcolepsy, in subjects who were responders at the end of OLP.
- There was no statistically significant difference between GSK189254 and placebo in any of the other efficacy parameters, except the severity of nocturnal symptoms which increased between the end of the OLP and the last week of the DBP (Days 36-42) to a significantly ($p < 0.05$) greater extent on GSK18924 than on placebo, in subjects who were responders at the end of OLP.
- The POMS-B summary results showed a possible trend towards improvement, from baseline to the end of the DBP (Day 42), in Vigor/Activity and Depression/Dejection on GSK189254 and in Fatigue/Inertia on placebo, in subjects who were responders at the end of OLP.
- Adverse events most commonly reported (≥10% subjects) during the OLP were headache (42%), nasopharyngitis (14%), diarrhoea (12%) and nausea (10%). During the DBP, the adverse event profile for GSK189254 was similar to that of placebo, with headache being the most commonly reported event (13% in both treatment groups).
- The GSK189254 concentrations were similar in responders and non-responders.

Date of Report: October 2007