A Randomised, Placebo Controlled, Ascending, Repeat Dose Study in Healthy Volunteers Investigating Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK356278

Published: 08-11-2011
Last updated: 30-04-2024

To investigate the safety and tolerability of repeat oral doses of GSK356278 in healthy volunteers.To investigate the pharmacokinetics of repeat oral doses of GSK356278 in healthy volunteers.To evaluate the PK/PD relationship between plasma...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON35301

Source
ToetsingOnline

Brief title
GSK356278 MAD study

Condition

- Other condition

Synonym
Genetic disorder that affects the muscle coordination, Huntington's disease

Health condition

Ziekte van Huntington

Research involving
Human

Sponsors and support

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

Intervention

Keyword: GSK356278, Healthy subjects, Huntington's disease

Outcome measures

Primary outcome

Pharmacodynamics :EEG, cognitive tests, BNDF

Pharmacokinetics: Plasma GSK356278 concentrations, pharamkinetic parameters

Safety: adverse events, vital signs, ECG-parameters, telemetry ECG-parameters,

laboratory parameters, physical examination, Rhodes index of nausea, vomiting &

retching (INVR), self-rated alertness using bond and lader visual analogue

scales (VAS)

Secondary outcome

n/a

Study description

Background summary

The drug to be given, GSK356278, is a new, investigational compound that may eventually be used for the treatment of Huntington*s disease. Huntington*s disease is a progressive, fatal genetic disorder that affects certain parts of the brain. This disease affects muscle coordination and leads to mental decline and dementia. The earliest symptoms are a general lack of coordination and an unsteadiness.
Huntington*s disease is caused by changes in a particular part of the DNA (contains our genetic information), that normally provides information for a

protein called Huntingtin. This so-called mutation results in a different form of the Huntingtin protein.
Activation of the mutated Huntingtin protein can eventually lead to damage of specific areas of the brain that results in Huntington*s disease.

GSK356278 can inhibit the activity of the mutated Huntingtin protein, and therefore can be useful in the treatment of Huntington*s disease.

Study objective

To investigate the safety and tolerability of repeat oral doses of GSK356278 in healthy volunteers.
To investigate the pharmacokinetics of repeat oral doses of GSK356278 in healthy volunteers.
To evaluate the PK/PD relationship between plasma concentrations and changes in pharmaco-EEG metrics, cognition and nausea.
To explore food effect on nausea in relation to PK.

Study design

Design :
This is a randomised, placebo controlled, ascending repeat dose study in one cohort of eight healthy volunteers (group 1), one cohort of 12 healthy volunteers (group 2) and one cohort of 16 healthy volunteers (group 3). Group 1 will receive a repeated dose of GSK356278 or placebo (six active and two placebo) for 10 days. Group 2 will receive a repeated dose of GSK356278 or placebo (nine active and three placebo) for 14 days. Group 3 will receive a single dose of GSK356278 or placebo (twelve active and four placebo), followed by a repeated dose of GSK356278 or placebo for 28 days.

Group 1
Procedures and assessments
Screening and follow-up: Demographic data, physical examination, medical history, 24 hr holter, 12-lead electrocardiogram (ECG), vital signs, alcohol and drug screen, pregnancy test (females only), hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and anti-human immunodeficiency virus (HIV)1/2, clinical laboratory (including clinical chemistry, haematology, urinalysis and LFT's), previous and concomitant medication, and Columbia suicidality assessment;
at eligibility screening: brief physical examination, alcohol and drug screen, pregnancy test (females only), echocardiography and Columbia suicidality assessment;
at follow-up: brief physical examination, 12-lead ECG, vital signs and clinical laboratory (including clinical chemistry, haematology, urinalysis and troponine, BNP and LFT's)

Observation period: One period in the clinic from Day -2 until Day 14

Blood sampling: For pharmacokinetics of GSK356278 in plasma: pre-dose and 1, 2, 3, 6, 12, 24, and 72 h post-dose Day 1, pre-dose Day 6, pre-dose Day 8, pre-dose and 1, 2, 3, 6, 12, 24 and 72 h post-dose Day 10.

Safety assessments: Adverse events: throughout the study; 12-lead ECG: pre-dose predicted Day -1, pre-dose and 1, 2, 4, 6, 12, 24 h post-dose Day 1, pre-dose and 3 h post-dose Day 5, pre-dose and 1, 2, 4, 6, 12, 24 h post-dose Day 10 and Day 14; telemetry ECG: Day -1, 1 and 10; vital signs: pre-dose predicted and 1, 2, 3, 4, 6, 12 h post-dose predicted Day -1, pre-dose and 1, 2, 3, 4, 6, and 12 h post-dose Day 1, pre-dose and 3 h post-dose Day 2, 3, 4, 5, 6 and 7, pre-dose, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h post-dose Day 10 and Day 14; clinical chemistry, haematology, troponin, BNP and LFT's: Day -1, 2, 4 (LFT's only), 7 and 11; urinalysis: Day -1, 2 and 11; bond and lader VAS: Day -1, 1, 5 and 10; columbia suicidality assessment: Day 14; echocardiography: Day 12; inflammation panel and BDNF: Day -1, 2, 7 (inflammatory panel only) and 11

Group 2
Procedures and assessments
Screening and follow-up: Demographic data, physical examination, medical history, 24 hr holter, 12-lead electrocardiogram (ECG), vital signs, alcohol and drug screen, pregnancy test (females only), hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and anti-human immunodeficiency virus (HIV)1/2, clinical laboratory (including clinical chemistry, haematology, urinalysis and LFT's), previous and concomitant medication, and Columbia suicidality assessment;
at eligibility screening: brief physical examination, alcohol and drug screen, pregnancy test (females only), cognitive tests, EEG, echocardiography and Columbia suicidality assessment;
at follow-up: brief physical examination, 12-lead ECG, vital signs and clinical laboratory (including clinical chemistry, haematology, urinalysis and troponin, BNP and LFT's)

Observation period: One period in the clinic from Day -2 until Day 18

Blood sampling: For pharmacokinetics of GSK356278 in plasma: pre-dose and 1, 2, 3, 4, 6, 12, 24, and 72 h post-dose Day 1, pre-dose Day 4, 6, 8, 10, 12, pre-dose and 1, 2, 3, 4, 6, 12, 24, 48 and 72 h post-dose.

Safety assessments: Adverse events: throughout the study; 12-lead ECG: pre-dose predicted Day -1, pre-dose and 1, 2, 4, 6, 12, 24 h post-dose Day 1, pre-dose and 3 h post-dose Day 7, pre-dose and 1, 2, 4, 6 and 12 h post-dose Day 14; telemetry ECG: Day -1, 1 and 14; vital signs: pre-dose predicted and 1, 2, 3, 4, 6, 12 h post-dose predicted Day -1, pre-dose and 1, 2, 3, 4, 6 and 12 h post-dose Day 1, pre-dose and 3 h post-dose Day 2, 3, 4, 5, 6, 7, 9 and 11, pre-dose, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h post-dose Day 14 and Day 18;

clinical chemistry, haematology, troponin, BNP and LFT's: Day -1, 2, 4 (LFT's only), 7, 10 (LFT's only) and 15; urinalysis: Day -1, 2 and 15; bond and lader VAS: Day -1, 1, 7 and 14; cognitive tests: Day 2 and 12; EEG: Day 3 and 13; columbia suicidality assessment: Day 18; echocardiography: Day 16; infalmmation panel and BDNF: Day -1, 2, 7 (inflammation panel only) and 15

Group 3
Procedures and assessments
Screening and follow-up: Demographic data, physical examination, medical history, 24 hr holter, 12-lead electrocardiogram (ECG), vital signs, alcohol and drug screen, pregnancy test (females only), hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and anti-human immunodeficiency virus (HIV)1/2, clinical laboratory (including clinical chemistry, haematology, urinalysis and LFT's), previous and concomitant medication, and Columbia suicidality assessment;
at eligibility screening: brief physical examination, alcohol and drug screen, pregnancy test (females only), EEG, echocardiography and Columbia suicidality assessment;
at follow-up: brief physical examination, 12-lead ECG, vital signs and clinical laboratory (including clinical chemistry, haematology, urinalysis, troponin, BNP and LFT's)

Observation period:Two periods in the clinic: Period 1: Day -2 until Day 4; Period 2: Day -1 until Day 32

Blood sampling: For pharmacokinetics of GSK356278 in plasma: pre-dose and 1, 2, 3, 6, 12, 24, 36, 48 and 72 h post-dose Day 1 of period 1, pre-dose and 2 h post-dose Day 1, pre-dose Day 3 and 5, pre-dose and 3 h post-dose Day 7, pre-dose Day 9, pre-dose and 2, 4 and 6 h post-dose Day 14, pre-dose Day 21, 24 and 26, pre-dose and 1, 2, 3, 6, 12, 24, 48, 72, 96 h post-dose Day 28 of period 2.

Urine sampling: For pharmacokinetics: 24 hour collection on Day 28 of period 2.

Safety assessments: Adverse events: throughout the study; 12-lead ECG: pre-dose predicted Day -1, pre-dose and 1, 2, 4, 6, 12, 24 h post-dose Day 1 of period 1, pre-dose and 3 h post-dose Day 1, 4 and 7, pre-dose and 2 and 4 h post-dose Day 14, pre-dose and 3 h post-dose Day 21, pre-dose and 1, 2, 3, 6, 12, 24 and 48 h post-dose Day 28 of period 2; telemetry ECG: Day -1 and 1 of period 1 and Day 28 of period 2; vital signs: pre-dose predicted and 1, 2, 3, 4, 6 and 12 h post-dose predicted Day -1, pre-dose and 1, 2, 3, 4, 6, 12, 24, 36, 48 and 72 h post-dose Day 1 of period 1, pre-dose and 2 or 4 h post-dose Day 1, 3, 5, 7, 9 and 11, pre-dose, 2, 4 and 6 h post-dose Day 14, pre-dose and 2 or 4 h post-dose Day 21, pre-dose and 1, 2, 3, 4, 6, 12, 24, 48, 72 and 96 h post-dose Day 28 of period 2; clinical chemistry, haematology, troponin, BNP and LFT's: Day -1 and 2 of period 1, Day 1 (no troponin and BNP), 7, 14, 21 (troponin, BNP and LFT's only) and 29 of period 2; urinalysis: Day -1 and 2 of period 1, Day

1, 7, 14 and 29 of period 2; bond and lader VAS: Day -1 and 1 of period 1, Day 2 ,7, 14 and 28 of period 2; columbia suicidality assessment: Day -1, 15 and Day 32 of period 2; EEG: Day -1, 1 and 25 of period 2; cognitive tests: Day -1, 2 and 26 of period 2; echocardiography: Day 13 and 30 of period 2; inflammation panel: Day -1, 2 of period 1 and Day 4,7,14,21 and 29 of period 2; BDNF: Day 1 and 2 of period 1 and Day 1 and 29 of period 2

Intervention

Study Medication
Active substance: GSK356278
Activity :PDE4 inhibitor
Indication: Huntington*s disease
Strength: 0.5 * 14 mg
Dosage form: Oral tablet

Treatments
Cohort 1: a repeated dose of 2 mg GSK356278 or placebo on Day 1 until Day 10
Cohort 2: a repeated dose of 5 mg GSK356278 or placebo on Day 1 until Day 14
Cohort 3: a single dose of 10 mg GSK356278 or placebo on Day 1 of period 1, and a repeated dose of 10 mg GSK356278 or placebo on Day 1 until Day 28 of period 2

Study burden and risks

Procedures: pain, light bleeding, heamatoma, possibility of an infetcion

See E9

Contacts

Public
GlaxoSmithKline

980 Great West Road
TW8 9GS Brentford
GB
Scientific
GlaxoSmithKline

980 Great West Road
TW8 9GS Brentford
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Healthy male and female volunteers
- Age between 18 - 65 years
- BMI between 19.0 - 30.0 kg/m2
- Only non-smokers

Exclusion criteria

Suffering from: Hepatitis B or C, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 90 days from the start of the study of in case of donating more than 1.5 liters of blood (for men) or more than 1.0 liters of blood (for women) in the 10 months prior the start of this study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-12-2011
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	08-11-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2011-005314-11-NL
CCMO	NL38688.056.11