A Multi-center, Parallel-group, Double-blind, Placebo-controlled, Randomized, Ascending Dose Trial to Determine the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous Infusions of OPC-108459 Administered to Subjects with Paroxysmal and Persistent Atrial Fibrillation.

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Objective(s): Part 1: To determine the safety, tolerability, pharmacokinetics (PK), and efficacy of single ascending doses of OPC-108459 following one 10-minute constant rate infusion in adultsubjects diagnosed with paroxysmal or persistent AF. Part...

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

Summary

ID

NL-OMON41577

Source
ToetsingOnline

Brief title
OPC-108459 in Subjects with Paroxysmal & Persistent Atrial Fibrillation

Condition

- Cardiac arrhythmias

Synonym
cardiac arrhythmias, irregular hartbeat

Research involving
Human

Sponsors and support

Primary sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.
Source(s) of monetary or material Support: Otsuka Pharmaceutical Development & Commercialization;Inc.

Intervention

Keyword: OPC-108459, Paroxysmal Atrial Fibrillation, Persistent Atrial Fibrillation

Outcome measures

Primary outcome

Primary Endpoints (Part 1):

PK:

•*For OPC-108459: Cmax and area under the concentration-time curve from time 0

to time of the last measurable concentration (AUCt).

Safety:

•*Maximum change from baseline in Holter collected QTcF in the 24-hour postdose

interval;

•*Maximum change from baseline in Holter collected ventricular rate in the

24-hour postdose interval;

•*Maximum change from baseline in diastolic and systolic blood pressure

collected during vital sign measurements in the 24-hour postdose interval.

Primary Endpoints (Part 2):

Efficacy:

•*Percent of subjects with NSR, defined as NSR for at least 1 minute within 30 minutes of the end of OPC-108459 infusion.

PK: (Subjects to be analyzed separately for 1 or 2 infusions)

•*For OPC-108459: Cmax and AUCt.

Safety:

•*Maximum change from baseline in Holter collected QTcF in the 24-hour postdose interval;

•*Maximum change from baseline in Holter recorded ventricular rate in the 24-hour postdose interval;

•*Maximum change from baseline in diastolic and systolic blood pressure collected during vital sign measurements in the 24-hour postdose interval.

Secondary outcome

Secondary Endpoints (Part 1):

Efficacy:

•*Percent of subjects with NSR, defined as NSR for at least 1 minute within 30 minutes of the end of OPC-108459 infusion.

Secondary Endpoints (Part 2):

Efficacy:

•*Time to achievement of NSR (for those that convert);

•*Duration of NSR up to 24 hours and presence of NSR at 168 hours (8 days).

Study description

Background summary

Atrial fibrillation (AF) is the most common type of arrhythmia and is a major risk factor to form blood clots, making a person five to seven times more likely to suffer a stroke. AF may be treated with anti-arrhythmia medication or also with therapeutic interventions such as electric cardioversion or catheter ablation procedure.

Otsuka Pharmaceutical Co., Ltd. discovered the new compound OPC-108459, being developed as a therapeutic agent for the rapid conversion of paroxysmal and persistent AF to sinus rhythm. OPC-108459 potently inhibits Kv1.5 and GIRK1/4 channel currents and is expected to show potent efficacy in the cardioversion of AF to sinus rhythm in humans with little effect on ventricular functions. Currently, other drugs (eg, ibutilide, amiodarone) used to treat AF also have cross-reactivity to sodium and/or potassium channels in ventricular tissue, producing delays in repolarization of ventricular tissue and increasing the risk of Torsade de pointes.
As OPC-108459 is capable of being developed as an injection formulation, rapid defibrillation of AF is anticipated, and therefore the compound is being developed as an injection product for cardioversion of AF.

Study objective

Objective(s): Part 1: To determine the safety, tolerability, pharmacokinetics (PK), and efficacy of single ascending doses of OPC-108459 following one 10-minute constant rate infusion in adult
subjects diagnosed with paroxysmal or persistent AF. Part 2: To determine the efficacy and safety of OPC-108459 following up to two 10-minute constant rate infusions in adult subjects diagnosed with paroxysmal or persistent AF.

Study design

Study design:
The trial will consist of 2 parts. Each part will evaluate 2 populations of subjects presenting for cardioversion in a hospital setting; one diagnosed with paroxysmal AF (duration 3 hours to 7 days) and the second diagnosed with persistent AF (duration > 7 and <= 30 days). Classification of AF is to be current at the time of randomization.

Part 1: The safety, tolerability, PK, and efficacy of single ascending doses of

OPC-108459 will be studied following administration of a 10-minute constant rate infusion in cohorts of 5 subjects. Subjects will be randomized 4:1, OPC-108459:placebo- (vehicle-) control. Once the dose has been administered, subjects will be followed for up to 30 days postdose. The initial follow-up period will be 24 hours postdose to perform PK and safety evaluations. During this initial 24-hour monitoring period, no further AF treatment is required per protocol. However, rescue therapy, including
electrical cardioversion, may be initiated if: Symptoms/conditions of a trial subject worsen; Rescue treatment is deemed necessary at the discretion of the principal investigator.
Subjects will then return for a visit on Day 8 for safety evaluations. Subjects will also receive a phone call on Day 31 as a final follow-up on their overall health status. Cohorts of paroxysmal and persistent AF subjects may have their dose increased independently. Each cohort will be evaluated separately for all analysis parameters. The decision on whether or not to escalate the dose will be made for a completed cohort using blinded safety data obtained through at least 24-hours postdose.

The safety review team will consist of the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) project leader, the Clinical Safety & Pharmacovigilance representative, the trial medical
monitor, and an independent medical reviewer. If a subject has a serious adverse event (SAE), or at least 2 of the 5 subjects were not considered to have tolerated the dose, the independent reviewer will be unblinded to assess the relationship of the events to the investigational medicinal product (IMP). Should the nontolerated or SAE events be considered related to IMP, dose escalation will be stopped. If the relationship to IMP is not clear, an additional cohort at the same dose may be enrolled or the dose escalated. Changes in vital signs should be confirmed with a repeat measurement. Values of QT interval corrected for heart rate using the Fridericia formula (QTcF) > 500 msec or changes from baseline in QTcF of > 15 msec will receive further review by the safety team. The OPDC clinical pharmacologist will analyze blinded OPC-108459 concentrations for linearity and dose selection for the next targeted maximum (peak) plasma concentration (Cmax) value; selection of the next dose will be reviewed and agreed upon by the safety team. Analysis of existing PK data arising from both the 269-11-215 trial and the 269-11-001 trial, a parallel trial being conducted in Japan, indicates that there is no inter-regional variation. Therefore, at dose escalation meetings, decisions regarding
selection of the next higher dose will be made using available safety and PK data from both trials.

Part 2: Expanded cohorts of 21 adult male and female subjects with either paroxysmal or persistent AF (42 total) will be evaluated for efficacy and safety at a dose of OPC-108459 that has been selected based on the safety, tolerability, and efficacy profile observed in Part 1. Subjects will be randomized 2:1, OPC-108459:placebo- (vehicle-) control. Different doses may be

used for paroxysmal and persistent AF subjects. Subjects will be administered a 10-minute constant rate infusion of OPC-108459/placebo. If the subject fails to convert to sinus rhythm within 10 minutes postinfusion, a second 10-minute constant rate infusion of OPC-108459/placebo will be administered; the dose will be determined by the safety and tolerability profile observed in Part 1.

Intervention

Investigational Medicinal Product, Dose, Formulation, Mode of Administration:
OPC-108459 powder, 50 mg, will be packaged in 50-mL sterile vials. OPC-108459 powder in 50-mL vials will be reconstituted with 25 mL sterile water for injection to produce a 0.2% solution of OPC-108459/1% solution of Captisol®. OPC-108459 placebo powder, 0 mg of active drug, will be packaged and prepared similarly.
Part 1: OPC-108459 will be administered as a 10-minute constant rate intravenous (IV) infusion. OPC-108459 doses will be based on achieving expected target OPC-108459 Cmax values of 1.0, 1.6, 2.4, 3.6, 5.4, 7.0, 8.0, 9.0, and 10.0 µg/mL. The concentrations correspond to estimated doses of 0.26, 0.4, 0.6, 0.9, 1.35, 1.75, 2.0, 2.25, and 2.5 mg/kg for those subjects with ideal body weight; the estimates are based on a slope of 4,000 ng/mL per mg/kg dose of OPC-108459 that was observed in the healthy subject trial (269-09-201). Should the slope change, doses will be adjusted to produce the target Cmax values. Exact dose selection will be communicated formally to the sites should dose adjustment be necessary.
Part 2: OPC-108459 will be administered as a 10-minute constant rate IV infusion. If the subject fails to convert to sinus rhythm within 10 minutes postinfusion, a second 10-minute constant rate infusion of OPC-108459 will be administered. The doses of the first and second infusions will be determined based on the safety and tolerability profile observed in Part 1.

Study burden and risks

The length of time of participation in this study is approximately 31 days not including the screening visit. This study requires 24 hours of monitoring, after administering the study drug intravenously, while patient is admitted to the hospital, followed by a 1 outpatient visit and 1 follow-up telephone call. A screening visit is required within 7 days prior to the start of the study.

The following data is collected and following examinations are performed which could burden the patient:
1) Screening:
- inclusion and exclusion criteria will be reviewed
- a comprehensive medical history will be assessed
- concomitant medications will be recorded within 30 days of dosing.
- demographic information will be collected (i.e. date of birth, age, gender,

race, ethnicity)
- patients will be measured for height and weight and IBW will be calculated
- vital signs (oral temperature, respiratory rate, blood pressure, and heart rate)
- a complete physical exam will be performed
- a resting 12-lead ECG will be performed after the subject has been recumbent and at rest for at least 10 minutes prior to the ECG
Burden/Risks associated with ECGs:
ECG patches may cause a skin reaction such as redness or itching. Patients may also experience skin discomforts where the ECG patch was placed and/or hair loss associated with the placement of ECG leads.

- blood samples will be collected for serum chemistry, hematology, and urine sample for analysis
- blood sample will be collected for screening for hepatitis B and C
Burden/Risks associated with Blood Sampling:
Blood samples will be taken approximately 20 times throughout the course of the study. Approximately 197 mL of blood, will be drawn throughout the study. Additional blood samples may be required if any of the laboratory tests are abnormal or if the study doctor considers it necessary for monitoring the patient*s health.
During the collection of blood samples, one may experience pain and/or bruising at the needle injection site. Although rare, clots may form and infections may occur near the injection site. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.
Blood will be drawn through a small needle placed in the vein. An intravenous catheter may be used for some blood draws. Study staff will remove the catheter before the patient leaves the clinic.
- urine sampling will be done for alcohol and drug screening
- a urine pregnancy test will be performed. If a positive urine pregnancy test is observed, a serum pregnancy test will be performed for confirmation.

Reproductive Risks:
There are unknown risks in taking most drugs during conception, pregnancy, or while breast-feeding. Therefore female patients/ partners of male patients should not get pregnant during this study or for 30 days after taking the study drug. Female subjects should also not breast-feed or use breast milk during or for one month after this trial.

2) Day 1 (Dosing):
Patient will be admitted to the hospital by his/her regular doctor, as part of the treatment for his/her AF.
- vital signs (before and after administration study drug)
- abbreviated physical examination
- resting 12-lead ECGs will be performed locally after the subject has been recumbent and at rest for at least 10 minutes prior to the ECG.
Electrocardiograms should be performed at predose (within 45 minutes of dosing)

and 5, 10, 30, and 40 minutes and 1, 4, 8, and 12 hours post-start-of-infusion.
- blood samples for Hematology, Serum Biochemistry and urine sample for analysis
- urine pregnancy test
- High resolution, 24-hour, 12-lead Holter monitoring will be initiated at predose (within 45 minutes of dosing) and continue through 24 hours post-start-of-infusion.
- cardiac telemetry monitoring from predose (within 45 minutes of dosing) to 24 hours post-start-of-infusion. If NSR is observed, a 12-ECG will be taken to confirm NSR. Telemetry monitoring should be continuous. Any brief interruptions in order to accommodate movement of the subjects should be documented.
- a neurological exam will be completed at predose
- administration study drug or placebo: in Part 1, a single 10-minute constant rate IV infusion of OPC-108459 or placebo will be administered. In Part 2, if sinus rhythm is not observed after the first infusion, a second infusion will be administered after a 10-minute wait.

Risks associated with IV infusion of a study drug:
OPC-108459 will be given as a IV infusion. At the area where the needle is inserted, you may experience mild pain, bruising and swelling. There is a possibility that the area may become infected. Medications given itravenously can sometimes cause pain, swelling and redness of the vein and surrounding tissues, which may not go away quickly, even if the medication is stopped.

Risks and Discomforts associated with study drug:
This research study is the fourth time that the study drug is being tested in humans. Therefore the exact side effects caused by the study drug are not yet clear.
In 127 healthy subjects previously studied, the complaints that have been reported after receiving OPC-108459 include major depression, headache, back pain, joint pain, musculoskeletal pain, soreness in the mouth, fatigue (feeling tired and weak), feeling hot, infusion site reactions (like pain and itching), joint swelling, muscle tightness and pain, dry skin, upset stomach, nausea, swelling in the feet and legs, syncope (fainting), decreased heart rate, decreased diastolic blood pressure, unstable angina (chest pain) and increased liver function test results in the urine (urobilinogen). These may or may not be caused by OPC-108459.
In this study, the levels of the drug in the blood may approach but are not expected to exceed the same level shown to produce seizures in animals. The meaning of these findings for humans is not known, however there are study procedures in place to make sure that you are monitored for any similar side effects as seen in the animal studies, like seizures.

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this study drug, including allergic reaction or interaction with another medication, including reactions that may be life threatening.
Patients must report all problems and worries to a member of the study staff.

During this study patients will be observed closely for any bad or harmful effects. The study doctor will decide if it is safe for the patient to continue in the study.

- after dosing, a shorter neurological exam will be performed
- blood samples for PK analysis:
- blood samples for PK analysis of OPC-108459 and its designated metabolites will be collected at predose (within 45 minutes of dosing) and 10 and 30 minutes (**1 minute) and 1, 2, 4, and 8 hours (**10 minutes) post-start-of-infusion.
In Part 2, if the second infusion is given, an additional PK blood draw should be taken 20 minutes (**1 minute) after the start of the first infusion (predose of the second infusion).
- blood samples for PK analysis of Captisol**will be collected at predose (within 45 minutes of dosing) and 10 and 30 minutes (**1 minute) and 1, 2, 4, and 8 hours (**10 minutes) post-start-of-infusion. In Part 2, if the second infusion is given, an additional PK blood draw should be taken 20 minutes (**1 minute) after the start of the first infusion (predose of the second infusion).
- in all cases, successful cardioversion will be followed by a minimum of 4 weeks
of anticoagulation in patients who can tolerate this.

Restrictions/Rescue therapy
Rescue therapy, including electrical cardioversion, may be performed as soon as medically necessary at the discretion of the PI. Subjects that do not convert after 1 hour of the end of the last infusion with IMP may receive rescue therapy (e.g. cardioversion) and will be considered as treatment failures.
The use of other antiarrhythmic agents (e.g. procainamide, lidocaine, flecainide, propafenone, amiodarone, bretylium, dofetilide, dronedarone ibutilide, adenosine) is discouraged until 24 hours after the last infusion of IMP (in order to determine the efficacy endpoints of OPC-108459) unless rhythm should be restored earlier in the opinion of the PI.
Any subject requiring rescue therapy will continue to be monitored for safety. Subjects will return for a visit on Day 8 for safety evaluation. Subjects will also receive a phone call on Day 31 as a final follow-up on their overall health status.

Meals:
Standardized meals and snacks will be served at regular times when patients are in the hospital for the study, except when fasting is required or otherwise noted.

3) Day 2 (Discharge):
- vital signs
- physical examination
- a resting 12-lead ECG will be performed after the subject has been recumbent

and at rest for at least 10 minutes prior to the ECG at 24 hours post-start-of-infusion.
- blood samples for Hematology, Serum Biochemistry and urine sample for analysis
- 24 hour Holter monitoring will conclude at 24 hours post termination of the last infusion of IMP.
- 24 hour cardiac telemetry monitoring will conclude at 24 hours post termination of the last infusion of IMP.
- blood samples for PK analysis as described for Day 1

After completion of all study procedures, you may be discharged from the hospital.

4) Day 8 (Follow-up visit with study staff):
- any changes in health since last study visit
- vital signs
- physical examination
- a resting 12-lead ECG will be performed after the subject has been recumbent and at rest for at least 10 minutes prior to the ECG.
- blood samples for Hematology, Serum Biochemistry and urine sample for analysis
- blood sample for PK analysis not on Day 8 but at Early Termination, if Early Termination is 24hours prior to post dose
- urine pregnancy test

5) Day 31 (Follow-up Telephone Call):
The patient will complete a follow-up telephone call with the study staff 30 days after the last dose of study medication to determine if he/she is having any side effects and what medications he/she is taking. After completion of the telephone call, the participation in the study will be complete.

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. Male and female subjects, ages of legal consent up to 85 years old, inclusive.
2. Patients with paroxysmal AF (recent or new onset) duration defined as 3 hours to <= 7 days (Group 1 only); or patients with persistent AF duration defined as >7 days and <= 12 months (Group 2 only) at the time of randomization. Duration of AF will be based on clinical assessments, review of subject medical records, and the judgment of the PI, and should be documented to establish the date of onset and duration of AF.
3. Patients must be hemodynamically stable defined as a screening systolic blood pressure between 90 to 160 mmHg, diastolic < 100 mmHg.
4. Low risk of thromboembolic potential as documented by
* Subjects with AF lasting < 48 hours (by ECG);
* Subjects with AF duration longer than 48 hours who have had: a) 3 weeks of anticoagulation therapy with warfarin and an International Normalized Ratio (INR) of 2.0-3.0 prior to dosing, or 3 weeks of another locally-approved anticoagulant therapy such as dabigatran or a factor Xa inhibitor, or b) a TEE to establish the absence of atrial main body or appendage thrombus within 24 hours prior to dosing. Adequate anticoagulation with warfarin (requires INR monitoring), dabigatran, or a factor Xa inhibitor needs to be in place at the time of drug infusion and continued after cardioversion as per local guidelines.
5. Subjects managed in accordance with American College of Cardiology/American Heart Association/European Society of Cardiology anticoagulation guidelines or in accordance with more recently-approved compounds as approved for this indication by the FDA. Prescreening treatment with beta-adrenergic blocking agents, calcium antagonists and digoxin for control of ventricular rate is permitted.
6. Male and female subjects who are surgically sterile (ie, have undergone orchidectomy or hysterectomy, respectively); female subjects who have been postmenopausal for at least 12 consecutive months; male and female subjects who agree to remain abstinent or to practice double-barrier forms of birth control from trial screening through 30 days from the last dose of IMP. Double barrier forms of birth control include use of two of the following precautions: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth

control implant, or birth control depot injections combined with either condom, or sponge with spermicide.

Exclusion criteria

1. History of long QT syndrome, Torsade de Pointes or an uncorrected QT interval of > 450 msec.
2. QRS interval > 120 msec at Screening.
3. History of myocardial infarction within 6 months of Screening.
4. Symptoms of acute coronary syndrome, angina, or active myocardial ischemia diagnosed by ECG, or imaging stress testing within 6 months of Screening.
5. History of ventricular tachycardia, fibrillation, or resuscitated cardiac arrest.
6. History of clinically significant congenital heart disease.
7. Presence of severe aortic or mitral stenosis (valve area < 1.0 cm-sq), aortic or mitral regurgitation (greater than moderate severity), atrial septal defect, greater than mild pulmonary hypertension, or other conditions leading to AF with echo confirmation of this within the 12
months prior to Screening.
9. Part 1: Any subject with a diagnosis of heart failure NYHA Class II - IV or with an EF < 40%. Part 2: Subjects with a diagnosis of heart failure NYHA Class IV or NYHA I, II or III with an EF < 35%, as determined by any imaging method within 6 months of Screening.
10. Subjects that have received concomitant treatment with class I or III antiarrhythmic agents unless the medication was discontinued more than 5 half-lives before dosing.
11. History of seizures.
12. Current diagnosis of atrial flutter.
13. Diagnosis of stroke, transient ischemic attack, or any transient neurological deficit within 1 year of Screening or known carotid artery stenosis of >50%.
14. Cardiac surgery within 3 months of Screening.
15. Bradycardia (< 50 bpm) or sick sinus syndrome, unless controlled by a pacemaker.
16. Current reversible cause of AF such as hyperthyroidism, pulmonary embolism, alcohol intoxication, pericarditis.
17. Wolff-Parkinson-White syndrome.
18. Subject diagnosed with any congenital abnormality, severe valve disease eg, aortic or mitral stenosis, severe right or left systolic dysfunction or severe pulmonary hypertension. This can be confirmed by TEE during Screening.
21. The following laboratory results at Screening: serum potassium < 3.5 mEq/L, magnesium < 1.5 mEq/L, serum creatinine >= 1.8 g/dL, hemoglobin < 9 g/dL in women or < 11 g/dL in men and liver enzymes 1.5 upper limit of normal.
22. Administration of another investigational product within 30 days of dosing.
24. Any medical condition, in the opinion of the investigator, which could
interfere with evaluation of the trial objectives or safety of the subjects (eg, antiarrhythmic agents, previous cardiac ablation or cardioversion).
25. Persons who are confined in an institution or jail
26. Women who are pregnant or breast-feeding

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):	05-01-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	niet van toepassing

Ethics review

Approved WMO Date:	10-12-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-05-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-07-2014

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-005090-31-NL
CCMO	NL46575.042.13