A randomised, double blind (sponsor unblinded), placebo-controlled, first time in human study to evaluate the safety, tolerability and pharmacokinetics of single and repeat oral doses and the food effect of GSK2556286 in healthy adult participants

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To investigate the safety and tolerability of GSK2556286 after single ascending and repeat oral doses in healthy adult participants.To determine the pharmacokinetics of single and repeat oral doses of GSK2556286 in healthy participants.To assess the…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mycobacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON55164

Source
ToetsingOnline

Brief title
CS0343-190570

Condition

- Mycobacterial infectious disorders

Synonym
Tuberculosis

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: Clinical activity is supported with funding from the EU and GSK.

Intervention

Keyword: pharmacokinetics, safety, tolerability

Outcome measures

Primary outcome

Safety and tolerability of GSK2556286:

Number and severity of Serious and Non-Serious Adverse Events.

Plasma concentrations of GSK2556286 plus derived parameters, as data allow.

For Single Ascending Dose (SAD) part: Derived pharmacokinetic parameters for GSK2556286 including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-*), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax) and apparent terminal half-life (t1/2) as data allow.

For Multiple Ascending Dose (MAD) part: AUC(0-t), AUC(0-*), AUC(0-*), Cmax, tmax, trough plasma concentration (C*) and t1/2.

Secondary outcome

For SAD part: Derived pharmacokinetic parameters for GSK2556286 following single dose (fasted and fed) including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-*), Cmax, tmax, t1/2 as data allow.

Dose-proportionality assessment using derived PK parameters, as data allow:

For SAD part: AUC(0-*), AUC(0-t), Cmax

For MAD part: AUC(0-*), Cmax

Observed accumulation ratio based on AUC (Ro) and Cmax (RCmax) and steady-state

ratio (Rss) following repeat dosing.

Trough plasma concentrations at the end of the dosing interval (C*) to assess

the achievement of steady-state of GSK2556286 following repeat oral doses.

Study description

Background summary

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb). According to the WHO 2019 report it was the top infectious disease killer worldwide accounting for more than 10 million cases and 1.5 million deaths in 2018.
The study will evaluate the safety, tolerability and pharmacokinetics (PK) profile of single and repeat ascending doses of GSK2556286. A food effect (FE) cohort will investigate the influence of food on the PK of GSK2556286. Results of this study are intended to be used to identify doses of GSK2556286 to be used in further studies. This study will be conducted at a single centre.

Study objective

To investigate the safety and tolerability of GSK2556286 after single ascending and repeat oral doses in healthy adult participants.
To determine the pharmacokinetics of single and repeat oral doses of GSK2556286 in healthy participants.
To assess the effect of food on the pharmacokinetics of GSK2556286 following an oral dose in healthy participants.
To assess preliminary dose proportionality of GSK2556286 following single and repeat oral doses.
To examine the extent of accumulation and achievement of steady-state following repeat oral doses of GSK2556286.

Study design

The study is a randomised, double blind (sponsor unblinded), placebo-controlled

study. Inclusion of the placebo arm will allow for an evaluation of adverse events attributable to treatment versus those independent of treatment. There are two parts to the study:

Part A will be a single-ascending dose, sequential, parallel cohort design including up to 8 cohorts. Each dosing cohort will comprise of 8 participants (6 active: 2 placebo) dosed under fasted conditions. Each participant will only participate in one cohort, where they will be randomised to receive a single dose of either GSK2556286 or matching placebo, administered in a 3:1 ratio according to the randomisation schedule in a blinded manner. Sentinel dosing will be used in each cohort. One cohort will investigate the effect of food administration (high fat meal) on safety, tolerability and PK after a single dose of GSK2556286. Based on emerging data, a second food effect cohort may also be included using a higher dose of GSK2556286.

The food effect cohorts may be dosed in parallel with the ascending dose cohorts, based on review of safety and PK data of the fasted cohorts by the Dose Escalation Committee (Section 5.4.2).

Part B will be a multiple-ascending, sequential, parallel dose cohort design including up to 4 cohorts. Each cohort will comprise of 8 participants (6 active: 2 placebo). Each participant will only participate in one cohort, where they will be randomised to receive a daily dose of GSK2556286 or matching placebo over a period of up to 14 days, administered in a 3:1 ratio according to the randomisation schedule in a blinded manner. Sentinel dosing will be used in each cohort. Part B may include drug administration after either fed or fasted conditions, dependent on the results from Part A.

Intervention

GSK2556286 Tablets for oral administration are available as white tablets containing 25 mg, 75 mg, or 250 mg of the drug substance GSK2556286A (free base).

Study burden and risks

Since the study is being executed in healthy volunteers, there are no anticipated benefits of the IMP. Please see the protocol for further information.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Participant must be 18 to 60 years of age inclusive, at the time of signing the informed consent. Participants aged 51 to 60 years must have received at least one dose of an EMA-approved COVID-19 vaccine at least 3 weeks prior to signing the consent form.
Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the normal reference range for the population being studied may be included only if the Investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
Note: Screened participants with laboratory values outside of the normal range may be rescreened once for inclusion into the study at the discretion of the Investigator.
Body weight *50kg, and body mass index (BMI) within the range 19 to 29.9 kg/m2 inclusive.
Male and/or Female Participants:

Male participants:
A male participant with a female partner of reproductive potential must agree to use contraception as detailed in Appendix 4 of this clinical study protocol during the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.
Female participants:
A female participant is eligible to participate if she is not a woman of childbearing potential (WONCBP) as defined in Appendix 4 of this clinical study protocol.
The participant is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions.

Exclusion criteria

Significant history of or current, cardiovascular, respiratory (including asthma), hepatic, renal, gastrointestinal, endocrine, haematological, infectious or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs: constituting a risk when taking part in the study or interfering with the interpretation of data.
Alanine aminotransferase (ALT) >1.5xupper limit of normal (ULN)
Total bilirubin >1.5xULN (isolated total bilirubin >1.5xULN may be acceptable, after consultation with the GSK Medical Monitor, if total bilirubin is fractionated and direct bilirubin <35%).
Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert*s syndrome or asymptomatic gallstones) or cholecystectomy.
Current or past history of significant renal disease including renal stones.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-11-2020
Enrollment:	96
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nap
Generic name:	Nap

Ethics review

Approved WMO Date:	30-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2022

Application type:	Amendment
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	EUCTR2019-004420-38-NL
CCMO	NL74338.056.20