A Study to Investigate Potential Interactions between GSK598809 and Ethanol in Healthy Subjects

Published: 21-07-2008
Last updated: 06-05-2024

Primary:* To investigate the safety and tolerability of the co-administration of GSK598809 at175 mg and ethanol in healthy volunteers.* To examine the potential pharmacokinetic interactions between GSK598809administered at 175mg and ethanol in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Psychiatric disorders NEC
Study type	Interventional

Summary

ID

NL-OMON32561

Source
ToetsingOnline

Brief title
GSK598809 and alcohol interaction

Condition

- Psychiatric disorders NEC

Synonym
addiction, alcoholism

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: Farmaceutische industrie (GSK)

Intervention

Keyword: addiction, alcohol, interaction

Outcome measures

Primary outcome

Primary:

* Safety and tolerability:

* Vital Sign measurement

* 12 Lead ECG and telemetry during dosing

* Safety Laboratory sampling (Clinical Chemistry, Haematology and urinalysis)

including Prolactin and lipid measurements.

* Adverse Event monitoring.

* Barnes Akathisia Scale (BAS)

* Simpson-Angus Scale (SAS)

* Abnormal Involuntary Movement Scale (AIMS).

Pharmacokinetics:

Concentrations will be measured at times specified in the study schedule, for

the

following:

* Breath ethanol concentrations (BrAC),

* Blood ethanol concentrations,

* Main pharmacokinetic parameters of GSK598809 and its metabolite

(GSK685249): AUC*, Cmax, Tmax and t*.

Pharmacodynamic:

* Saccadic eye movements (saccadic reaction time, saccadic peak velocity and saccadic accuracy), to assess sedation,

* Smooth pursuit eye movements (percentage of time the subjects eyes are in smooth pursuit of the target), to assess attention and eye movement coordination,

* Body sway (antero-posteral sway in mm/2min), to assess body movements in a single plane, providing a measure of postural (in)stability. During sway measurements, subjects will be instructed to keep their eyes closed for two minutes,

* Adaptive tracking, to assess visuo-motor control and vigilance,

* Visual Verbal Learning Test (VVLT), to assess memory.

Secondary outcome

Pharmacodynamic/biomarker endpoints:

* Saccadic eye movements (saccadic reaction time, saccadic peak velocity and saccadic accuracy), to assess sedation,

* Visual Analogue Scales (VAS) according to Bond & Lader to assess mood, alertness and calmness,

* Visual Analogue Scales for *alcohol effects* to assess the subjective effects of
ethanol (VAS alcohol effects).

Study description

Background summary

GSK598809 is a potent, selective antagonist of the dopamine-3 (D3) receptor that is under development as a novel treatment for substance dependence disorders. GSK598809 reduces the reinforcing efficacy of a wide range of drugs of abuse including alcohol, nicotine, cocaine and heroin. The World Health Organization estimates that there are 2 billion people worldwide who consume alcoholic beverages and 76.3 million with diagnosable alcohol use disorders, including abuse and dependence (WHO, 2004). Economic costs related to problem alcohol use are high, with estimates of $185 billion per year in the US alone (Harwood, 2000). Approximately 4% of global disability adjusted life years (DALYs) can be attributed to the use of alcohol, and the estimate is more than twice as high (9%) for developed countries (WHO, 2004).

There have been no completely effective pharmacotherapies developed for the cessation of use, long term abstinence and relapse prevention for these disorders, in spite of the significant societal burden of these disorders. The expectation that a D3 receptor antagonist would be efficacious for the treatment of substance dependence, including alcohol dependence, is based on the following key observations. There is a relatively high density of D3 receptors in brain regions known to be involved in behaviors controlled by drug-associated cues. Postmortem studies of cocaine addicts show up-regulation of D3 receptors in the ventral striatum. The density of these receptors and or their mRNA has been shown to be increased in brains of rodents trained to dependency on cocaine, nicotine or morphine. But, most importantly, selective blockade of D3 receptors by another of GSK*s compounds, SB277011A, effectively reduces reinstatement of drug use in nicotine, cocaine, opiate and ethanol conditioned rats (for recent reviews in support of these claims see (Heidreder, 2004; Heidreder, 2005; Joyce, 2005; Newman, 2005).

The pre-clinical profile of GSK598809 indicates that it will have efficacy to potentially induce cessation and/or relapse, to prevent relapse (maintenance of abstinence) for several substances known to produce dependence, and to do so without an apparent abuse liability, effects on motor coordination or on normal sexual motivation and sexual behavior.

Since one of the key areas for investigation is the treatment of alcohol dependence, it is necessary to evaluate the possible pharmacokinetic and pharmadynamic interaction effects of GSK598809 with alcohol in human subjects. Alcohol is one of the most widely used central nervous system (CNS) active substances in Western society. It causes impairment over a wide range of CNS-functions, including reduction of alertness, motor stability and hand-eye coordination. These effects are dose-dependent, but there is high intersubject variability, which is partly related to differences in gender and ethnic background and to habituation with regular drinking. The effects of ethanol can be potentiated by other drugs through pharmacokinetic and/or pharmacodynamic

interactions, particularly drugs that show CNS-side effects by themselves. Pharmacokinetic interactions between ethanol and GSK598809 are unlikely, but theoretically possible to occur, since GSK598809 metabolite, GSK685249 shows in vitro to have a potential for inhibiting CYP2E1 (GSK685249 IC50= 0.534µM corresponding to concentration at least 6 times higher than the observed in human plasma in previous clinical studies) which is the main metabolic pathway for ethanol. There is no specific reason to think that ethanol might modify the pharmacokinetics of GSK598809. The effect that ethanol might potentially have (unlikely being GSK598809 a BCS I drug) on the oral absorption of GSK598809 will not be evaluated during this study being ethanol administered intravenously. In addition, as both are CNS active compounds, pharmacodynamic interactions are also possible, particularly since each affects that dopaminergic system. Drug alcohol interactions can be highly relevant, because an unsuspected increase of the effects of alcohol by concomitant use of a drug can cause serious problems in traffic or daily life.

Study objective

Primary:
* To investigate the safety and tolerability of the co-administration of GSK598809 at
175 mg and ethanol in healthy volunteers.
* To examine the potential pharmacokinetic interactions between GSK598809 administered at 175mg and ethanol in healthy volunteers.
* To determine if co-administration of GSK598809 at 175mg with ethanol potentiates
the subjective and CNS impairing effects of ethanol in healthy volunteers.
* To determine the effects of co-administration of GSK598809 at175mg with ethanol
as compared to placebo with ethanol.

Secondary:
* To determine if GSK598809 administered at a dose of 175mg affects selected CNS function in healthy volunteers.
* To investigate the effects of ethanol on selected CNS function in healthy volunteers.

Study design

This is a single-blind, randomised, placebo-controlled, double-dummy, four-period crossover study to investigate the psychomotor and cognitive effects of GSK598809 alone and in combination with ethanol in healthy subjects. Subjects will be medically screened prior to participation in the study. There are four study periods (each consists of two overnight stays and two return visits). A follow-up visit will be performed within 7 days after the last dose.

Intervention

Ethanol 10% w/v solution in 5% glucose will be delivered by intravenous infusion to maintain blood ethanol concentration near 0.60 g/L for 300 minutes. The target concentration of 0.60 g/L is expected to be well tolerated, since this concentration has been safely employed in several previous CHDR studies (CHDR0313 and CHDR0502 * data on file) for even longer periods (up to 5 hours). In these previous studies the 0.6 g/L ethanol clamp showed statistically significant pharmacodynamic CNS effects. Furthermore these levels are routinely achieved during social drinking. To avoid local pain in the beginning of the ethanol infusion, a parallel infusion with glucose 5% will be given. Glucose 5% will be used as a placebo.

At the same time 175 mg GSK598809 will be administered as a single oral dose to study the interaction effects in combination with alcohol.

The study consists of the following treatments:

1. Alcohol (0.6 g/L) + GSK598809 (175 mg)
2. Alcohol (0.6 g/L) + Placebo
3. Placebo + GSK598809 (175 mg)
4. Placebo + Placebo.

Study burden and risks

* The expected side-effects for GSK598809, alcohol and for the combination are currently described in section E9. Prior studies show that the side effects for alcohol and GSK598809 alone were mild and transient. The potential side-effects associated with the combination of alcohol and GSK598809 are increases in symptoms observed with either alcohol or GSK598809 alone, particularly, nausea, dizziness and sedation, which are common effects of both alcohol and GSK598809.

* Bloodsamples will be taken through a canulla to reduce the amount of venapunctures. Approximately 490 mL of blood will be drawn during the complete study (i.e. over 9/10 weeks).

* To reduce local discomfort in the infusion arm at the beginning of the 5 hr. ethanol administration (due to the high flow ethanol infusion), a parallel infusion of glucose 5% will be administered in the first 10 infusion minutes to minimize these symptoms.

* The study consists of a medical screening and 4 study periods.
Each study period consists of the following study days:
- evening day -1: admission
- day 1: study day
- morning day 2: discharge

- day 3: 1st return visit (bloodsampling: approximately 1 hour)
- day 4: 2nd returnvisit (bloodsampling: approximately 1 hour)
Within 7 days after the last study visit a follow-up visit is planned.

Contacts

Public
GlaxoSmithKline

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Healthy as determined by a responsible physician, based on a medical evaluation including medical history, psychiatric history, physical examination including mental status examination, laboratory tests and cardiac monitoring (12-lead ECG).
2. Male or female between 18 and 65 years of age.
3. A female subject is eligible to participate if she is of:
* Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12

months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/ml and estradiol < 40 pg/ml (<140 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) will not be included in the study.
* Child-bearing potential and agrees to use one of the contraception methods listed in Section 8.1.1 for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 90 days post final dose.
4. Male subjects must agree to use appropriate contraception methods (listed in Section 8.1.2. of the protocol). This criterion must be followed from the time of the first dose of study medication until 90 days post final dose.
5. Body weight ><= 50 kg and BMI within the range 18 * 30 kg/m2 (inclusive).
6. Occasional, non-daily smokers.
7. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
8. QTcB or QTcF < 450 msec.

Exclusion criteria

1. The subject has a positive pre-study drug/alcohol screen.
2. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.
3. A history of or findings on evaluation consistent with any Axis I or Axis II disorder as defined in the DSM IV.
4. A positive test for HIV antibody.
5. History of regular alcohol consumption within 6 months of the study defined as:
an average weekly intake of greater than 21 units or an average daily intake of greater than 3 units (males), or defined as an average weekly intake of greater than 14 units or an average daily intake of greater than 2 units (females).
6. The subject has participated in a clinical trial and has received an investigational product within the 90 days prior to the first dosing day in the current study
7. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
8. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John*s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication.
9. History of sensitivity to any of the study medications, or components thereof or a history of drug or other clinically significant allergies.
10. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 90 day period.
11. Pregnant females as determined by positive serum or urine beta-hCG test at screening and prior to dosing.
12. Lactating females or those who have lactated in last month.

13. Unwillingness or inability to follow the procedures outlined in the protocol.
14. History of sensitivity to heparin or heparin-induced trombocytopenia.
15. Subjects, who have asthma or a history of asthma, (e.g., for any FTIH where risk of bronchoconstriction is unknown, or compound specific where risk of bronchoconstriction).
16. Subjects who smoke on a daily basis.
17. Consumption of red wine, seville oranges, grapefruit or grapefruit juice [and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices] from 7 days prior to the first dose of study medication.
18. Any subject who is not prepared to eat the standard meals provided by the clinic.
19. Liver function tests (LFT) that are above the laboratory reference range at screening and that remain elevated when repeated.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-09-2008
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GSK598809
Generic name:	GSK598809

Ethics review

Approved WMO Date:	21-07-2008
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	24-09-2008
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-003699-23-NL
CCMO	NL24173.058.08