An open-label, single ascending dose study to evaluate the safety and pharmacokinetics of a tablet formulation of CG-549 in healthy subjects

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

Summary

ID

NL-OMON48209

Source
ToetsingOnline

Brief title
CG-549 tablet pharmacokinetics study

Condition

- Bacterial infectious disorders

Synonym
bacterial infections

Research involving
Human

Sponsors and support

Primary sponsor: CrystalGenomics, Inc

Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: CG-549, SAD

Outcome measures

Primary outcome

PK:

- Plasma and urine CG-549 concentrations will be measured.

- The following plasma PK parameters will be estimated using noncompartmental analysis from the plasma concentration-time data: Cmax, tmax, kel, t*, AUC0-t, AUC0-inf, CL/F, and Vd/F.

- The following urine PK parameters will be estimated using noncompartmental analysis from the urine concentration-time data: Aeurine and CLR.

Secondary outcome

Safety : Adverse events, clinical laboratory, vital signs, 12-lead electrocardiogram, and physical examination.

Study description

Background summary

CG-549 is a new compound that may potentially be used for the treatment of bacterial infections involving Staphylococcus aureus, including methicillin resistant Staphylococcus aureus. CG-549 is an antibacterial drug that obstructs a particular enzyme in the making of fatty acids. Since fatty acids are part of the wall of bacterial cells, its making is critical for the survival of bacteria. CG 549 is an antibiotic that only impacts bacteria that rely on this particular enzyme (e.g., Staphylococcus aureus); it thus does not impact other bacteria. This should allow preservation of the normal gut microbiota as well as reduction of spread of antibiotic resistance across

multiple bacterial species.

Study objective

The purpose of this study is to investigate how quickly and to what extent a new tablet formulation of CG-549 is absorbed and eliminated from the body. This information will be used to select a dose of CG-549 which is expected to be safe and potentially efficacious. It will also be investigated whether the intake of food has an impact on the pharmacokinetics of CG-549. At last, it will be investigated how safe the new compound CG-549 is and how well it is tolerated when it is administered to healthy volunteers.

This study will be performed in 24 healthy male and female volunteers. The study will be performed in 2 parts, Part A and Part B.

Study design

Part A:

The study will consist of 3 periods during which the volunteer will stay in the research center for 5 days (4 nights). These periods will be separated by a period of at least 2 weeks.

Day 1 of each period is the day of administration of the study compound. The volunteers are expected at the research center at 2:00 PM in the afternoon prior to the day of administration of the study compound, so on Day -1 of each period. They will leave the research center on Day 4 of each period.

The volunteer will receive CG-549 three times as oral tablets with 240 milliliters of water. The volunteer will receive CG-549 after eating a high-fat standardized breakfast. This breakfast must be started exactly on time and must be finished within 20 minutes. The entire breakfast must be consumed. One of the investigators will inspect the hands and mouth after the study compound intake.

Part B:

The study will consist of 2 periods during which the volunteer will stay in the research center for 5 days (4 nights). These periods will be separated by a period of at least 2 weeks.

Day 1 of each period is the day of administration of the study compound. The volunteers are expected at the research center at 2:00 PM in the afternoon prior to the day of administration of the study compound, so on Day -1 of each period. They will leave the research center on Day 4 of each period.

All volunteers will receive the study compound once with a breakfast and once without a breakfast. The order in which this will occur will be determined by chance. The breakfast will be high-fat or medium-fat and is standardized. The breakfast must be eaten exactly on time (early in the morning) and within 20 minutes. The entire breakfast must be consumed. The 2 doses of CG-549 will be given as oral tablets with 240 milliliters (mL) of water. One of the investigators will inspect your hands and mouth after the study compound intake. The amount of CG-549 that will be administered and whether the breakfast will be high-fat or medium-fat (for a part of the subjects) will be determined based on the results of Part A.

Intervention

Part A:

The volunteer will receive CG-549 three times as oral tablets with 240 milliliters of water. The volunteer will receive CG-549 after eating a high-fat standardized breakfast. This breakfast must be started exactly on time and must be finished within 20 minutes. The entire breakfast must be consumed. One of the investigators will inspect the hands and mouth after the study compound intake.

Part B:

All volunteers will receive the study compound once with a breakfast and once without a breakfast. The order in which this will occur will be determined by chance. The breakfast will be high-fat or medium-fat and is standardized. The breakfast must be eaten exactly on time (early in the morning) and within 20 minutes. The entire breakfast must be consumed. The 2 doses of CG-549 will be given as oral tablets with 240 milliliters (mL) of water. One of the investigators will inspect your hands and mouth after the study compound intake. The amount of CG-549 that will be administered and whether the breakfast will be high-fat or medium-fat (for a part of the subjects) will be determined based on the results of Part A.

Study burden and risks

CG-549 has been previously tested in the laboratory and on animals. The dose at which no side effects were observed in rats was 100 mg per kilogram body weight (mg/kg). Side effects that occurred at doses up to 400 mg/kg in rats resolved within 2 days. The dose at which no side effects were observed in dogs was 400 mg/kg. Repeated dosing at an extremely high dose of 1000 mg/kg for 7 days in dogs resulted in disturbances in the gastrointestinal tract. Overall, toxicity studies with rats and dogs revealed no noteworthy findings.

CG-549 in capsule format has been administered to humans before in 3 studies.

In the first study, single-dose treatments of CG-549 at doses ranging from 80 to 1920 mg were considered safe and well tolerated in healthy male volunteers. There were no side effects that were related to administration of CG-549.

In the second study, treatment with CG-549 once daily for 5 days at doses ranging from 320 to 960 mg was considered safe and was well tolerated in healthy male volunteers. However, 4 out of 6 volunteers who received CG 549 twice daily for 5 days at a dose of 640 mg had increased liver enzymes (indicating liver toxicity) after they had left the research center. These increased liver enzymes were related to administration of CG-549. All 4 volunteers recovered well without treatment. There were no other side effects that were related to administration of CG-549.

In the third study, patients with bacterial skin infections due to methicillin-resistant Staphylococcus aureus were treated with CG-549 once daily for 10 to 14 days at a dose of 960 mg. The following side effects were observed which were related to administration of CG 549: increased levels of enzymes which are produced by the pancreas (amylase and lipase), headache, diarrhea, nausea, vomiting, an increased heart rhythm, abnormal dreams, and flatulence. Most side effects resolved well without treatment; only in 1 subject, pancreatic enzymes were still elevated at the follow-up visit.

Taken together, the following side effects of CG-549 may occur: increased liver enzymes, increased pancreatic enzymes, headache, diarrhea, nausea, vomiting, an increased heart rhythm, abnormal dreams, and flatulence. The study compound may also have side effects that are still unknown.

Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising. On the days of administration of the study compound, blood will be sampled frequently to determine the course of the concentration of CG-549 in the blood over time.

In total, we will take about 260 mL of blood from you. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time.

To make a heart tracing, electrodes will be pasted at specific locations on your arms, chest, and legs. Prolonged use of these electrodes can cause skin irritation.

The high-fat breakfast is a big breakfast consisting of 2 fried eggs, fried potatoes, and bacon among other things. The volunteer must consume the breakfast entirely. Particularly for light eaters, it can be difficult to consume the entire breakfast.

Contacts

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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. Sex: male or female; females may be of childbearing potential or of nonchildbearing potential (i.e., either surgically sterilized, physiologically incapable of becoming pregnant, or at least 1 year postmenopausal [amenorrhea duration of 12 consecutive months and a serum follicle stimulating hormone (FSH) >33.4 IU/L]).
2. Age: 18 to 55 years, inclusive, at screening.
3. Body mass index (BMI): 18.0 to 30.0 kg/m2, inclusive, at screening.
4. Weight: >=50 kg at screening.
5. Status: healthy subjects.

Exclusion criteria

1. Previous participation in the current study.
2. Employee of PRA or the Sponsor.
3. History of bacterial or viral infection requiring treatment with antibiotics or antivirals within 1 month prior to screening.
4. Presence or history of esophageal or gastroduodenal ulceration within 1 month prior to screening.
5. History of diseases or abnormalities of the liver or biliary system, other than uncomplicated hepatitis A.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-09-2019
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	28-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-09-2019

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-11-2019
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	EUCTR2019-003009-91-NL
CCMO	NL71288.056.19