A phase 1, double-blind placebo-controlled single and multiple ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics and food effects of IFM-2427 in healthy subjects

Published: 16-01-2019
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Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON49211

Source
ToetsingOnline

Brief title
IFM 2427 SAD MAD FE study to investigate safety, PK and PD

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn□s disease, Inflammatory diseases

Research involving

Human

Sponsors and support

Primary sponsor: IFM Therapeutics
Source(s) of monetary or material Support: Ministerie van OC&W,Farmaceutical Industry

Intervention

Keyword: IFM 2427, MAD, SAD

Outcome measures

Primary outcome

Safety : Adverse events (AEs), clinical laboratory, vital signs, 12-lead

electrocardiogram (ECG), 24 hour Holter monitoring and physical examination

Pharmacokinetics : Plasma concentrations of IFM 2427, and plasma PK parameters

estimated using noncompartmental analysis (NCA), as appropriate: Cmax, tmax,

AUC0-last, AUC0 inf, t1/2, CL/F, and Vz/F (single-dose PK; Parts A, B, and D),

Cmax, tmax, AUC0-*, t1/2, CLss/F, Vzss/F, Rac,AUC, and Rac,Cmax (multiple-dose

PK; Part C)

Metabolite profiling in plasma samples taken from subjects of Group 2 in Part C

Urine IFM 2427 concentrations and urine PK parameters including, but not

limited to: Ae0-*, Fe0-*, and CLr (Part C)

Secondary outcome

Pharmacodynamics : PD parameters and exploratory biomarkers:

- Blood cell release of IL-1β and IL-18 following ex vivo stimulation with an

activator of the NLRP3 inflammasome compared to control conditions (Parts A and

C)

- Exploratory PD (possible analyses of ribonucleic acid [RNA] transcriptomics

and proteomics in the future) (Parts A and C)

- Potential induction of CYP3A due to IFM-2427 based on calculating whether a change from baseline in the plasma 4β hydroxycholesterol/cholesterol ratio is observed (Part C)

Pharmacogenomics : Sequencing of deoxyribonucleic acid (DNA) isolated from whole blood may be performed to:

- Determine carriers of clonal hematopoiesis of indeterminate potential based on a pre-specified list of variants in up to 100 genetic loci

- Genotype the NLRP3 genetic locus

- Genotype loci related to NLRP3 signalling

- Analysis of whole-exome or whole genome sequencing derived variants

Study description

Background summary

IFM-2427 is a new compound that may eventually be used for the treatment of many diseases in which inflammation is important; one example is Crohn*s disease. Conditions that IFM-2427 may eventually treat are characterized by many symptoms. Chron*s disease for example causes abdominal pain, persistent diarrhea, and loss of appetite. IFM-2427 is in development and is not yet approved or registered as a drug.

Study objective

The purpose of this study is to investigate how safe the new compound IFM-2427 is and how well it is tolerated when it is administered to healthy volunteers. IFM-2427 has not been administered to humans before; it will be administered to healthy volunteers for the first time in Part A of this study. It has been previously tested in the laboratory and on animals. IFM-2427 will be tested at various dose levels.

This study will be performed in up to 136 healthy male and female volunteers. The study will be performed in 4 parts, Parts A, B, C and D.

Part A of study will consist of up to 8 groups of 8 volunteers each.
Part B of study will consist of up to 2 groups of 6 volunteers each.
Part C of study will consist of up to 6 groups of 8 volunteers each.
Part D of study will consist of up to 2 groups of 6 volunteers each.

It will also be investigated how quickly and to what extent IFM-2427 is absorbed and eliminated from the body (this is called pharmacokinetics) and what the effect of IFM-2427 is on the immune response (this is called pharmacodynamics). Furthermore, it will be investigated whether certain effects of IFM 2427 may be attributed to specific genes.

Study design

Part A:
The study will consist of 1 period during which the volunteer will stay in the research center for 4 days (3 nights).

IFM-2427 or placebo will be given once, as an oral drink. After administration of the study compound, the vial will be rinsed twice with water which the volunteer will also be required to drink. The volunteer may need to drink an additional amount of water.

Administration of the study compound will be done after an overnight fast (no eating and drinking, except water) of at least 8 hours. A light meal will be given on the evening before fasting. During fasting the volunteer is allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound. Following administration, the volunteer will fast for another 4 hours. Then the volunteer will be given a lunch.

Whether the volunteer will receive IFM-2427 or placebo will be determined by chance. Per group, 6 volunteers will receive IFM-2427 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if IFM-2427 or placebo will be administered; we call this a double-blinded study. However, if it is important for the volunteers health, for example in case of a serious side effect, this information can be looked up during the study.

For safety reasons, initially 2 volunteers in Group 1 will receive the study compound. One volunteer will receive IFM-2427, and 1 will receive placebo. After administration, the safety and tolerability of the study compound in these 2 volunteers will be closely monitored. If there are no concerns about the safety and tolerability 24 hours after administration, then the remaining 6 volunteers (5 will receive IFM-2427 and 1 will receive placebo) in Group 1 will receive the study compound.

Please refer to the table below to see the planned dose levels for each group. The doses of Groups 2 and higher can be adjusted based on the results of the previous group(s). However, the dose will not be lower than 3 milligram (mg)

and not higher than 600 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigators, unacceptable side effects appear.

The planned dose levels for the study are as follows:

Group Day Treatment* How often
1 1 IFM-2427 3 mg or placebo once
2 1 IFM-2427 10 mg or placebo once
3 1 IFM-2427 30 mg or placebo once
4 1 IFM-2427 100 mg or placebo once
5 1 IFM-2427 300 mg or placebo once
6 1 IFM-2427 600 mg or placebo once
7** 1 tbd once
8** 1 tbd once
mg=milligram; tbd=to be determined
* In case the dose level will be lower or higher than planned, the volunteer will be informed verbally.
** Two additional groups may be added depending on the results of the study. The doses of Groups 7 and 8 will be determined based on the results of the previous groups.

Part B:
The study will consist of 2 periods during which the volunteer will stay in the research center for 4 days (3 nights). Between periods, the volunteer will go home for at least 3 days.

IFM-2427 will be given twice (once per period) as oral tablets with 240 milliliters (mL) water. One of the investigators will inspect the hands and mouth after the study compound intake. Two different tablet forms of IFM 2427 will be compared. The order in which the 2 different tablets will be administered will be determined by chance.

Administration of the study compound will be done after an overnight fast (no eating and drinking, except water) of at least 8 hours. A light meal will be given on the evening before fasting. During fasting the volunteer id allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound. Following administration, the volunteer will fast for another 4 hours. Then the volunteer will be given a lunch.

The dose level will be determined based on the results in Part A. The volunteer will be informed verbally of the dose level. The dose will however not be lower than 3 milligram (mg) and not higher than 600 mg.

Part C:

The study will consist of 1 period during which the volunteer will stay in the research center for 17 days (16 nights).

IFM-2427 or placebo will be given once daily for 14 days as an oral drink. After administration of the study compound, the vial will be rinsed twice with water which the volunteer will also be required to drink. The volunteer may need to drink an additional amount of water.

Administration of the study compound will be done after an overnight fast (no eating and drinking, except water) of at least 8 hours. A snack will be given on the evening before fasting. During fasting the volunteer is allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound. Following administration, the volunteer will fast for another 2 hours. Then the volunteer will be given a breakfast. Fasting following administration may be increased to 4 hours; in this case, the volunteer will be given a light meal on the evening before fasting.

Whether the volunteer will receive IFM-2427 or placebo will be determined by chance. Per group, 6 volunteers will receive IFM-2427 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if IFM-2427 or placebo will be administered; we call this a double-blinded study. However, if it is important for the volunteers health, for example in case of a serious side effect, this information can be looked up during the study.

Based on results from previous groups it may be decided to dose twice daily. In the 2 optional groups (Groups 5 and 6), participants may receive 2 doses of IFM-2427 per day from Day 1 through Day 13. In this case, the volunteer will receive one dose every 12 hours: 1 in the morning and 1 in the evening. The morning doses will be administered after an 8-hour fasting period. The evening doses will be administered 2 hours after the evening meal. The volunteer will be informed at the start of the study whether he/she will receive 1 or 2 daily doses.

The dose levels of each group will be determined based on the results in Parts A and B, and of the previous group(s) in Part C. The volunteer will be informed verbally of the dose level. The dose however will not be lower than 3 milligram (mg) and not higher than 600 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigators, unacceptable side effects appear.

Part D:
The study will consist of 3 periods during which the volunteer will stay in the research center for 4 days (3 nights). Between periods, the volunteer will go home for at least 3 days.

IFM-2427 will be given 3 times (once per period); once as an oral drink of 20 milliliters (mL) and twice as an oral tablet together with 240 mL water. After intake of the oral drink, the vial will be rinsed twice with water which the volunteer will also be required to drink. The volunteer may need to drink an additional amount of water. After intake of the tablets, one of the investigators will inspect the volunteers hands and mouth.

The drink will be given without breakfast and the tablets will be given once with breakfast and once without breakfast. The order in which this occurs will be determined by chance. The breakfast is a high fat breakfast with a standard composition which must be started exactly on time and must be consumed entirely within 20 minutes. When no breakfast is provided, administration of the study compound will be done after an overnight fast (no eating and drinking, except water) of at lea

Intervention

Part A:
IFM-2427 or placebo will be given once, as an oral drink. After administration of the study compound, the vial will be rinsed twice with water which the volunteer will also be required to drink. The volunteer may need to drink an additional amount of water.

Administration of the study compound will be done after an overnight fast (no eating and drinking, except water) of at least 8 hours. A light meal will be given on the evening before fasting. During fasting the volunteer is allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound. Following administration, the volunteer will fast for another 4 hours. Then the volunteer will be given a lunch.

Whether the volunteer will receive IFM-2427 or placebo will be determined by chance. Per group, 6 volunteers will receive IFM-2427 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if IFM-2427 or placebo will be administered; we call this a double-blinded study. However, if it is important for the volunteers health, for example in case of a serious side effect, this information can be looked up during the study.

For safety reasons, initially 2 volunteers in Group 1 will receive the study compound. One volunteer will receive IFM-2427, and 1 will receive placebo. After administration, the safety and tolerability of the study compound in these 2 volunteers will be closely monitored. If there are no concerns about the safety and tolerability 24 hours after administration, then the remaining 6 volunteers (5 will receive IFM-2427 and 1 will receive placebo) in Group 1 will receive the study compound.

Please refer to the table below to see the planned dose levels for each group. The doses of Groups 2 and higher can be adjusted based on the results of the

previous group(s). However, the dose will not be lower than 3 milligram (mg) and not higher than 600 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigators, unacceptable side effects appear.

The planned dose levels for the study are as follows:

Group Day Treatment* How often
1 1 IFM-2427 3 mg or placebo once
2 1 IFM-2427 10 mg or placebo once
3 1 IFM-2427 30 mg or placebo once
4 1 IFM-2427 100 mg or placebo once
5 1 IFM-2427 300 mg or placebo once
6 1 IFM-2427 600 mg or placebo once
7** 1 tbd once
8** 1 tbd once
mg=milligram; tbd=to be determined
* In case the dose level will be lower or higher than planned, the volunteer will be informed verbally.
** Two additional groups may be added depending on the results of the study. The doses of Groups 7 and 8 will be determined based on the results of the previous groups.

Part B:
IFM-2427 will be given twice (once per period) as oral tablets with 240 milliliters (mL) water. One of the investigators will inspect the hands and mouth after the study compound intake. Two different tablet forms of IFM 2427 will be compared. The order in which the 2 different tablets will be administered will be determined by chance.

Administration of the study compound will be done after an overnight fast (no eating and drinking, except water) of at least 8 hours. A light meal will be given on the evening before fasting. During fasting the volunteer id allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound. Following administration, the volunteer will fast for another 4 hours. Then the volunteer will be given a lunch.

The dose level will be determined based on the results in Part A. The volunteer will be informed verbally of the dose level. The dose will however not be lower than 3 milligram (mg) and not higher than 600 mg.

Part C:
In Group 4, the volunteer will receive IFM-2427 or placebo once daily for 14 days as an oral drink. In Group 5, the volunteer will receive IFM-2427 or placebo twice daily as a capsule. Participants in Group 6 will receive IFM-2427

or placebo once or twice daily as either an oral drink or a capsule. After administration of the study compound, the vial will be rinsed twice with water which the volunteer will also be required to drink. The volunteer may need to drink an additional amount of water.

In Groups 1 to 4, administration of the study compound will be done after an overnight fast of at least 8 hours. A snack will be given on the evening before fasting. During fasting the volunteers are allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound. Following administration, the volunteer will fast for another 2 hours. Then the volunteer will be given a breakfast. Fasting following administration may be increased to 4 hours; in this case, the volunteer will be given a light meal on the evening before fasting.

In Group 5 (and optionally Group 6), participants will receive 2 doses of IFM-2427 per day from Day 1 through Day 13, followed by a single morning dose on Day 14. In this case, the volunteer will receive one dose every 12 hours: 1 in the morning and 1 in the evening. The morning doses will be administered after an 8-hour fasting period. The evening doses will be administered 2 hours after the evening meal. In Group 6, the volunteer will be informed at the start of the study whether the volunteer will receive 1 or 2 daily doses.

In Group 5 (and optionally in Group 6), the study compound will be administered twice daily together with food:
• Before each morning dose, the volunteer will fast overnight for at least 8 hours. During fasting the volunteer is allowed to drink water, except from 2 hour before until 1 hour after administration of the study compound.
• From Day 1 to Day 14, breakfast will be served 30 minutes before to the morning dose and the volunteer must consume this meal within 20 minutes. After the morning doses on Days 1 and 14, the volunteer will fast until he/she will receive lunch approximately 4 hours after dosing. On all other days, the volunteer will fast until approximately 2 hours after the morning dose.
• From Day 1 to Day 13, dinner will be served approximately 45 minutes prior to the evening dose and the volunteer must consume this meal within 30 minutes.
• On Days 1 and 14, the volunteer will receive standardized meals which the volunteer will need to eat entirely.

Whether the volunteer will receive IFM-2427 or placebo will be determined by chance. Per group, 6 volunteers will receive IFM-2427 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if IFM-2427 or placebo will be administered; we call this a double-blinded study. However, if it is important for the volunteers health, for example in case of a serious side effect, this information can be looked up during the study.

The dose levels of each group will be determined based on the results in Parts A and B, and of the previous group(s) in Part C. You will be informed verbally of the dose level. The dose however will not be lower than 3 milligram (mg) and

not higher than 600 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigators, unacceptable side effects appear.

The planned dose levels for the study are as follows:
Group Day Treatment How often
1 1 - 14 10 mg IFM-2427 (oral drink) Once daily
2 1 - 14 30 mg IFM-2427 (oral drink) Once daily
3 1 - 14 100 mg IFM-2427 (oral drink) Once daily
4 1 - 14 200 mg IFM-2427 (oral drink) Once daily
5* 1 - 14 100 mg IFM-2427 (oral capsule) Twice daily
6* 1

Study burden and risks

All drugs have the potential to cause side effects; the extent to which this occurs differs. As IFM-2427 will be administered to humans for the first time in this study, side effects of IFM-2427 in humans have not been reported to date.

IFM-2427 has been studied extensively in laboratory assays and in animals. Doses up to 300 mg/kg were tested in rats and up to 150 mg/kg in monkeys. In these studies with rats and monkeys, no adverse effects on blood pressure, heart rate, body temperature, breathing, heart function, lung function, body weight, or food consumption were seen. No macroscopic or microscopic changes in the organs were observed. Oral administration of IFM 2427 at doses of 300 mg/kg was not associated with effects on neurobehavioral function in rats. Furthermore, no toxic effects were seen at any of the tested dose levels. Laboratory studies could not detect that IFM-2427 causes changes to the genetic material of an organism. The effects of IFM-2427 on conception, pregnancy and lactation are not known.

There is a risk that IFM-2427 impairs the immune status that might expose the volunteer to infectious diseases like tuberculosis, influenza, toxoplasmosis (a parasite), the Epstein-Barr virus (Pfeiffer*s disease), and/or the cytomegalovirus. You will be closely followed during the study on any signs or symptoms of infection, such as fever, cough, sore throat, or skin abscess.

Allergic reactions can occur with any drug and this can be in the form of itching, difficulty breathing, and a skin rash and/or drop in blood pressure. Life threatening allergic reactions are rare, but possible.

There is a low risk that IFM-2427 interacts with other medication; such interactions are not yet known. Therefore, combination of IFM-2427 with other medications should be avoided or given with caution.

As stated earlier, IFM-2427 is a new compound that has not yet been tested in humans. For this reason, the side effects in humans are not known at this time. As with any new drug, there is a risk that (possibly serious) side effects occur that have so far not been seen in studies with animals.

Drawing blood and insertion of the indwelling cannula (tube in an arm vein) may be painful or cause some bruising. In total, we will take about 250 mL (Part A) 220 mL (Part B) 500 mL (Part C) 310 mL (Part D)of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time.

Heart tracing and Holter
To make a heart tracing and record your heart rhythm using a Holter device, electrodes will be pasted at specific locations on different parts of your body. Prolonged use of these electrodes can cause skin irritation.

Skin biopsy
If the volunteer develop a skin rash, we will take a skin biopsy from the affected area. This procedure is expected to cause minimal discomfort.

Nose and throat swab for coronavirus test
Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause the volunteer to gag. When the sample is taken from the back of the nose, the volunteer may experience a stinging sensation and the eyes may become watery.

Contacts

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Scientific
IFM Therapeutics

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Gender : male or female; females must be of non-childbearing potential
- Age : 18 to 64 years, inclusive, at screening.
- Body mass index (BMI) : 18.5 to 30.0 kg/m2 at screening.
- Weight : >=50 kg at screening.

Exclusion criteria

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

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-02-2019
Enrollment:	136
Type:	Actual

Ethics review

Approved WMO Date:	16-01-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	28-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-08-2020
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	EUCTR2018-004402-26-NL
CCMO	NL68649.056.19

Study results

Date completed: 26-04-2021

Results posted: 16-02-2022

First publication
22-11-2021