A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy and Safety of Botulinum Toxin Type A (AGN 151607) Injections into the Epicardial Fat Pads to Prevent Post-Operative Atrial Fibrillation in Patients Undergoing Open-Chest Cardiac Surgery

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Primary:- To compare the efficacy of AGN-151607 with placebo to prevent post-operative atrial fibrillation (POAF) in participants who are undergoing open chest cardiac surgerySecondary:- To compare the efficacy of AGN-151607 with placebo to reduce...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON55701

Source
ToetsingOnline

Brief title
Allergan 1925-201-008

Condition

- Heart failures

Synonym
post-operative atrial fibrillation; heartfailure

Research involving
Human

Sponsors and support

Primary sponsor: Allergan Ltd.
Source(s) of monetary or material Support: Allergan

Intervention

Keyword: AGN-151607, Botulinum Toxin Type A, Open-Chest Cardiac Surgery, Post-Operative Atrial Fibrillation

Outcome measures

Primary outcome

Percentage of participants with at least 1 continuous atrial fibrillation (AF)

episode >= 30 seconds during the first 30 days post surgery

Secondary outcome

- Percentage of time spent in AF (AF burden) during the first 30 days post

surgery

- Percentage of participants with at least 1 event of symptomatic AF during the

first 30 days post surgery

- Time to first occurrence of AF during the first 30 days post surgery

- Percentage of participants with at least 1 continuous AF episode >= 2 minutes

during the first 30 days post-surgery

- Percentage of participants with at least 1 continuous AF episode >= 5 minutes

during the first 30 days post-surgery

- Percentage of participants with at least 1 continuous AF episode >= 30 minutes

during the first 30 days post-surgery

- Percentage of participants with at least 1 continuous AF episode >= 1 hour during the first 30 days post surgery

- Percentage of participants with at least 1 continuous AF episode >= 4 hours during the first 30 days post surgery

- Percentage of participants with at least 1 continuous AF episode >= 24 hours during the first 30 days post surgery

Safety:

- Adverse events (AEs), physical examination, clinical laboratory tests, vital signs, electrocardiogram (ECGs), pulmonary function

- Potential immunogenicity response

Study description

Background summary

Post-Operative Atrial Fibrillation (POAF) is a serious condition, associated with: recurrent AF, longer hospital stays (including in intensive-care settings), increased healthcare costs (in-hospital and post-discharge), higher risk of stroke, and increased mortality; all of which reflect an increased clinical burden due to POAF, including the need for medical/procedural interventions.
Current standard-of-care therapies have been unable to successfully prevent POAF in cardiac surgery patients and most conventional therapies are applicable only after AF occurs. Thus, there is an unmet need in this patient population to prevent the occurrence of POAF. Non-clinical studies have demonstrated that injections of botulinum toxin type A into discrete regions of the heart can prevent AF and 2 clinical studies have demonstrated that botulinum toxin type A injections can prevent POAF with no noted safety issues.
This Phase 2, placebo-controlled study will evaluate the efficacy and safety of one time injections of AGN 151607-125U (25U per fat pad) and 250U (50U per fat pad) distributed across each of the 5 major epicardial fat pads for the prevention of POAF in participants undergoing open-chest cardiac surgery. Injections will be administered during the open-chest cardiac surgery. Primary

and secondary efficacy will be assessed for 30 days post-surgery; participants will be followed for additional efficacy and safety through Day 367 post surgery.
The AE profile of AGN-151607 has not yet been fully characterized in humans. However, extensive safety data are available from clinical studies and post-marketing experience with BOTOX. BOTOX experience is considered relevant to the current program, having a similar dose range and other similarities with AGN-151607, as outlined in the Investigators Brochure.

Study objective

Primary:
- To compare the efficacy of AGN-151607 with placebo to prevent post-operative atrial fibrillation (POAF) in participants who are undergoing open chest cardiac surgery
Secondary:
- To compare the efficacy of AGN-151607 with placebo to reduce AF burden in participants who are undergoing open-chest cardiac surgery
- To compare the efficacy of AGN-151607 with placebo to prevent POAF using alternative definitions for AF in participants who are undergoing open-chest cardiac surgery

Safety:
- To compare the safety of AGN-151607 with placebo in participants undergoing open-chest cardiac surgery

Study design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of botulinum toxin type A (AGN-151607) injections into the epicardial fat pads, foci of ganglionic plexi, to prevent POAF in patients undergoing open-chest cardiac surgery.

Intervention

One-time injections of AGN-151607 or Placeboduring scheduled cardiac surgery. There are three study arms:
- 125 E (25 E per fat pad)
- 250 E (50 E per fat pad)
- Placebo

Study burden and risks

Subjects are asked to undergo procedures described on pages 10 - 12 of the study protocol. These procedures include physical examination, blood draw,

vital signs, measurement of weight and abdominal circumference, ECG, pulmonary function test, completion of questionnaires, answer questions of investigator and study team and administration of study drug (during planned heart surgery). Additionally, fertile subjects are asked to use contraceptives, and female subjects of childbearing potential will have pregnancy tests.
The study medication as well performing the study-related procedures may cause discomforts and risks. The risks associated with AGN-151607 are not well known. However, the risks associated with BOTOX (another botulinum toxin type A) are well known and subjects may experience them after receiving AGN-151607. Side effects and discomfort that have been observed with other botulinum toxin type A (treatments similar to AGN-151607) when used to treat other diseases (i.e., not prevention of post-operative atrial fibrillation) include the following: Shortness of breath; respiratory depression and/or respiratory failure; breathing of food, saliva, liquids or vomit into the lungs; slurred or slow speech; hoarse voice; dry mouth, dry eye, blurred vision, visual disturbance, cross eyed, abdominal pain, diarrhea, nausea, vomiting, fever, loss of appetite, partial loss of hearing, ringing in the ear, sensation of feeling off balance, weakness of the facial muscles, loss of facial movement, pins and needles, weakness, numbness and pain (usually in hands and feet), lack of movement and lack of feeling in the arm and shoulder, pinched nerve, painting, reduced sense of touch, general feeling of discomfort, illness or uneasiness (malaise); general bodily weakness or discomfort, weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and leg; rash, rash that appears as red, target-shaped ("bulls-eye") patches; itching, itchy, red and inflamed skin rash; excessive sweating, hair loss including in the eyebrows and eyelashes.
For botulinum toxin type A such as BOTOX, serious and/or immediate intolerance(hypersensitivity reactions such as anaphylaxis and serum sickness) have been reported, as well as other manifestations of intolerance (hypersensitivity) including hives (urticaria), soft tissue swelling (edema), and shortness of breath (dyspnea).
People with certain muscle-weakening neurological conditions (such as Lou Gehrig*s disease/amyotrophic lateral sclerosis, myasthenia gravis, Lambert-Eaton syndrome, or motor neuropathy) or unrecognized neurological conditions (neuromuscular junction disorders) can be extra-sensitive to the effects of botulinum toxin and could develop problems such as severe difficulty swallowing or breathing. In some cases, these problems may last for several months and feeding tubes may be required.
Side effects have been reported hours to weeks after dosing with drugs in the botulinum toxin class, which includes BOTOX. Spread of the study drug away from the injection site may cause effects in other areas of the body, including: muscle weakness, eyelid drooping (ptosis), double vision (diplopia), blurred vision, facial weakness, difficulty swallowing (dysphagia), speech disorders, constipation, pneumonia, difficulty breathing and slow and ineffective breathing (respiratory depression).
Swallowing and breathing difficulties can be life-threatening, and death has been reported. It is not known if botulinum toxin type A actually caused these

problems.

There have also been reports of heart problems (including abnormal heart rhythm and heart attack, some leading to death) after injection with botulinum toxin type A. However, it is not known if botulinum toxin type A actually caused these problems; some of these people were already at risk for heart disease. New onset or recurrent seizures have been reported, typically in people who are predisposed to experiencing these events. It is not known if botulinum toxin type A actually caused the seizures.
Risks of study procedures:
Epicardial Fat Pad Injection: There is a risk that the injection of the study treatment in the surrounding structures of the heart (the epicardial fat pads) result in piercing of the epicardium or bleeding. This may lead to surgical complications.
Blood samples: Taking blood may cause faintness and/or swelling, pain, redness, bruising, bleeding at the collection site, or infection (infection rarely happens) at the site where the needle is inserted.
Electrocardiogram (ECG): Skin irritation is rare but could occur during an ECG from the electrode patches or gel that is used.
Self-Adhesive Patch Risk: Subjects may experience an allergic reaction to the adhesive used on the patch (the patch adhesive is hydrogel). This may result in local irritation and skin redness.
Pulmonary Function Tests Risks: This involves some breathing and rapid breathing, which may cause temporary shortness of breath and lightheadedness or transient pain in the upper chest right after the tests.
Washout Risks: If subjects are taking antiarrhythmic medications (medications to treat pre-existing abnormalities of the heart rhythm - also known as Atrial Fibrillation), they may be asked to stop some or all of these medications before the study treatment injection. During this time, the symptoms of any pre-existing AF may get worse.
This Phase 2, placebo-controlled study will evaluate the efficacy and safety of one time injections of AGN 151607-125U (25U per fat pad) and 250U (50U per fat pad) distributed across each of the 5 major epicardial fat pads for the prevention of POAF in participants undergoing open-chest cardiac surgery. Injections will be administered during the open-chest cardiac surgery. Primary and secondary efficacy will be assessed for 30 days post-surgery; participants will be followed for additional efficacy and safety through Day 367 post surgery.
The AE profile of AGN-151607 has not yet been fully characterized in humans. However, extensive safety data are available from clinical studies and post-marketing experience with BOTOX. BOTOX experience is considered relevant to the current program, having a similar
dose range and other similarities with AGN-151607.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1.01- Participants must be 55 to 90 years of age, inclusive, at the time of signing the informed consent.
2.01- Participants who are scheduled to undergo open-chest cardiac surgery. Includes: coronary artery bypass graft (CABG) and/or valve repair/replacement.
3.01- Male or female
4.01- Male participants willing to minimize the risk of inducing pregnancy up to Day 60.
A male participant must agree to use contraception as detailed in Appendix 7, Section 10.7 of this protocol until Day 60 and refrain from donating sperm during this period.
4.02- Female participants willing to minimize the risk of inducing pregnancy up to Day 60.
A female participant is eligible to participate if she is not pregnant (has a

negative urine pregnancy result prior to randomization) not breastfeeding, and at least 1 of the following conditions applies:
a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 7, Section 10.7
• OR
b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 7, Section 10.7 of this protocol until after Day 60.
5.01- Capable of giving signed informed consent as described in Appendix 1, Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
5.02- Written informed consent from the participant has been obtained prior to any study related procedures.
5.03- Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent (European Union [EU] sites).
6.01- In sinus rhythm for the last 48 hours prior to surgery (prior history of paroxysmal atrial fibrillation (AF) is acceptable).
6.02- Willing to wear an electrocardiogram (ECG) patch for 30 days post-surgery and for 7 days after each study visit
6.03- Able, as assessed by the investigator, and willing to follow study instructions and likely to complete required study visit.

Exclusion criteria

1.01- Any uncontrolled clinically significant medical condition other than the one under study that, in the investigator*s opinion, would put the participant at an unacceptable risk with exposure to botulinum toxin type A.
1.02- Any medical condition that may put the participant at increased risk with exposure to botulinum toxin type A, including diagnosed muscular dystrophy (eg, Duchenne*s muscular dystrophy), myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, mitochondrial disease, or any other significant disease which might interfere with neuromuscular function.
1.03- Participants with presence or history of any of the following within 3 months prior to the Day 1 visit that may indicate a vulnerable respiratory state per the investigator*s clinical judgment: aspiration pneumonia, lower respiratory tract infections, uncontrolled asthma, severe chronic obstructive pulmonary disease, or otherwise compromised respiratory function.
1.04- Permanent/persistent atrial fibrillation (AF)
1.05- Has a known allergy or sensitivity to any botulinum toxin type A preparation.
1.06- Has a known allergy or sensitivity to medical adhesive (eg, ECG patch adhesive; hydrogel-based adhesive).
1.07- Severe (> 55mm) atrial enlargement
1.08- Left ventricular ejection fraction (LVEF) < 25%

1.09- Presence or history of symptomatic atrioventricular block > 1st degree within the last 30 days
2.01- Class I or III antiarrhythmic drugs unless proper washout was documented (Section 6.5.1)
2.02- Botulinum toxin type A (of any serotype) use within 6 months of randomization
2.03- Has been immunized for any botulinum toxin type A serotype as determined by participant medical history
2.04- Preoperative need for inotropes/vasopressors or intra-aortic balloon pump
2.05- Prior cardiac surgery
2.06- History of ablation for AF
2.07- Planned ablation procedure for AF at the time of surgery
2.08- Emergency surgery
3.01- Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
4.01- Participants have diagnostic assessments which in the opinion of the investigator prevent participation in the study.
4.02- Impaired prognosis defined as EuroSCORE II greater than 7% perioperative mortality
5.01- Females who are pregnant, nursing, or planning a pregnancy during the study
5.02- The participant has a condition or is in a situation which, in the investigator*s opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant*s participation in the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	AGN-151607
Generic name:	Clostridium botulinum neurotoxin type A (BoNT/A) complex

Ethics review

Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
Other	135000
EudraCT	EUCTR2017-004399-68-NL
CCMO	NL67919.018.19

Study results

Results posted: 05-03-2024

Summary results
Trial never started

First publication
04-03-2024