GSK598809

Selective D₃ receptor antagonist

The dopamine D₃ receptor (D₃R) has been investigated as a potential target for medication development to treat substance use and appetite control disorders. Novel compounds with high affinity and D₃R selectivity have been evaluated in numerous animal models of drug abuse and favourable outcomes in nonhuman primate models of self-administration and relapse have provided compelling evidence to advance these agents into the clinic. GSK598809 was originally being developed by GlaxoSmithKline as part of their decade-long programme to identify novel and high affinity D₃R-selective molecules. GSK598809 has been identified as a viable candidate for clinical investigation to treat substance use disorders and already completed several Phase 1 clinical trials with mixed results. Unfortunately, GlaxoSmithKline decided in 2010 to end investment in some areas of neuroscience research, and halted work on GSK598809 as part of that decision. The compound is now part of a research project using imaging scans to explore brain mechanisms behind impulsivity, stress and addiction.

Receptor Binding, Selectivity and Biodistribution

GSK598809 is a high-affinity, competitive antagonist at D₃Rs, with more than 100-fold selectivity over D₂Ls and fast association and dissociation kinetics. Overall, the results showed that the PK/O relationship was consistent between the rat, baboon, and human species.

GSK598809 exhibited fpKᵢ values of 8.9 and 6.2, at D₃ and D₂ receptors, respectively (approximately 500-fold selectivity) from the results of in vitro ³⁵S-GTPyS functional inhibition studies against quinelorane on membranes obtained from CHO cells expressing human D₃ and D₂ receptors.

Without changing basal [³⁵S]GTPyS levels in human D₃R/inducible membranes, GSK598809 caused a parallel right-ward shift of the quinelorane-induced increase of [³⁵S]GTPyS, with a potency value (A₂) of 0.5 nM (pA₂=9.3±0.1, n=3). Functional assays showed that GSK598809 has greater than 100-fold selectivity for dopamine D₃ receptors over dopamine D₂, histamine H₁, muscarinic M₁, M₂, M₃, M₄, serotonin 5-HT₁A, 5-HT₁B and 5-HT₁D receptors (data on file).

Kinetic experiments showed that GSK598809 bound to rat D₃Rs with an association rate constant (Kₒₐ) value of 0.0508±0.0081/nM/min (n=3) and a dissociation rate constant (Kᵦₒ) value of 0.2601±0.0616/min (n=3), respectively, from which it was calculated a kinetically derived dissociation constant value of 5.1 nM (pKᵦₒ=8.29). Half-time (t½) values of few minutes for association and 3 min for dissociation were calculated from such rate constant values.
GSK598809 did not change the dissociation kinetics of the radioligand, confirming the competitive interaction with the receptor.

With an *ex vivo* $^{[125]}$I7OH-PIPAT autoradiography protocol for the measurement of occupancy of brain D$_3$Rs, GSK598809 inhibited $^{[125]}$I7OH-PIPAT binding to rat D$_3$/stable membranes, with a K$_i$ of 1.5 nM (pK$_i$=8.83±0.004, n=3) and showed that GSK598809 occupies rat brain D$_3$Rs with a direct (time-independent) relationship between exposure and occupancy, and with a potency, expressed as a function of the bio-phase concentration (OC$_{brain}^{50}$=2.3 nM), in agreement with the binding affinity (K$_i$=1.5 nM for rD$_3$R).

In the absence of truly selective D$_2$ or D$_3$ PET radioligands, the combination of radiolabelled D$_2$/D$_3$ agonist, PHNO and GSK598809, a selective D$_3$ receptor antagonist provides a method for dissecting D$_3$ and D$_2$HIGH receptor availability in mixed regions such as ventral striatum and globus pallidus.

Using *ex vivo* $^{[125]}$I7OH-PIPAT autoradiography and $[^{11}C]$PHNO PET study, a dose-dependent occupancy of the D$_3$Rs by GSK598809 in rat, baboon, and human brains was demonstrated. GSK598809 displaced $[^{3}H]$PHNO binding to human D$_3$/stable and human D$_2$/stable membranes, with K$_i$ values of 6.2 nM (pK$_i$=8.21±0.09, n=3) and 740 nM (pK$_i$=6.13±0.02, n=3), respectively (data not shown).

A nonhuman primate PET study with radiolabelled D$_2$/D$_3$ agonist, $[^{11}C]$(+)-PHNO and GSK598809 (three baboons, 16 PET scans, dose range 0.1–1 mg/kg IV, unpublished data) in various brain regions revealed the in vivo regional distributions with following rank order: substantia nigra> globus pallidus>ventral striatum> thalamus> dorsal caudate> dorsal putamen.

In human PET studies with radiolabelled D$_2$/D$_3$ agonist, $[^{11}C]$(+)-PHNO (19 healthy volunteers, 7 PET scans), the 175 mg oral dose of GSK598809 had little effect in the dorsal striatum but induced nearly 100% displacement in the substantia nigra.

**Pharmacokinetic Parameters**

A preliminary investigation of GSK598809 PKs following intraperitoneal administration in rat showed that the total GSK598809 concentration in blood reached the peak concentration after 20 min, and was then relatively steady for 40 min (at 1 h=84±5%), halved at 2 h (47±16%), and was almost undetectable after 24 h (1±0.3%).

The lowest dose of GSK598809 giving maximal effect in the rodent nicotine CPP model was 0.3 mg/kg. Rats from the same group (0.3 mg/kg) of the satellite occupancy experiment had a median total GSK598809 blood concentration of 37.7 ng/ml, which corresponded to an occupancy of brain D$_3$Rs value of 72% in the rat PK/O curve.

Oral administration of GSK598809 (175 mg) in human volunteers resulted in peak levels (C$_{max}$ 1320 ng/mL) after roughly 2–3 hours (mean t$_{max}$ = 2.07h) with an apparent bi-exponential decline (AUC = 14000 ng.h/ml) and a half-life of roughly 20 hours (mean = 19.3h).

Following administration of an oral dose of 75 mg, GSK598809 was absorbed with a median T$_{max}$ of 1.5 h and a mean t$_{1/2}$ value of 17 h. The maximum concentration in the plasma was 520 ng/ml. From these values of actual concentration in the plasma and the PK/O relationship established with the PET studies, it was estimated that the occupancy of brain D$_3$Rs passed from zero at pre-dose to 89% at the T$_{max}$ (1.5 h) and then decreased slowly to 80% at 17 h.
Pharmacodynamics

Previous studies in healthy volunteers demonstrated that GSK598809 (175 mg) is generally well tolerated (data on file).

Adverse effects were assessed in 20 volunteers (10 males and 10 females) with a mean age of 32.8 years, mean weight of 73.5 kg and mean BMI of 23.6 kg/m$^2$ after an oral dose of 175 mg GSK598809. All adverse events were transient and mild or moderate in severity and no serious adverse events occurred during the study. Overall, the most frequent adverse effect were headache, somnolence, feeling drunk, dizziness, fatigue, pain at infusion site, nausea and vomiting. GSK598809 did not induce any significant extrapyramidal symptoms. There were no consistent and clinically relevant changes on the Barnes Akathisia Rating Scale, Simpson–Angus Scale and Abnormal Involuntary Movement Scale. There were no consistent and clinically relevant changes in vital signs, blood chemistry and haematology or any of the ECG intervals.

Following single oral dose (175 mg) of GSK598809, transient increases in serum prolactin were observed in healthy human volunteers. Peak prolactin levels which increased much more in females than in males ($p<0.0001$), were reached roughly 3h after study drug administration and normalized within 12h. The role of dopamine D$_3$ receptor antagonism in the control of prolactin secretion is unknown. The possibility is that GSK598809 could be acting at the level of the hypothalamus or on extra-dopaminergic mechanisms of prolactin control or by causing enough D$_2$ receptor antagonism to modestly increase prolactin secretion.

Administration of GSK598809 also caused a small decrease in adaptive tracking performance indicating slight impairment in visuo-motor performance/coordination, which was maximal between 2 and 6 hours after dose administration (175 mg).

No statistically significant effects were observed on any of the other pharmacodynamic parameters (smooth pursuit and saccadic eye movements to evaluate oculomotor performance and sedation; postural stability in the sagittal plane - body sway; alertness, mood and calmness - visual analogue scales, VAS; visual verbal learning test – an adapted version of the auditory verbal learning test/delayed word recall), which clearly demonstrates the pharmacological distinctions between GSK598809 and antipsychotic drugs.


Drug Seeking Behaviour

Nicotine

Previous research has shown that GSK598809 (derivative 74) is a selective and potent competitive D₃R antagonist with good physicochemical, pharmacokinetic (PK), and safety properties, which dose dependently decreased the expression of nicotine-induced conditioned place preference (CPP) in rats.

Conditioned place preference (CPP) experiments in animal models indicated that GSK598809 significantly reduced nicotine- and cocaine-seeking behaviour in a dose-dependent manner (data on file).

In addition, GSK598809 significantly prevented relapse to nicotine-seeking behaviour, although no effect was observed on reducing alcohol consumption in rats (data on file).

GSK598809 dose dependently reduced the expression of nicotine-induced CPP in rats, with an effect proportional to the exposure and occupancy of brain D₃Rs at every time point, and 100% effect at occupancy of brain D₃Rs values >72%.

In humans, a single oral dose of 75 mg of GSK598809, giving submaximal levels (72–89%) of occupancy of brain D₃Rs, transiently alleviated craving (partially reversed the attentional bias and significantly decreased subjective craving; though such effects were not maintained at later time points) in smokers after 14h of overnight abstinence, providing the first clinical evidence of potential efficacy of a selective D₃R antagonist for the treatment of substance-use disorders.

The study also established a relationship between the ability of GSK598809 to reduce nicotine-seeking behaviour preclinically and decrease craving in humans, based on the occupancy of brain D₃Rs and provide a model to early predict the right doses of novel D₃R antagonists for the treatment of addiction in larger Phase II clinical trials. These data also suggest that either higher occupancy of brain D₃Rs is required for a full effect in humans or that nicotine-seeking behaviour in CPP rats only partially translates into craving for cigarettes in short-term abstinent smokers.

No differences were detected between a single oral dose of 75 mg GSK598809 and placebo when measuring the relative reinforcing value of smoking and nicotine with the Behavioural Economic task and Cigarette Choice paradigm. Nevertheless, GSK598809-treated subjects, as compared with placebo, slightly increased cigarette consumption and puffs/cigarette when subjects were allowed to smoke freely in the natural environment subsequent to the experimental session, suggesting less satisfaction from the same number of puffs and compensatory increases.


**Food Cues**

Using a stimulus-response compatibility task, approach bias was indexed by response latency to move an image of a manikin towards, versus away from, pictures of food, relative to non-food stimuli. Data from the first session (which were unaffected by repeated testing) indicated that approach bias scores were significantly reduced in overweight and obese participants who received GSK598809 (175 mg capsule), compared with those who received placebo.

The acute effects of GSK598809 (175 mg capsule) on attentional bias to food-related cues in overweight to obese individuals (26 participants; 15 males, 11 females; aged between 18 and 45 yr) who reported binge and emotional eating were studied utilizing a randomized, counterbalanced, double-blind, placebo-controlled, two-way cross-over design. Attentional bias was tested with two commonly used tasks, the modified (food) Stroop task and the visual probe task.

Overall, GSK598809, at a dose (175 mg) that associated >90% D2/3 receptor occupancy, appeared to have no overall effect on attention bias to food-related cues (as measured behaviourally). However, individual differences in eating styles impacted on the effect of GSK598809 on attentional bias, as evident from a significant negative correlation between restraint and the effect of GSK598809 on attentional bias for each task.

GSK598809, has a moderating effect on attentional bias to food-related cues in overweight and obese individuals, which is dependent on individual differences in eating styles, with a stronger drug effect observed in those with lower levels of restrained eating. These findings suggest that, in low-restrained eaters, D3 receptor antagonism with GSK598809 reduces selective attention allocated to rewarding food cues.

The lack of overall effect of GSK598809 on attentional bias seems likely to be explained by the fact that the high-restraint group did not show an attentional bias to food cues during placebo treatment. It has been suggested that restrained eaters are more attuned to food cues in the environment and attempt to avoid these in order to control their body weight.

The effect of GSK598809 on brain activation to food images was studied using fMRI in a sample of overweight and obese binge-eating subjects. Consistent with previous studies, processing of food images was associated with activation of a network of reward areas including the amygdala, striatum and insula. However, brain activation to food images was not modulated by GSK598809. The results demonstrate that D3 receptor manipulation does not modulate brain responses to food images in overweight and obese subjects.


**Alcohol**

A metabolite of GSK598809 shows *in vitro* to have a potential for inhibiting CYP2E1, which is one of the main enzymes involved in alcohol metabolism.

Contrary to the promising finding in experimental animals, a recent clinical trial (te Beek *et al.*, 2012) with GSK598809 for the treatment of alcoholism demonstrated that it produces an additive, not an expected inhibitory, effect on alcohol intake.

Co-administration of GSK598809 and alcohol resulted in additive effects on several pharmacodynamic parameters, compared with either treatment alone in healthy human volunteers.

Co-administration of GSK598809 and alcohol resulted in a significant impairment on saccadic eye movements. No significant supra-additive effects were found on any of the pharmacodynamic parameters, except a small increase in saccadic reaction time and a small decrease in delayed word recall on the visual verbal learning test. These findings suggest that caution may be needed in the use of GSK598809 in individuals who consume alcohol moderately or excessively, although the effects will probably be dominated by alcohol.


**Clinical Trials**

http://clinicaltrials.gov/ct2/results?term=GSK598809

No Study Results/Publications provided

**PHASE I TRIALS**

1. **Study To Investigate If Repeat Doses Of GSK598809 Are Safe And Well Tolerated And To Evaluate Blood Levels Of GSK598809** - Completed August 2008 Phase 1
   Conditions: Substance Dependence; Compulsive Behavior
   Intervention: Drug: GSK598809/Placebo

2. **A Study To Investigate The Safety, Tolerability And Blood Levels Of GSK598809** – Completed Phase 1
   Conditions: Smoking; Healthy Subjects
   Intervention: Drug: GSK598809

3. **A Healthy Volunteer Study to Investigate the Relative Bioavailability of Two Forms of GSK598809 Capsules** – Completed July 2008 Phase 1
   Condition: Substance Dependence
   Intervention: Drug: GSK598809

4. **A Human Volunteer Study Investigating Single Oral Doses of GSK598809 in Otherwise Healthy Smokers** – Completed August 2008 Phase 1
Condition: Substance Dependence
Intervention: Drug: GSK598809, placebo

5 Effects of GSK598809 on Brain Activation in Abstinent Alcoholics – Terminated July 2009 Phase 1
Conditions: Substance Dependence; Alcohol Dependence
Intervention: Drug: GSK598809

6 A Study To Assess The Effects Of A Single Dose Of GSK598809 In Modulating Nicotine Reward – Completed December 2008 Phase 1
Conditions: Substance Dependence; Smoking
Intervention: Drug: GSK598809

7 Study of Safety, Blood Levels and Brain Receptor Occupancy of GSK598809 Using PET Imaging in Health Males – Completed May 2008 Phase 1
Condition: Healthy Subjects
Intervention: Drug: GSK598809, using [11C]-(+)-PHNO

8 EtOH Interaction Study – Completed December 2008 Phase 1
Conditions: Substance Dependence; Healthy Volunteer
Interventions: Drug: GSK598809; Other: Ethanol

9 Effects of the D3 Antagonist GSK598809 on Food Reward and Reinforcement – Completed April 2010 Phase 1
Conditions: Food Addiction; Substance Dependence; Obesity; Overweight
Interventions: Drug: GSK598809 Capsules; Drug: GSK598809 Placebo Capsules

10 To Investigate If Single Doses Of GSK618334 Are Safe And To Investigate Blood Levels Of GSK618334 – Completed October 2007 Phase 1
Conditions: Substance Dependence; Compulsive Behavior
Intervention: Drug: GSK618334

PHASE II TRIALS

GSK598809 is currently under Phase II clinic trial for treatment of nicotine dependence. The effects of GSK598809 on cocaine dependence have not yet been evaluated.

1 Effectiveness of GSK598809, a Selective D3 Antagonist, Added to Cognitive Behavioral Therapy and Nicotine Replacement Therapy for Smoking Cessation and Prevention of Very Early Relapse to Smoking - Active, not recruiting October 2013 (estimated) Phase 2
Condition: Nicotine Dependence
Interventions: Drug: GSK598809; Drug: Placebo

2 Relapse Prevention Study in Newly Abstinent Smokers – Terminated March 2010 Phase 2
Conditions: Substance Dependence; Smoking
Interventions: Drug: double blind treatment; Drug: open label
**GSK Clinical Study ID: DAN109710 (phase 1)**

A single-blind, randomized, placebo controlled, two-period crossover fMRI study to investigate the effects of the D3 antagonist GSK598809 on neural and behavioural responses to food reward and reinforcement after a single oral dose of GSK598809 in overweight and obese subjects.

**Objectives:**
To test the hypothesis that a single oral dose of GSK598809 (compared with placebo) in fasted overweight and obese subjects modulated brain activity as measured with fMRI, within the reward circuitry during task assessing appraisal of food stimuli and inhibitory control over responding to food cues. To test the hypothesis that a single dose of GSK598809 (compared with placebo) in fasted overweight and obese subjects affected performance on behavioural neurocognitive tasks assessing associative learning, motivational processes and attentional bias related to food stimuli.

**Pharmacodynamics and biomarkers:** Statistical analysis results of food stroop task for GSK598809 versus placebo are summarised below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSmean GSK598809</th>
<th>LSmean Placebo</th>
<th>Diff</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non palatable RT (msec)</td>
<td>913.03</td>
<td>859.06</td>
<td>53.96</td>
<td>(19.58, 88.32)</td>
<td>0.003</td>
</tr>
<tr>
<td>Neut. Non palatable RT (msec)</td>
<td>877.53</td>
<td>811.40</td>
<td>66.13</td>
<td>(-28.59, 103.86)</td>
<td>0.001</td>
</tr>
<tr>
<td>Palatable RT (msec)</td>
<td>911.86</td>
<td>876.31</td>
<td>35.55</td>
<td>(-8.74, 75.64)</td>
<td>0.115</td>
</tr>
<tr>
<td>Neut. Palatable RT (msec)</td>
<td>900.22</td>
<td>857.43</td>
<td>42.79</td>
<td>(-5.61, 91.20)</td>
<td>0.081</td>
</tr>
<tr>
<td>Congruent RT (msec)</td>
<td>816.53</td>
<td>805.22</td>
<td>11.31</td>
<td>(-37.83, 60.45)</td>
<td>0.639</td>
</tr>
<tr>
<td>Neut. Congruent RT (msec)</td>
<td>788.99</td>
<td>812.37</td>
<td>-23.38</td>
<td>(-86.20, 46.33)</td>
<td>0.496</td>
</tr>
<tr>
<td>Incongruent RT (msec)</td>
<td>1008.48</td>
<td>981.34</td>
<td>26.13</td>
<td>(-25.84, 82.21)</td>
<td>0.294</td>
</tr>
<tr>
<td>Neut. Incongruent RT (msec)</td>
<td>884.90</td>
<td>870.81</td>
<td>14.09</td>
<td>(-39.36, 67.54)</td>
<td>0.592</td>
</tr>
</tbody>
</table>

RT = reaction time, Neut. = neutral

Additional statistical analysis on the interference score for colour words, palatable words and non-palatable words for GSK598809 versus placebo are summarised below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSmean GSK598809</th>
<th>LSmean Placebo</th>
<th>Diff</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloured words</td>
<td>125.25</td>
<td>110.57</td>
<td>14.68</td>
<td>(-53.52, 82.88)</td>
<td>0.661</td>
</tr>
<tr>
<td>Palatable food</td>
<td>5.70</td>
<td>20.57</td>
<td>-14.87</td>
<td>(-60.41, 39.67)</td>
<td>0.586</td>
</tr>
<tr>
<td>Non Palatable</td>
<td>34.60</td>
<td>47.63</td>
<td>-13.04</td>
<td>(-52.88, 26.81)</td>
<td>0.506</td>
</tr>
</tbody>
</table>

**Safety results:** Adverse events (AEs) and serious AEs were collected from the start of GSK163090 and until the follow-up contact. Adverse events reported in two or more subjects in any treatment group are presented below.

**Most Frequent Adverse Events**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=28)</th>
<th>GSK598809 (N=29)</th>
<th>Follow-up (N=27)</th>
<th>Total (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any AE related to investigational product</td>
<td>15 (54%)</td>
<td>12 (41%)</td>
<td>1 (4%)</td>
<td>20 (69%)</td>
</tr>
</tbody>
</table>

Most frequently reported AEs (more than one subject in any group)

- Headache: 8 (29%) / 6 (21%)
- Nausea: 1 (4%) / 1 (4%)
- Arthralgia: 2 (7%) / 0
- Ventricular tachycardia: 0 / 2 (7%)

**Serious Adverse Events:** None

**Pharmacokinetics:** Selected plasma GSK598809 pharmacokinetic parameters is presented below.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N</th>
<th>GSK598809 175 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>28</td>
<td>824 (43)</td>
</tr>
<tr>
<td>AUC(0-24) (ng h/mL)</td>
<td>20</td>
<td>9680 (25)</td>
</tr>
<tr>
<td>AUCex (%)</td>
<td>20</td>
<td>12.6 (41)</td>
</tr>
<tr>
<td>AUC(0-t) (ng h/mL)</td>
<td>28</td>
<td>8340 (26)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>28</td>
<td>1.50 (0.50-4.23)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>20</td>
<td>26.2 (18)</td>
</tr>
</tbody>
</table>

**Pharmacokinetics:** Selected plasma GSK5986249 pharmacokinetic parameters is presented below.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N</th>
<th>GSK598009 175 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>28</td>
<td>15.2 (45)</td>
</tr>
<tr>
<td>AUC(0-t) (ng h/mL)</td>
<td>28</td>
<td>59.8 (58)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>28</td>
<td>1.00 (0.50-1.57)</td>
</tr>
</tbody>
</table>

1. geometric mean (CV%), 2. median (range)
GSK Clinical Study ID: DAN106593 (phase 1)

A randomized, double-blind, placebo controlled, two-way cross-over study to assess the effects of a single dose of GSK598809, a Selective DRD3 Antagonist, in Modulating Nicotine Reward

Objectives:
- This human behavioural pharmacology study was set up to investigate GSK598809 effects on the following pharmacodynamics (PD) parameters in healthy smokers:
  - Cigarette craving as measured objectively by attentional bias and by subjective craving measures
  - The relative reinforcing value of smoking as measured by a behavioural economic paradigm (exploratory)
  - The relative reinforcing value of nicotine as measured in a cigarette choice paradigm
  - Cigarette consumption in a free smoking setting
- To assess the safety and tolerability of single oral doses of GSK598809 in healthy smokers
- To assess the pharmacokinetics (PK) of GSK598809 and a metabolite, GSK685249
- As an exploratory objective, Cotinine (COT) to trans-3'-hydroxycotinine (3HC) metabolism rate as a marker of cytochrome P450 2A6 activity

Safety Results: Adverse event (AE) and serious adverse event (SAE) data were recorded starting on Day 1 and continuing until the end of the confinement period. There were changes observed during Holter monitoring, similar to those observed in chronic smokers, and these changes occurred on placebo, during baseline and on GSK598809. There were no observed changes on Holter monitoring attributable to drug. There were no clinically significant ECG findings or changes in vital signs. There were no clinically significant laboratory findings (clinical chemistry or hematology).

### Adverse Events Occurring in ≥ 2 Subjects any Treatment Period:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>75mg GSK598809</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (ITT)</td>
<td>44</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>No. subjects with any AEs n (%)</td>
<td>14 (32)</td>
<td>14 (32)</td>
<td>22 (46)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory electrocardiogram abnormal</td>
<td>9 (20)</td>
<td>8 (18)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

### Serious Adverse Events, n (%)
- No [0] fatal or [0] non-fatal SAEs were reported during the study.

### Pharmacokinetics Endpoints:

**Summary of Selected Plasma GSK598809 and metabolite GSK685249 following 75mg GSK598809**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>GSK598809</th>
<th>N</th>
<th>GSK685249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>44</td>
<td>520 (34)</td>
<td>44</td>
<td>10.7 (34)</td>
</tr>
<tr>
<td>AUC(0-∞) (ng*h/ml)</td>
<td>31</td>
<td>4240 (30)</td>
<td>11</td>
<td>78.0 (36)</td>
</tr>
<tr>
<td>AUC(0-t) (ng*h/ml)</td>
<td>44</td>
<td>3630 (33)</td>
<td>44</td>
<td>61.4 (40)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>44</td>
<td>15.3 (0.53-8.15)</td>
<td>44</td>
<td>1.52 (0.52-3.07)</td>
</tr>
</tbody>
</table>

1 Geometric mean (CV%)
2 Median (Range)

The estimated ratios of trans-3'-hydroxycotinine vs. cotinine for pharmacokinetic parameters were similar following 75mg GSK598809 compared to placebo.

### Pharmacodynamic Endpoints:

No difference was observed between 75mg GSK598809 and placebo on the Stroop task performance, behavioural economic task or cigarette choice paradigm.

A significant effect of 75mg GSK598809 on behaviour was observed during ad lib-smoking. In general subjects smoked more (puffs and number of cigarettes) after receiving 75mg GSK598809 compared to placebo. No effect was observed on latency to first puff. In general females took more puffs per cigarette than males.

- MNWS self reported withdrawal was slightly higher for placebo at 0.25hr to 1.25hr post-dose.

No baseline measures were available. Some indication for reduced self reported withdrawal in
female subjects after subjects were dosed with 75mg GSK598809 compared to placebo. The site pairwise individual analysis showed a statistically significant reduction in craving (QSU-B Factor 1 - intention and desire to smoke and the anticipation of positive reinforcement) shortly after subjects were dosed with 75mg GSK598809 compared to placebo. Mean results showed a trend toward a reduction in craving for males under the same conditions. Pairwise individual analyses showed a statistically significant decrease on GSK598809 as compared to placebo on item 4 of the MNWS (desire/craving to smoke). Mean analyses showed an indication for reduced self reported withdrawal in female subjects after subjects were dosed with 75mg GSK598809 compared to placebo. No baseline measures were available. The CES subscale of psychological reward was smaller on placebo compared to 75mg GSK598809 for females. This effect was not observed for males.

From the Rose-SQ, there was some signal suggesting that females gave a higher assessment of strength of nicotine vs. denicotinized Quest cigarettes when on 75mg GSK598809 compared to placebo. This effect was not observed for males.

No effect of 75mg GSK598809 was observed on the levels of carbon monoxide.

Overall, GSK598809, in a single oral dose of 75mg as compared to placebo, increased cigarette consumption and puffs/cigarette in an open smoking paradigm following a day in the laboratory and showed signals of reduced craving in overnight abstinent smokers. There was no apparent statistically significant effect of GSK598809 at this single dose on other parameters including attentional bias, withdrawal, or reward/detection of nicotine vs denicotinized Quest cigarettes. Despite the lack of evidence of a clear and generalized gender effect, signals suggesting a different behaviour between males and females were noted. This could have reduced the power of the study to detect the potential efficacy of the drug.

**Summary of Results from Statistical Analysis of Adlib Smoking (All Subjects): 75mg GSK598809 vs. Placebo**

<table>
<thead>
<tr>
<th>Response Variable</th>
<th>Arithmetic mean 75mg</th>
<th>Arithmetic mean Placebo</th>
<th>Difference</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Puffs</td>
<td>31.32</td>
<td>27.27</td>
<td>4.05</td>
<td>(1.67, 6.43)</td>
</tr>
<tr>
<td>Number of Cigarettes</td>
<td>3.30</td>
<td>2.95</td>
<td>0.35</td>
<td>(0.12, 0.59)</td>
</tr>
<tr>
<td>Latency (secs)*</td>
<td>87.00</td>
<td>151.82</td>
<td>0.57</td>
<td>(0.27, 1.23)</td>
</tr>
</tbody>
</table>

*Geometric means and ratios presented