A randomized, two-part, double-blind, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ZGN-1061 in healthy normal weight, overweight and obese male and female volunteers

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

Summary

ID

NL-OMON42985

Source
ToetsingOnline

Brief title
ZGN-1061 SAD, MAD, safety, PK and PD study

Condition

- Other condition

Synonym
Obesity

Health condition

Obesitas

Research involving

Human

Sponsors and support

Primary sponsor: Zafgen, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: MAD, Obesity, SAD, ZGN-1061

Outcome measures

Primary outcome

To evaluate the safety and tolerability of single and multiple ascending doses

of ZGN-1061 in healthy normal weight, overweight and obese volunteers

Secondary outcome

To evaluate the pharmacokinetic (PK) profiles of single and multiple ascending

doses of ZGN-1061 in healthy normal weight, overweight and obese volunteers

Study description

Background summary

ZGN-1061 is a new investigational compound that may eventually be used for the treatment of obesity and/or metabolic diseases. ZGN-1061 is a compound based on fumagillin, which is an antibiotic. ZGN 1061 is able to inhibit a protein called methionine aminopeptidase 2 (MetAP2). This ability of ZGN 1061 to inhibit this protein may result in weight loss. All of this may lead to substantial loss of body weight. This is the first time that this study compound is being given to humans.

Study objective

The study will be performed in 2 segments, Segment 1 and Segment 2. The purpose of the study is to evaluate safety and to investigate to what extent ZGN-1061 is tolerated.

This study will also investigate how quickly and to what extent ZGN-1061 is absorbed and taken into and removed from the body (this is called pharmacokinetics). In addition, the effect of ZGN 1061 on body weight, the fat mass and fat breakdown parameters in blood and blood cells will be investigated (this is called pharmacodynamics).

Study design

Segment 1:

The actual study will consist of 1 period during which the volunteer will stay in the clinical research center in Groningen (location Martini Hospital) for 5 days (4 nights).

Segment 2:

The actual study will consist of 1 period during which the volunteer will stay in the clinical research center in Groningen for 19 days (18 nights) followed by 5 days during which you will visit the clinical research center in Groningen (location Martini Hospital) for a short visit.

Intervention

Segment 1:
The study will consist of 1 period during which the volunteer will receive ZGN-1061 or placebo once. ZGN 1061 and placebo will be given as an injection given into the fat layer beneath the skin (subcutaneous) in the abdomen (stomach).

Group Day Treatment How often
1 1 ZGN-1061 0.2 mg or placebo Once a single subcutaneous injection
2 1 ZGN-1061 0.6 mg or placebo Once a single subcutaneous injection
3 1 ZGN-1061 2 mg or placebo Once a single subcutaneous injection
4 1 ZGN-1061 6 mg or placebo Once a single subcutaneous injection
5 1 ZGN-1061 12 mg or placebo Once a single subcutaneous injection
6 1 ZGN-1061 20 mg or placebo Once a single subcutaneous injection

Segment 2:
The study will consist of 1 period during which the volunteer will receive ZGN-1061 or placebo twice a week for approximately 4 weeks (a total of 8 doses). ZGN 1061 and placebo will be given as an injection given into the fat layer beneath the skin (subcutaneous) in the abdomen (stomach).

Group Days Treatment How often
1 1, 4, 8, 11, 15, 18, 22 and 25 ZGN-1061 X mg or placebo Twice a week for 4 weeks
2 1, 4, 8, 11, 15, 18, 22 and 25 ZGN-1061 Y mg or placebo Twice a week for 4 weeks
3 1, 4, 8, 11, 15, 18, 22 and 25 ZGN-1061 Z mg or placebo Twice a week for 4 weeks

Study burden and risks

Some of the possible adverse effects of the investigational procedures are described in Chapter 8 of the information booklet.

All drugs have the potential to cause side effects (also referred to as *adverse effects*) with the types and degree of the side effects being different for different drugs. Since ZGN-1061 is a new, experimental compound that has not yet been studied in humans, we do not know of the side effects that may occur in humans.

ZGN-1601 has been administered to animals. In dogs, which are the most sensitive animal for testing this new compound to determine the dose to start in humans, doses up to 6 mg/kg (equals to 20 mg dose in humans) did not result in any safety concerns. This dose level, where there is no adverse effects in dogs, has been used to calculate a starting dose for humans. This calculated starting dose for humans is 0.2 mg, which is significantly lower than the dose level of 6 mg/kg (similar to 20 mg dose in humans) where there is no adverse effects in dogs. When ZGN-1061 was studied in animals using doses greater than 6 mg/kg, less bone marrow cells (the inside of our bones is called bone marrow that makes the blood cells) in the sternum (the flat bone in the front of the chest where the ribs meet) were observed. The number of bone marrow cells returned to normal levels when dosing with ZGN 1061 was stopped.

Side Effects from Similar Compounds
Although ZGN-1061 has not been studied in humans, there are similar compounds (fumagillin-type drugs) that have been studied in humans and where there is information of side effects that is still helpful in knowing about while you are participating in this research study.

Flisint®
Flisint® is a fumagillin-type drug that is approved in France for healthcare professionals to prescribe to treat severe diarrhea due to a fungal infection called *Enterocytozoon bieneusi* in adult patients infected with human immunodeficiency virus (HIV). It is given as a capsule to be taken by mouth at a total dose of 60 mg every day (20 mg three times a day) for a 14 -day period. This dose is significantly greater than what will be the starting dose of ZGN-1061 (0.2 mg).

In the 23 HIV patients that were studied, most of the side effects were from the intestinal system (called *gastrointestinal*) and the inner part of the bone (called *bone marrow*) that makes our blood cells. The following are the side effects reported from the Flisint® studies.

Very common (occurred in more than 3 patients)
* Thrombocytopenia: a decreased number of blood cells, called platelets, made by your bone marrow that are responsible for blood clotting
* Granulocytopenia: a decreased number of blood cells, called granulocytes, made by your bone marrow that are responsible for fighting infections
* Increased ALT and AST: proteins in your body (called enzymes) that when increased indicate liver inflammation or damage
* Increased lipase: an enzyme made in your body by an organ call the pancreas that helps breakdown and absorb the food that you eat
* Abdominal pain
* Fever
* Insomnia: difficulty falling sleeping
* Pruritus: itching

Frequent Side effects (occurred in more than 2 patients)
* Diarrhea
* Nausea
* Vomiting
* Asthenia (feeling weak)
* Pneumonia (infection of the lungs)
* Dyspnea (difficulty breathing)
* Rash

TNP-470
TNP-470 is a fumagilin-type drug that has been studied in humans, but is not approved for healthcare professionals to prescribe and is not sold. TNP-470 was administered intravenously (into the vein) in patients with different types of cancers. The doses patients received were greater than 60 mg based on the patient*s body size. These doses, just as with Flisint®, are at a significantly greater dose than what will be the starting dose for ZGN-1061 (0.2 mg).

Side effects seen in patients with cancer treated with TNP-470 included:

* Malaise (generally feeling unwell)
* Seizures
* Asthenia (feeling weak)
* Dysphoria (feeling anxious or agitated)
* Dizziness
* Lightheadedness
* Vertigo (feeling like the room is spinning)
* Insomnia (difficulty falling asleep)
* Pain

* Pulmonary embolism (blood clot to the lungs)
* Gastrointestinal hemorrhage (bleeding in the stomach and/or intestines)
* Hypotension (significant low blood pressure)

Beloranib
Beloranib is a fumagilin-type drug that was studied by the same Sponsor, Zafgen, that will be investigating ZGN-1061. ZGN-1061 has a different chemical structure than beloranib. Due to this difference, ZGN-1061 can be absorbed and eliminated from the body faster than beloranib, which is anticipated to result in less side effects because there is less time for ZGN-1061 to stay in the blood. Also, in the animal studies investigating ZGN-1061, the same amount of ZGN-1061 as beloranib was given to mice and rats, in order to see the same amount of a positive effects (like weight loss). In those studies ZGN-1061 did not cause the same degree/amount of side effects as did beloranib. This difference is called the *safety margin,* which is better with ZGN-1061.

These characteristics of ZGN-1061, compared to beloranib, are anticipated to result in less and/or less severe side effects in humans. Although it is important to keep in mind that the side effects, by type and severity, seen in animals studies are not always seen in human studies, and the side effects experienced by humans are not always seen in animal studies.

Beloranib was studied in a total of 412 patients with the following conditions:
* Obesity (some of whom also had diabetes) (291 patients)
* Prader-Willi Syndrome (PWS): a rare genetic disorder where obesity can be life threatening and includes other medical problems (117 patients)
* Hypothalamic Injury Associated Obesity (HIAO): obesity is a result of brain injury (13 patients)

In all of these studies there were also 158 patients who received placebo.

Obesity Studies
Common side effects (occurred in more than 5% of patients and more often in beloranib patients than in patients who received placebo):
* Diarrhea
* Vomiting
* Dizziness
* Sleep disorder
* Insomnia (difficulty falling asleep)
* Abnormal dreams
* Anxiety
* Injection site reactions like hematoma (blood found locally outside of a blood vessels), erythema (redness), pruritus (itching)
* Decreased appetite
* Cough
* Hot flush

Prader-Willi Syndrome Studies
Common side effects (occurred in greater than 5% of patients and more often in beloranib patients than in patients who received placebo):
* Diarrhea
* Anxiety
* Injection site reaction like bruising, and pain
* Fatigue
* Hyperphagia (abnormal increased appetite)

Hypothalamic Injury Associated Obesity (HIAO) Studies:
There were too few patients studied with HIAO to determine common side effects.

A serious type of side effect called venous thromboembolism (VTE) was experienced by 8 patients in the beloranib studies. VTE includes two medical conditions: one is called deep venous thrombosis (DVT), which is when a blood clot develops in a vein, typically in the legs. The other is called pulmonary embolism (PE), which is when a blood clot, most often from a DVT, travels to the lungs. Although a DVT is not necessarily life threatening, a PE can be life-threatening and/or result in death.

There are several risk factors that people can have that can make them more likely to develop a VTE, The following are some of those risk factors:

* Not moving for a significant amount of time like:
o prolonged bed rest or hospitalization
o traveling for a long time in the car or plane (such as more than 4 hours)
* Recent surgery
* Obesity
* Use of oral contraceptives or hormonal therapy
* Prior episodes of VTE
* Pregnancy
* Trauma to the lower legs
* Family history of VTEs
* Genetic predisposition to VTEs
* Cancer

In the beloranib studies with patients who had obesity, with and without diabetes, there were 2 patients who received beloranib and experienced DVTs and 3 patients who received beloranib experienced PEs. One of these patients had both a DVT and a PE. All of these side effects resolved except for one that was still ongoing, and was being treated, when the study was ended.

In the studies with patients who had PWS, 2 patients who received beloranib experienced DVTs and 2 patients who received beloranib experienced PEs. The patients with DVTs had their DVTs ongoing, and were being treated when the study was ended. Both PEs resulted in fatal outcomes. Although the two fatal outcomes occurred in medically complicated patients with PWS, given that all

the VTEs were experienced by patients receiving beloranib, and none receiving placebo, the studies were stopped with no further investigations of beloranib conducted.

ZGN-1061 is a different compound from beloranib, and in animal studies ZGN-1061 was shown to have an improved safety margin, compared to beloranib. ZGN-1061 is absorbed and eliminated from the body more quickly than beloranib, which is anticipated to result in less, or less severe, side effects. However, as a result of the serious side effect of VTE with beloranib, significant measures will be taken in this study to monitor the possibility of volunteers developing VTE. These measures include:
* All volunteers with a family history of blood clots will be excluded
* All volunteers will have blood taken to perform special testing to exclude anyone who may have a predisposition, or risk, of developing blood clots
* For those volunteers that will participate in the study, throughout the study blood will be taken to perform special tests that may suggest that a blood clot has developed, as well as an examination of the lower extremities, by ultrasound, to exclude DVTs.
* The dose that you will receive, if you are allowed to participate in the study, will not be greater than the highest dose that was well tolerated from those volunteers who participated in Segment 1 of the study

It is important to note that symptoms of a PE always require prompt medical attention. If you observe signs or symptoms at any point in time after you start taking study compound (which may be ZGN 1061 or placebo) you should notify any of the study staff while in confinement, or seek immediate medical attention if you are not in confinement, but are still participating in the study.

The following are symptoms and/or findings that may suggest DVT or PE that you should be aware of and for which you should seek medical attention if you experience any of them:

DVT (usually occurs in the legs)
o Swelling in the affected leg, typically in the calf
o Pain in the leg (may feel like cramping in the calf)
o Warmth and tenderness in the affected area
o A hardened, cord-like feeling along the calf
o Redness or other changes in skin color, such as the skin turning more pale or more blue than usual

PE:
o Difficulty breathing/ shortness of breath
o Sharp chest pain that worsens after taking deep breaths
o Coughing up blood
o Light-headedness, fainting, and unconsciousness

Procedures: pain, minor bleeding, bruising, possible infection

Contacts

Public
Zafgen, Inc.

Portland Street 175
Boston 02114
US
Scientific
Zafgen, Inc.

Portland Street 175
Boston 02114
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

healthy male or female subjects
18-55 years, inclusive
BMI: SAD segment: 23.0 to <30.0 kg/m2, MAD segment: 30.0-40.0 kg/m2, inclusive

Exclusion criteria

Suffering from hepatitis B, hepatitis 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 60 days from the start of the study. Donation or loss of more than 100 mL of blood within 60 days prior to (the first)
drug administration. Donation or loss of more than 1.5 liters of blood (for male subjects) / more than 1.0 liters of blood (for female subjects) in the 10 months prior to (the first) drug administration in the current study

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-06-2016
Enrollment:	72
Type:	Actual

Ethics review

Approved WMO Date:	21-06-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2016
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	20-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2017
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	EUCTR2016-001605-17-NL
CCMO	NL58169.056.16